The Eating Behaviours, Quality of Life and Cardiometabolic Risks of Adults with Type 1 Diabetes using Continuous Subcutaneous Insulin Infusion Therapy

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A thesis submitted in partial fulfilment of the requirements of Liverpool John Moores University for the degree of Doctor of Philosophy

This research programme was carried out in collaboration with the Royal Liverpool Hospital

July 2016

Acknowledgements

First and foremost I would like to acknowledge Dr Julie Abayomi, Dr Ian Davies and Professor Andrew Sparkes for their continued support, encouragement, guidance and good humour throughout my PhD studies. I could not have asked for a better supervisory team and my heartfelt thanks go out to all of you.

I would also like to acknowledge Dr Tejpal Purewal and Dr Phillip Weston (Consultant Diabetologists / Royal Liverpool Hospital) for not only their expertise in diabetes, but also their help, support and faith throughout the project. I would also like to thank Gillian Morrison (CSII Diabetes Specialist Nurse / Royal Liverpool Hospital) for her kind-heartedness during the early stages of the study and our lengthy evening discussions about issues concerning diabetes and CSII.

I also owe a debt of gratitude to all the patients who volunteered to take part in this study. No-one received any incentive and some made huge sacrifices to ensure the smooth running of the project. For that I would like to thank each and every one of you and wish you all the very best.

Last but certainly not least I would like to thank my Mum, Dad and my brother Martin who have always supported and encouraged me through everything.

Abstract

Evidence suggests continuous subcutaneous insulin infusion (CSII) is an effective method of achieving glycaemic control in those with Type 1 diabetes (T1D). Among the advantages of CSII is the opportunity for patients to potentially discard the dietary inflexibility imposed by other regimes such as multiple daily injections (MDI). There are also reported improvements in quality of life. Furthermore, patients with T1D who achieve good glycaemic control may present a normal quantitative lipid profile; however, various qualitative atherogenic lipid abnormalities may exist, potentially leading to increased cardiometabolic (CM) risks. Literature investigating this in those using CSII is sparse and frequently dated; as is evidence regarding their eating behaviours and quality of life and is therefore worthy of further research.

To investigate these issues an initial audit of CSII patients' medical records spanning 8 years was performed, with a focus on routinely measured clinical markers of risk (n = 260). Then a cross-sectional study was carried out to compare those using CSII (n = 40) vs. MDI (n = 40). This involved the use of a food diaries and food frequency questionnaires to determine eating behaviours; semi-structured interviews and questionnaires were used to ascertain quality of life and CM risks were assessed by further interrogating participants' medical records and analysing a sample of plasma for lipoprotein quality. Finally, using similar methods, longitudinal case studies (n = 5) were performed to elucidate the transition from MDI onto CSII over one year.

The results indicated that upon commencing CSII HbA_{1c} was significantly reduced from 8.3 to 7.6% (p = <0.001) and insulin dose significantly lowered from 54.5 to 46.4 IU (p = <0.001) after using CSII for 12 months and these improvements were maintained over the following 3 years. There were few changes in both quantitative and qualitative lipids; however, systolic blood pressure decreased significantly and unexpectedly both over the 4 year audit period (128.2 to 122.1 mmHg; p = 0.003) and when comparing those using CSII against their MDI counterparts (123.5 mmHg vs. 135.3 mmHg; p = 0.023). Significant reductions

were also shown in diastolic blood pressure (75.2 to 72.0 mmHg; p = 0.027). There was little variance in the diets of the two treatment groups; however, subtle differences existed and the intake of certain nutrients such as fibre and iron in females failed to meet the RNI. Many qualitative themes emerged from the interviews regarding participants' quality of life and in particular highlighted how the device was largely held in positive regard for its ability to improve glycaemic control and offer unprecedented flexibility which allowed a largely unrestricted lifestyle.

Despite limitations, this study offers useful information for those working in the field, allowing, for the first time, a deep insight into the eating behaviours, cardiometabolic risks and quality of life of a group of patients using contemporary CSII therapy. It is hoped these findings will assist with decision making processes in clinical practice, thus improving the lives of those with T1D.

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Glossary of terms

ADA	American Diabetes Association
Apo-A1	Apolipoprotein A-1
Apo-B	Apolipoprotein B
BMI	Body mass index
CETP	Cholesterol ester transfer protein
CHO	Carbohydrate
CM	Cardiometabolic
CSII	Continuous subcutaneous insulin infusion
CVD	Cardiovascular disease
DGUC	Density gradient ultracentrifugation
DRV	Dietary reference values
DUK	Diabetes UK
EAR	Estimated average requirement
EASD	European Association for the Study of Diabetes
FFQ	Food frequency questionnaire
GI	Glycaemic index
HbA_{1c}	Glycated Haemoglobin
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
HSCIC	Health and Social Care Information Centre
IDL	Intermediate density lipoprotein
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
MDI	Multiple daily injections

MUFA	Monounsaturated fatty acid
n-3	Omega 3
n-6	Omega 6
NDNS	National Diet and Nutrition Survey
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NRES	National Research Ethics Service
PBS	Phosphate buffer solution
PUFA	Polyunsaturated fatty acid
RNI	Reference nutrient intake
SACN	Scientific Advisory Committee on Nutrition
SFA	Saturated fatty acid
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TAG	Triglyceride
TC	Total cholesterol
VLDL	Very low density lipoprotein

Chapter 1

Introduction

1 - Introduction

1.1 Background of T1D

Introduction

Type 1 diabetes (T1D) is a chronic disease affecting a significant number of people worldwide; often having a severe impact upon the lives of those diagnosed with the condition. Physiological, psychological and social issues are among those which frequently challenge patients; however, over recent years our understanding of T1D has grown exponentially and improved knowledge and novel innovations have emanated in enhanced strategies for prevention and treatment. One such treatment is continuous subcutaneous insulin infusion (CSII) therapy. This employs a small, electronic pump device to facilitate the administration of insulin. The benefits of the therapy include the hypothetical ability for the patient to relax their diet, as well as potential improvements in quality of life and certain cardiometabolic (CM) risks. Unfortunately, evidence regarding these benefits and their impact upon the lives of patients is lacking. This thesis aims to correct this and will explain a study carried out to investigate these three key areas. This introduction section will offer the reader a broad overview of T1D and CSII therapy as well as briefly outlining the research problems and describing the structure of the thesis.

Epidemiology

Diabetes is thought to affect almost 387 million people worldwide (International Diabetes Federation, 2014). It is commonly cited that 10% of this population will be diagnosed with T1D, therefore equating to approximately 3.87 million people, with equal rates of incidence found in males and females (International Diabetes Federation, 2014; Krischer, 2004). Previous literature also suggests that global incidence rates have been increasing for decades and are predicted to rise by 3% annually, despite high levels of variability between countries (Gale, 2002; International Diabetes Federation, 2014). Results from the DiaMond study highlight this variability. This epidemiological study was the largest standardised survey for any disease and examined global T1D incidence rates in children less

than 14 years of age living in 50 countries. Differences were estimated to be 350-fold, with age-adjusted incidence ranging from as little as 0.1 per 100,000 in Venezuela and China through to 40.9 in Finland (The DiaMond Project Group, 2006). Although this study highlighted increased incidence in all observed countries, more pronounced increases were seen in those with low incidence (*Ibid*). While evidence such as this is useful to determine the global rates and patterns of T1D, there is a lack of good quality data originating from some developing countries due to poorly established research and surveillance infrastructures and current efforts focussed largely on infectious diseases (Maahs, 2010, International Diabetes Federation, 2014). This is an area of concern for the research community, with existing diabetes prevalence rates for these countries largely based upon age-specific estimations (Wild, 2004). Furthermore, little mortality data is also available for these countries with estimations usually based on the assumption that life expectancy is worse than in developed countries, meaning documented rates are thought to be conservative and the true extent of the disease in these areas is currently unknown (*Ibid*).

Large variances in the prevalence of T1D have also been observed within Europe. The European Prospective Complications Study: Aetiology of Childhood Diabetes on an Epidemiological Basis (EURODIAB ACE) study was based upon 16,362 reported cases of T1D out of a population of 28 million children and highlighted how rates ranged from 3.2 cases per 100,000 in Macedonia to 40.2 cases per 100,000 in Finland, with an average annual increase in incidence of 3.4% (95% C.I. 2.5-4.4%) (EURODIAB ACE Study Group, 2000). Despite these findings being 15 years old, more recent evidence from Diaz-Valencia (2015) shows how these variances remain and that differences even occur between countries with comparable healthcare systems; for example Sardinia presented incidence of 37.8 per 100,000, whereas its neighbour Italy had only intermediate prevalence of the disease (Diaz-Valencia, 2015). This intermediate prevalence was shown to be typical of Europe as a whole and occurred in 18 of the 39 populations examined, with the remainder displaying high or very high incidence and posing questions of concern for the continent as a whole (Karvonen, 2000).

The UK is no different in terms of high prevalence, with T1D accounting for 10% of all cases of diabetes, equating to approximately 320,000 out of the 3.2 million

people diagnosed with the disease (HSCIC, 2012; Quality and Outcomes Framework, 2013). Diagnosis most frequently occurs between the ages of 10 and 14 and incidence in children under 14 is high, with rates estimated at 28.2 per 100,000 (NHS, 2007; International Diabetes Federation, 2014). Additionally, it should also be noted that T1D incidence in the UK has doubled every 20 years since 1945 and that the greatest increases are in children under 5 (JDRF, 2010; NICE, 2008). These concerning figures are also met with equally troubling cost implications. An economic evaluation of T1D by Hex (2012) revealed that diabetes burdens the NHS with direct costs of approximately £9.6 billion and indirect costs of £13 billion, with T1D alone accounting for £1 billion of direct costs and £0.9 billion of indirect costs. These figures are forecasted to rise in line with the expected increases of disease prevalence, with projected 2035/36 costs for T1D predicted to be £1.8 billion for direct costs and £2.4 billion for indirect costs and with total diabetes costs expected to consume 17% of the NHS budget (*Ibid*). These projections offer a bleak glimpse into the future if the prevalence of T1D continues unchallenged.

Aetiology

T1D is a complex disease characterised by the progressive failure of the pancreatic, insulin-producing ß cells which reside in the islets of Langerhans, rendering skeletal muscle and fat cells unable to take up blood glucose. Autoimmunity appears to be the predominant mechanism by which ß cells are destroyed, resulting in a lifelong reliance on exogenous insulin as a therapeutic remedy (Atkinson, 2012). The current understanding of the natural history and pathology of this phenomenon remains incomplete, however great strides have been made in recent decades and existing evidence indicates that a combination of complex genetic, autoantibody and metabolic factors working in concert encourage this destructive process to take place (Figure 1.1).

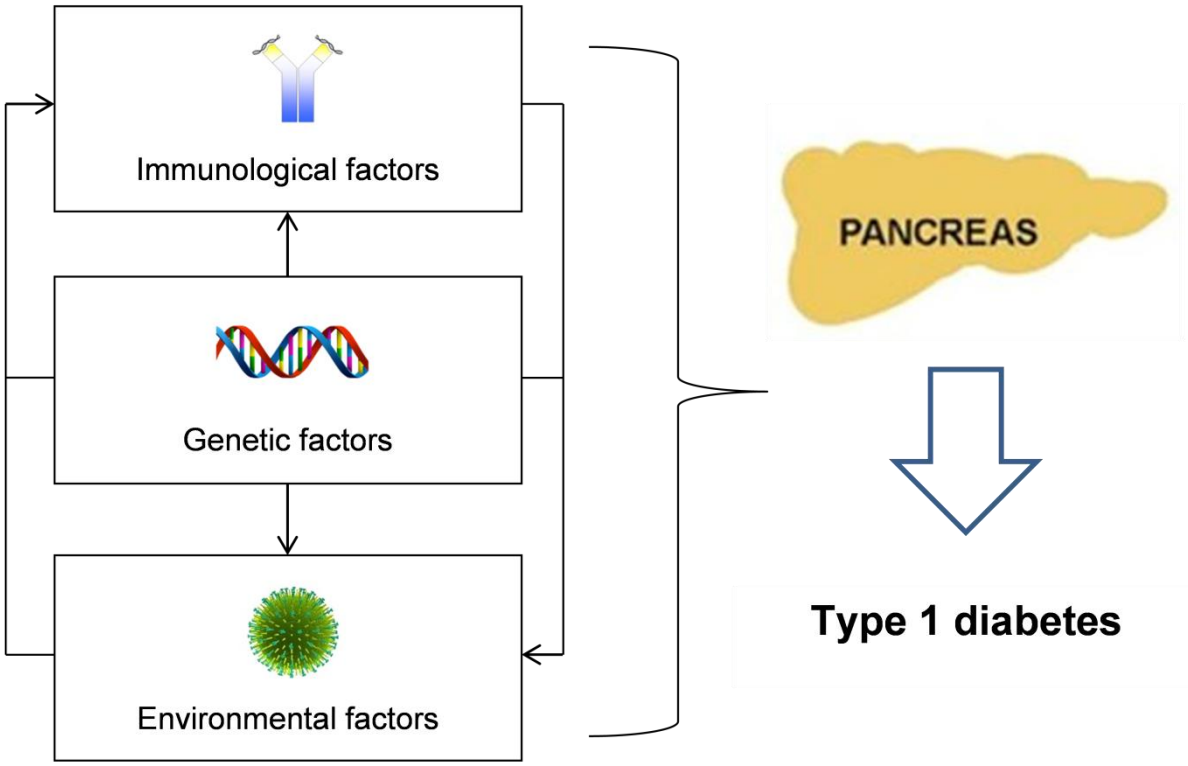


Figure 1.1 – Diagram showing events leading to ß cell death (Adapted from: Hober, 2010)

It was first proposed by Eisenbarth (1986) that those with genetic predispositions for T1D who were exposed to certain environmental provocations could be at risk of initiating this autoimmunity and that the destructive process is not immediate, but can be measured in months and years. Despite providing a valuable signpost for the research community, recent evidence has further elaborated and refined this model and it is now estimated that 40-50% of ß cell death is required for the onset of hyperglycaemia and that some cells may actually remain in patients diagnosed with T1D (Akirav *et al.* 2008; Meier *et al.* 2005). Furthermore, the decline in ß cell function is not linear and is in fact stepwise in nature, with recurrent, brief relapses of remission as described by Von Herrath *et al.* (2007). It is these typical elements of decline into T1D which may explain how insulin secretion can remain stable despite ongoing autoimmunity and why symptoms usually only develop after considerable damage has already been done.

The cascades of interacting events leading to ß cell death, as illustrated in Figure 1.1, although not fully understood, often appear to occur in those who are at an increased risk of the disease via a genetic predisposition. There are various candidate genes associated with T1D and the majority of loci appear to encode products implicated in immune function and to a lesser degree insulin expression and ß cell function (Noble, 2012). It is also apparent that there are a small number of genes which infer a larger risk of developing the disease and a large number of genes which infer a smaller risk. The commencement of research in the 1970's focussing on the Human Leukocyte Antigen (HLA) were of particular importance in determining this risk, with alleles such as DRB1*03-DQB1*0201 (DR3) or DRB1*04-DQB1*0302 (DR4) inferring risk, whereas others such as DQB1*0602 appearing to offer protection (Morran, 2015).

Another important genetic marker of interest is that of the IDDM2 locus which is implicated in insulin regulation (Kantárová, 2007). Although this insulin gene region is of primary importance in T1D pathogenesis (after the HLA region); it only confers approximately 10% of susceptibility to the disease and is highly variable between ethnicities (Bell, 1984). Various other candidate non-HLA and non-insulin regulating genes have also been implicated in T1D, albeit to a lesser degree. Examples being cytotoxic T lymphocyte-associated protein 4 (CTLA-4), protein tyrosine phosphatase nonreceptor type 22 (PTPN22) and interleukin (IL)-2 receptor–α (IL2RA) (Nisticò, 1996; Steck, 2011; Lowe, 2007). Although this overview has only briefly outlined a handful of selected candidate genes, the discovery of markers such as these have improved our understanding of the genetic basis of T1D and continue to hold promise for the future.

Despite well documented genetic circumstances predisposing individuals to develop T1D, many people with these genetic risk markers often fail to develop the condition. In fact as rates of T1D continue to increase the number of cases triggered by the high risk HLA genotype remain virtually static, which is in agreement with the hypothesis that environmental factors may be driving incidence rates (Gillespie, 2004). Furthermore, investigations into monozygotic twins with the disease have revealed a pairwise concordance of only 13-33% (Knip, 2005). This coupled with migration studies highlighting how the movement of people from low incidence areas to high incidence areas are frequently

accompanied by increased rates of T1D further emphasise how environmental elements may be at work (Åkerblom, 1998). With this in mind the research community has placed great importance on the investigation of many of these potentially diabetogenic triggers which may account for the disease. This has resulted in the production of a considerable body of evidence and many diverse and often contradicting rationales for the initiation of T1D.

Perhaps the most compelling environmental culprit for the development of T1D is that of a viral infection. Large-scale epidemiological studies have highlighted potential associations, with both the DiaMond study and the EURODIAB study suggesting that geographical differences of disease incidence could indicate a viral trigger (The DiaMond Project Group, 2006; EURODIAB ACE Study Group, 2000). Furthermore, the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study found disease onset was strongly associated with the seasons; with higher incidence occurring in the autumn and winter months, leading the authors to suggest that the autoimmunity preceding disease onset may be mediated by a viral infection (Kimpimäki, 2001). In addition Patterson *et al.* (1996) described a curious positive correlation between the incidence of T1D and poor household hygienic conditions. The authors suggested that this so-called 'hygiene hypothesis' was likely due to an increased probability of exposure to infections in environments with lower standards of hygiene, thus further emphasising the possibility of a viral component in the development of the disease. Furthermore, viruses such as rubella, mumps, rotavirus and cytomegalovirus have all been weakly implicated in the development of T1D; however, enteroviruses in particular are thought to be the most likely candidates (Coppieters, 2012; Honeyman, 2000; Pak, 1988; Hober, 2013). Gamble *et al.* first suggested the potential association of this genus of viruses with T1D in 1969 and since then many workers have attempted to further investigate this proposition, with evidence derived from epidemiological studies often being used to underpin the hypothesis. For example, a meta-analysis by Yeung (2011) illustrated a significant association with the virus and T1D; with children diagnosed with the disease displaying 10 times greater odds of having contracted an enterovirus than controls. Furthermore, histological studies utilising these human pancreatic tissue collections have clarified enterovirus mediated damage to ß cells and have illustrated 'hallmark' features of

T1D including insulitis and the upregulation of major histocompatibility complex (MHC) class 1 (Richardson, 2011; Foulis, 1987). It is thought that these processes create a suitable 'landscape' allowing a series of multifaceted inflammatory 'hits' to occur to the pancreatic islets, which over time ultimately promote the destruction of ß cells and the progression of T1D (Schneider, 2013).

Even with great strides being taken to understand the aetiology of T1D and initially convincing evidence suggesting the implication of enteroviruses it should be noted that important controversies in the literature remain. Despite large scale epidemiological studies providing compelling evidence in favour of viral triggers, there are others which present a different picture. The Diabetes Autoimmunity Study in the Young (DAISY) project, for example, found no viral association with islet autoimmunity in children with genetically high risk (Graves, 2003). This lack of association was also seen in stool samples collected from children in Norway and more recently The Environmental Determinants of Diabetes in the Young (TEDDY) study, which examined 8677 children with a high risk genotype for evidence of a viral causative agent also failed to find any association (Tapia, 2011; Lee, 2013). Furthermore, a systematic review of 26 published case-control studies by Green (2004) also concluded that there is insufficient evidence to implicate the coxsachie virus in the development of T1D. Moreover, research conducted in animal models suggests that the contraction of enteroviruses may actually infer protection against the disease (Filippi, 2008). This protective nature of enteroviruses has also been seen in a paradoxical twist of the 'hygiene hypothesis' described previously, where authors have described that it is in fact the absence of infection exposure, usually caused by near-sterile living conditions, which may increase risks of developing T1D and that contracting these viruses may therefore infer an element of protection from the disease (Bach, 2002). When weighing up conflicting evidence such as this it is clear that many of the findings concerning viral triggers are controversial and further research is certainly required.

T1D is frequently regarded as a disease which often (although not exclusively) presents in the young. As such there are various environmental factors associated specifically with early life which have been linked with the progression of the disease. Perhaps the most immediate of all potential factors is the actual birth process itself. It is widely documented that children born using a caesarean

section may be at an increased risk, with a meta-analysis by Cardwell *et al.* (2008) suggesting that rates of T1D are 20% greater in those who have been delivered using a caesarean section and that increased incidence of T1D has also been rising in parallel with rates of the procedures use. This increased risk was also illustrated in the BABYDIAB study where children born via caesarean section were shown to have a twofold greater risk of developing T1D than those born by vaginal delivery with incidence rates being 4.8% and 2.2% respectively (Bonifacio, 2011).

Parental behaviours may vary from family to family after child birth and in particular feeding patterns may be prone to differences. The scientific community at present is divided over the impact this may have upon T1D risk with some authors suggesting that breastfeeding has no effect on the development of the disease (Viner, 2008). Conversely, other authors propose that breastfeeding could in fact be an environmental candidate and that the length of time breastfeeding takes place is a key indicator of risk (Pereina, 2014; Alves, 2012). Furthermore, the early introduction of complex proteins such cow's milk (often in the form of infant formula) has also been implicated as an important factor in the development of T1D during early life, with the late introduction of cow's milk in conjunction with long duration breastfeeding being shown to reduce the incidence of T1D (Virtanen, 1991). However, findings from the TRIGR study are in disagreement with this. The authors found that that when comparing hydrolysed infant formula against cow's milk in infants at risk of developing T1D there was no difference in incidence after 7 years (Knip, 2014). However, the trial did not distinguish between the effects of breastfeeding versus consuming formula milk (as randomisation to either breastfeeding or formula feeding would pose ethical issues) and its impact on disease progression therefore remains unclear.

Recently there has been interest in the potential association between childhood obesity and the incidence of T1D, with the resulting 'accelerator' hypothesis being formed. This theory proposes that an increased demand for insulin overloads ß cells and that the subsequent weight gain and insulin resistance further propagates the disease and act as 'accelerants' (Vehik, 2011). This proposal has been investigated by various studies with mixed results. Some suggest that a raised BMI and insulin resistance in childhood is indeed associated with the development of T1D (Ljungkrantz, 2008; Kordonouri, 2005; Nokoff, 2012; Wilkin,

2006). Despite the research remains equivocal. For example Fourlanos (2008) and Raab (2013) both suggest that there is no association with insulin resistance and T1D and larger studies such as the BABYDIAB study concur that there is no link with either insulin resistance or BMI and islet autoimmunity (Winkler, 2013). This conflicting evidence suggests that the story is far from clear regarding the influence that early life growth may have upon the incidence of T1D.

Despite many environmental factors implicated in the decline of ß cell function occurring during early life, several may persist from childhood through to adulthood. One of perhaps the most prominent and frequently encountered is that of dietary intake; in particular the consumption of proteins. Specifically, the consumption of gluten may be an important factor. Gluten sensitivity has previously been shown to be a potentially important factor in the development of T1D, with various mechanistic hypotheses being proposed, usually centred around increased intestinal permeability or 'leaky gut', thus allowing peptides and even proteins to be absorbed into the circulation (de Kort, 2011). These infiltrating particles may then be presented as antigens which have been implicated in the immune response preceding T1D, a process which is further exacerbated by the habitual intake of gluten (Barbeau, 2007). This was demonstrated in the prospective cohort BABYDIAB study where Ziegler (2003) found babies at risk of T1D fed a gluten supplement were associated with a significant increase in islet autoantibody risk compared to controls, illustrating the impact gluten may have on those predisposed to the disease. Furthermore, those with T1D are at an increased risk of coeliac disease (also an autoimmune disorder) compared to the general population, with a meta-analysis by Elfström (2014) showing how 1 in 20 people with T1D are diagnosed with coeliac disease; strong enough evidence to make the case for routine screening.

Foods which are digested rapidly cause large glycaemic excursions which require a greater production of insulin, causing ß cell stress (Pickup, 2004). The varying effects carbohydrates have upon this process and their potential role in islet autoimmunity has been previously examined by other groups. Both Pundziute-Lycká (2004) and Dahlquist (1990) concluded that high intakes of carbohydrates (especially disaccharides and sucrose) increased diabetes risk and both suggest ß cell stress may be a catalyst for this response. Lamb (2008) investigated this

hypothesis in more detail and concluded that high glycaemic index (GI) foods in particular are associated with progression to T1D and a follow up study by the same author in 2015 investigating sugar intake as part of the DAISY study further corroborated this hypothesis. Specifically, the consumption of sugar sweetened beverages may be detrimental in those at the highest risk of developing the disease. This is reminiscent of the 'accelerator' hypothesis mentioned earlier and could potentially be a contributing factor for the development of T1D.

Vitamin D has also been identified as having a key role in the aetiology of various autoimmune diseases such as multiple sclerosis and arthritis (Cantorna, 2000). T1D is no exception. Many countries with higher incidence of T1D are frequently of a higher latitude north of the equator (see Figure 1.2) (Whiting, 2011). This pattern alludes to a 'north-south gradient hypothesis' where vitamin D status may not only be associated with these levels of incidence, but may actually be the cause (Karvonen, 2000; Atkinson, 2012). A meta-analysis by Feng (2015) further implicated vitamin D by demonstrating that those with T1D also had lower levels of serum 25 (OH) D concentrations than healthy controls. For the proposed 'north-south gradient' of T1D to be plausible the assumption has to be made that it is actually UV-B exposure which is modulating vitamin D levels; however, a cross-sectional study by Bierschenk (2009) illustrated that this was not the case and at a population level all study groups actually had suboptimal vitamin D regardless of equatorial position and recommended vitamin D supplementation. Although sounding like a sensible suggestion observational evidence remains undecided whether supplementation does or does not have a protective effect in the development of T1D (Mishra 2015; Stene, 2003).

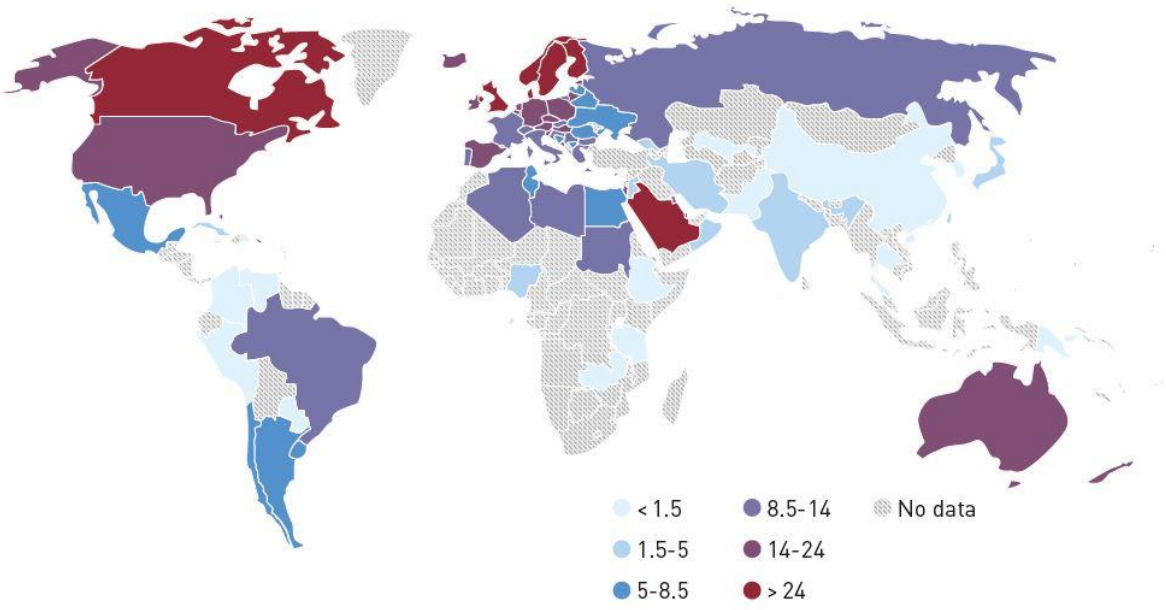


Figure 1.2 – Global incidence of T1D (IDF Atlas, 2015)

Although an exclusive cause of T1D is currently unknown there are various factors which may be implicated. Due to the stark contrasts in the geographical incidence of the disease and the large variations and disagreements in hypotheses it is likely that the cause may be multifactorial. It is clear that some populations are at a higher risk of developing T1D than others, making prediction easier but not definitive. With future research the elusive origins of T1D may hopefully be revealed in their entirety; however, in the meantime improving treatments to improve patients' lives remain of primary importance.

1.2 Therapies and treatments

Methods of achieving glycaemic control using insulin

Since insulin was first used to treat T1D it has remained a therapeutic cornerstone for the maintenance of glycaemic control. Just as there are a variety of insulin products for differing circumstances, there are a similarly diverse range of insulin administration methods; some may be more appropriate for the treatment of certain individuals than others. The most common method of insulin administration is subcutaneous injections, which traditionally consisted of drawing a desired quantity of insulin into a prepared syringe before injecting. During the 21st century

the advent of insulin pens have made the process more convenient, less painful and have been generally well accepted by patients (Pickup, 2004).

Conventional insulin therapy

Injection regimens using these devices vary and may consist of the patient taking 2 or 3 injections of pre-mixed insulin per day. This 'twice or thrice-daily' regimen is commonly referred to as 'conventional insulin therapy' and involves varied doses consisting of either a neutral protamine Hagedorn (NPH) or lente insulin which is given in the morning and with the evening meal and occasionally before lunch (see Figures 1.3 and 1.4). There are few studies comparing the two methods of conventional insulin therapy in terms of glycaemic control; however, an RCT by Razavi (2011) showed little different in the level of HbA_{1c} of patients using either twice or thrice daily injections, indicating that twice daily may be superior due to its simplicity and cost effectiveness. Furthermore, fewer injections may also be an advantage for those with needle phobias.

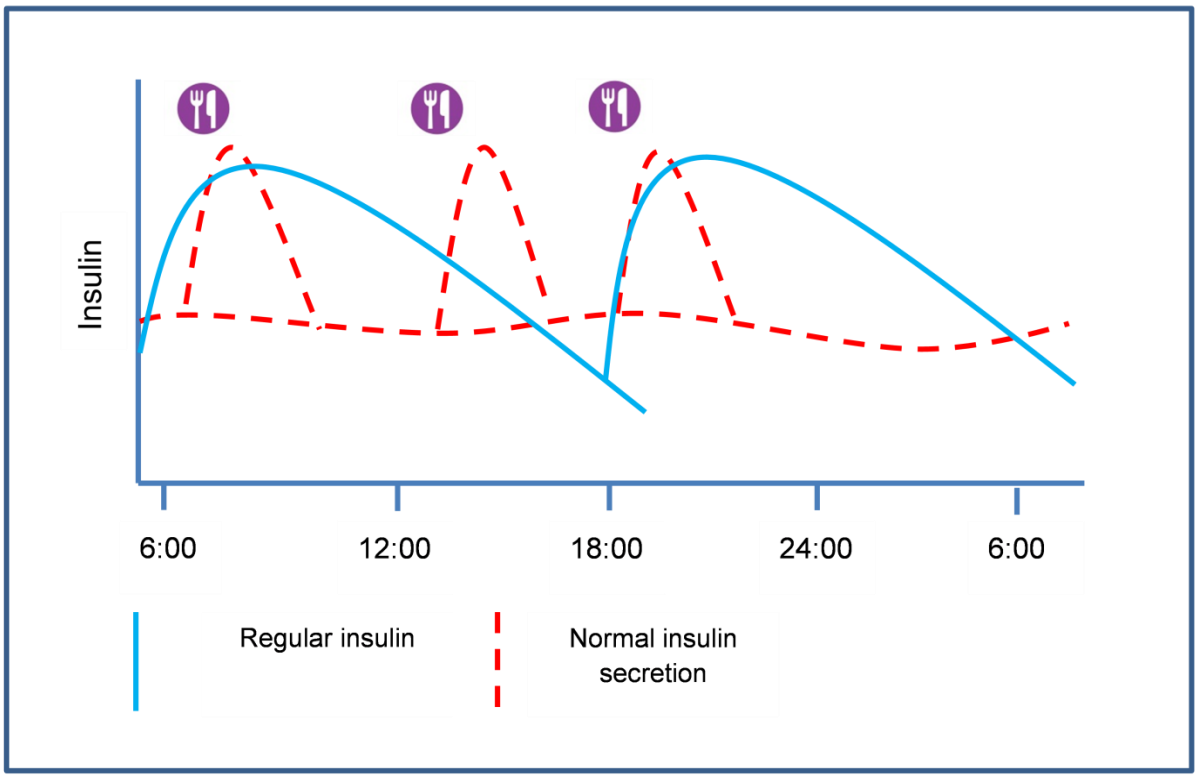


Figure 1.3 – Insulin action of twice daily conventional insulin therapy (Adapted from: Accu-Chek, 2016)

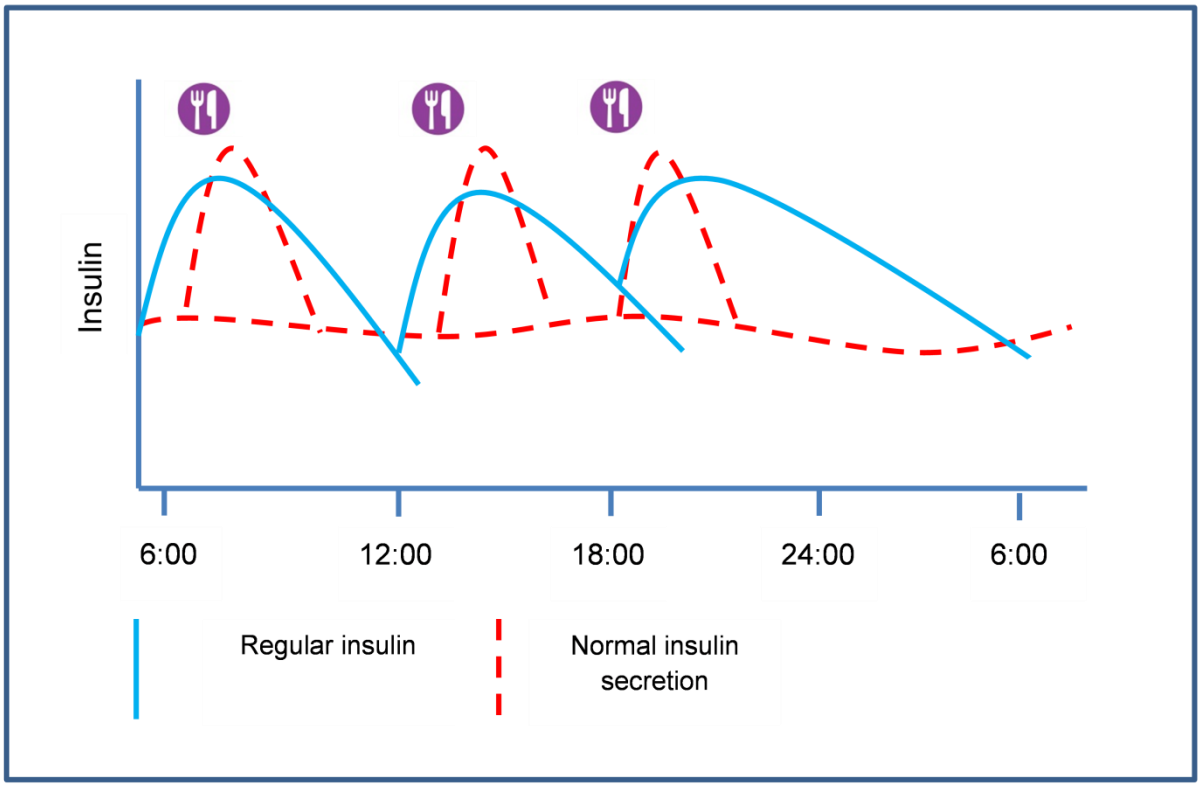


Figure 1.4 – Insulin action of thrice daily conventional insulin therapy (Adapted from: Accu-Chek, 2016)

Another typical injection strategy consists of basal (long-acting) and bolus (short-acting) injections to account for both glucose which is hepatically produced and that which is derived from the diet. This intensive 'basal-bolus' regimen is commonly known as 'multiple daily injections' (MDI) and mimics the pancreatic secretion of insulin more closely than conventional injections and has been shown in the literature to be superior at achieving glycaemic control whilst reducing the likelihood of hypoglycaemia (Kähler, 2014; Fullerton, 2014). As a result NICE now recommend that this MDI strategy is offered to all adults with T1D as opposed twice daily injections (NICE, 2015). An illustration outlining a typical daily schedule of MDI injections can be seen in Figure 1.5.

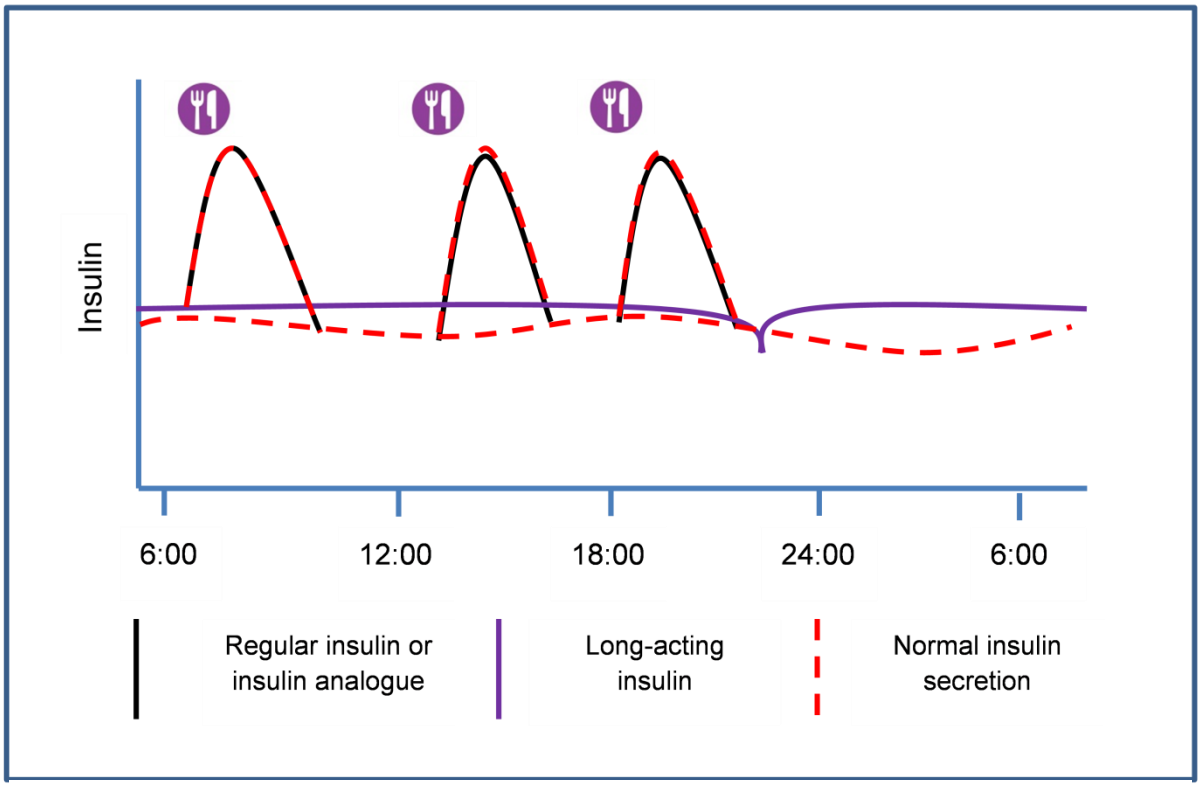


Figure 1.5 – Insulin action of multiple daily injections (Adapted from: Accu-Chek, 2016)

Continuous subcutaneous insulin infusion

If suitable glycaemic control cannot be achieved in an adult patient using MDI, the physician may recommend continuous subcutaneous insulin infusion therapy (CSII). To be considered for this intensive treatment NICE guidelines indicate adult patients and children over 12 must either be experiencing disabling hypoglycaemic episodes, or high HbA_{1c} levels (over 8.5% or above) on MDI therapy, even with a high level of clinical care (NICE, 2008).

The therapy itself consists of a small, electronic pump devise which injects a rapid-acting insulin analogue into the patient subcutaneously via a cannula attached to the skin. The pump is connected to the patient on a permanent basis, although the cannula must be changed every 3 days to avoid infection and the patient is permitted to remove the device for no longer than an hour (for example, whilst taking part in sporting activities etc.). Although there are various manufacturers of insulin pumps, all follow this basic premise and a diagram visualising this can be seen in Figure 1.6.

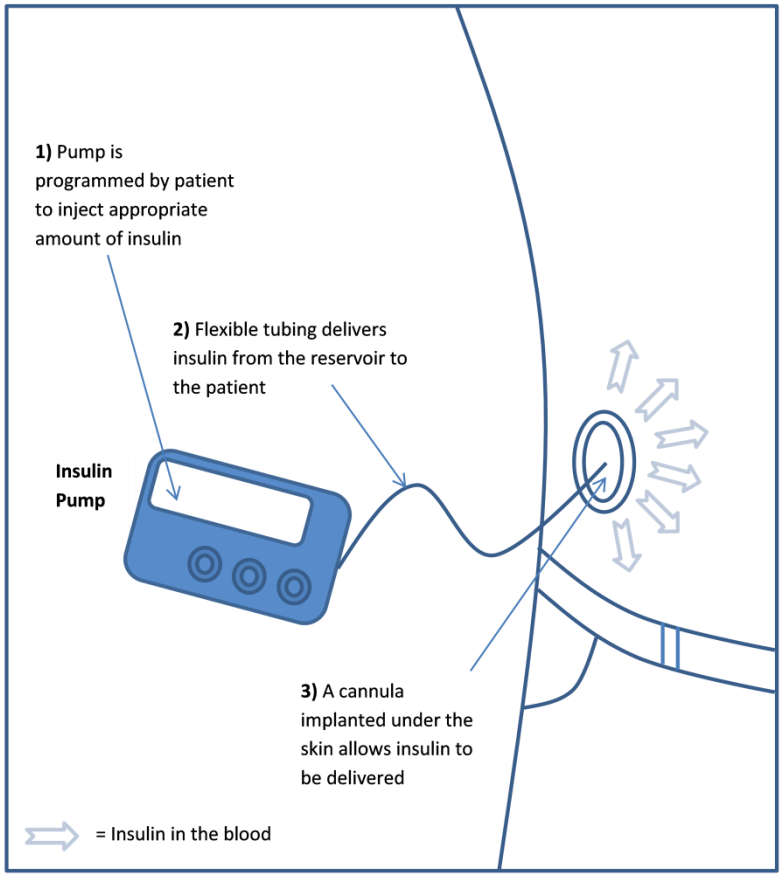


Figure 1.6 – Basic principle of CSII

Over the years insulin pumps have undergone many changes and become smaller in size, waterproof, more robust and significant advancements in the algorithms which control the insulin delivery process have been made which now allow for more complex basal and bolus injections (Skyler, 2010). Examples of these sophisticated algorithms are programmable basal rates which allow the patient to account for exercise or night time changes in glycaemia and split boluses such as those illustrated in Figure 1.7 which now allow mealtime doses to be injected over longer time periods, therefore meaning foods such as those high in fat which may take longer to digest can be easily accounted for (*Ibid*).

Figure 1.7 – Bolus options available with CSII (Adapted from: Healthline, 2016)

Before patients can take advantage of the features that CSII can offer they must be fully educated about how the device works. This is an important step as CSII therapy is very much unlike the injection therapies patients will often be used to. Patients will firstly be advised to take part in a DAFNE (or similar) carbohydrate counting programme to ensure an appropriate amount of insulin is injected per meal. Although current guidelines recommend all newly identified patients attend the course within 6-12 months of diagnosis it should be noted that many patients living with T1D may never have participated (NICE, 2015). It is well documented that the 5 day programme can improve glycaemic control and reduce hypoglycaemic events and whether the programme is delivered intensively over 5 consecutive days or spread over 5 weeks makes no difference to glycaemic outcomes (DAFNE Study Group, 2002; Elliott, 2014; Elliott, 2015).

After attendance at a carbohydrate counting course compulsory CSII structured education sessions developed in accordance with NICE guidelines should then be attended. These sessions should include information about how to use the pump, its limitations and very importantly, information about how to correctly determine the 'insulin to carbohydrate ratio' (ICR) and 'insulin sensitivity factor' (ISF). The importance of these factors is often underappreciated as small changes to these parameters may have large impacts upon glycaemic control (Morrison, 2013). The American Diabetes Association (ADA) suggest an estimated ICR of 1 unit of insulin per 10-15 g of carbohydrate; and an estimated ISF of 1:2.8 mmol/L for

adults; however, these can only be accurately checked when an appropriate basal rate has been set, therefore the temporary impact on glycaemic control which may occur during the commencement of the therapy should be fully explained to the patient during the education (ADA, 2003). Due to the multidisciplinary nature of CSII the sessions should ideally be developed by a specialist team involving consultant diabetologists, diabetes specialist nurses and dietitians (NICE, 2008). That said it is unfortunate that in the recent UK insulin pump audit only 40% of participating centres were found to actually provide or have access to CSII courses (White, 2013). Furthermore, in 72% of these centres courses were also shown to be delivered by representatives from pump manufacturers rather than clinical staff, although the audit did acknowledge that reliance on these trainers was decreasing (*Ibid*).

Due to this relatively steep learning curve a certain amount of discipline is required from patients and it is acknowledged that in addition to NICE criteria healthcare professionals may also subjectively select patients for the therapy who they believe to have certain psychological and personal attributes (Lawton, 2014). It is debatable whether using this applied clinical experience is a help or a hindrance, for example, on one hand patients with psychological disorders may be at an increased risk of manipulating their insulin dose, thus increasing their risk of diabetic ketoacidosis and therefore clinicians may initially be apprehensive (Fanik, 2014). Yet on the other hand, the recent RESPOSE trial found some staff had their assumptions challenged when they saw patients who they believed would struggle with the therapy actually have success (*Ibid*). The impact that these preconceptions have upon patients' access to the therapy is unknown, but would certainly make an interesting area for further research.

This issue of patient access to CSII spans further than the consulting room alone and in particular concerns about funding for the therapy have been previously raised (The Medical Technology Group, 2010). Due to the complex technology involved in the pumps, together with the expense of associated consumables, CSII is a costly therapeutic option. The average cost of a pump, assuming a 4 year lifespan, is £430 to £720 per annum with additional consumables totalling approximately £1800 to £2000 per year, producing an extra annual cost of £1700 compared to MDI (Cummins, 2010). Despite these expenses cost-effective

analysis reported the therapy as being favourable to MDI and a recent meta-analysis concluded that the higher direct costs are offset by reduced treatment costs associated with complications caused by poor glycaemic control and/or disabling hypoglycaemia (Cummins, 2010; Roze, 2015).

Unfortunately neither these benefits, nor guidance from NICE have prevented the so-called 'postcode lottery' of funding for CSII. Data by The Medical Technology Group (2010) illustrated significant inequalities in the provision of insulin pumps, with large disparities between regions within the UK with 13% of patients in Halton and St Helens receiving the therapy compared to 0.4% in Luton, totalling a nationwide average of only 3.7%. The insulin pump audit published 3 years later showed slight improvements with 6% of adult patients with T1D using the therapy (equating to 13,428 patients); however, this is still far below NICE targets of at least 12% (White, 2013).

When considering this low uptake of CSII, it is useful to remember that the audit also described how 80% of centres were constrained by fixed amounts of pump starts; however, this caused few problems with only 5% of centres experiencing commissioners decline applications for funding, affecting a total of 47 patients (*Ibid*). This therefore produces the conundrum of why the use of CSII is so rare, which might be answered in part because of a lack of available staff to deal with both the introduction of patients to the therapy and their subsequent management. The audit explored this and mentioned concerns about a shortfall in appropriate healthcare staff and that the professional time needed to manage a CSII service is often severely underfunded, with estimates suggesting 39% of consultant, 61% of diabetes specialist nurse and 60% of dietitian time is underfunded (White, 2013). These factors are likely to create barriers preventing patients access to CSII and may explain the 'selectiveness' healthcare professionals display when choosing suitable patients to commence the therapy. It is hoped that in time these issues may be appropriately dealt with to allow the therapy to be opened up to a greater number of patients.

Much has been discussed in this chapter regarding the hardware and software attributes of insulin pumps and the typical introduction that patients may receive when commencing the therapy; however, little has been mentioned in terms of the

benefits it may offer. CSII has been shown to have advantages for patients with T1D when compared with alternative intensive insulin treatments. These advantages include better control of blood glucose, indicated by reductions in HbA_{1c} and a decrease in hypoglycaemic episodes (NICE, 2008). A review of the literature also illustrates some reduction in insulin requirements and a decrease in high early morning blood glucose levels; often associated with growth hormone and referred to as the dawn phenomenon (Cummins, 2010).

The use of CSII may also allow patients to potentially break free from relatively inflexible mealtimes and carbohydrate requirements imposed by the fixed insulin regimes of multiple daily injections (MDI) (NICE, 2008). Previous research indicates patients with T1D frequently gravitate towards the consumption of additional carbohydrate rich foods during hypoglycaemia; a trend which suggests hypoglycaemic episode reductions may lead to a potential decrease in carbohydrate consumption (Strachan, 2004). Conversely, other studies provide evidence illustrating how when an opportunity is presented for patients to liberalise the diet, for example when participating in intensive insulin treatments such as CSII where the incidence of hypoglycaemia is reduced, increased carbohydrate consumption frequently occurs (Mühlhauser, 2009). Despite this conflicting evidence, available literature focussing on eating behaviours, particularly relating to patients using CSII therapy, is sparse and often dated. Therefore, due to the dearth of data this area warrants further research, hence the rationale for the present study. The current literature surrounding this area will be discussed in more detail in the Literature Review chapter (see page 30) and within the appropriate experimental chapter (see page 95).

Although the theoretical opportunity for patients to relax their diet is a potential benefit of CSII, there are additional quality of life implications associated with the therapy. Examples are greater freedom, decreased physical complaints and a reduced sense of physical restriction (Ritholz, 2007). However limited literature exists to convincingly support this premise and specific qualitative research into adult CSII users' quality of life is even less well documented. The available studies tend to observe small numbers of people over short periods of time and others often utilise problematic methods (Todres, 2010). More rigorous and extensive research would be beneficial to not only help increase the existing knowledge

base, but also to improve the quality of research in this area and allow a better understanding of how insulin pumps may affect the quality of life of patients. Again, the existing evidence surrounding this will be critically appraised in the following literature review chapter (see page 30) and investigations made by the author will be described in the appropriate experimental chapter (see page 173).

This underrepresentation in the literature is not exclusive to the previously described issues. Research investigating the cardiometabolic (CM) risks of this population is also lacking. This term is used to describe a loosely defined 'cluster' of risk factors associated with cardiovascular disease (CVD) and Type 2 diabetes, such as blood pressure, BMI and glycaemic control, but it is the dearth of literature investigating lipids and lipoproteins in those with T1D using CSII which is perhaps most striking. T1D is associated with several lipid abnormalities, with quantitative disorders often present in patients with poor glycaemic control. However, in patients with good control, lipid profiles are regularly comparable to those without diabetes, yet even in this well controlled population rates of CVD remain the principle cause of mortality (Vergès, 2009). Interestingly, despite this apparent normality, several potentially atherogenic, qualitative abnormalities may reveal themselves. These measures of lipid and lipoprotein quality may be important markers above and beyond standard clinical measures used to determine CM risk in those with T1D and further investigation focussing on this at risk population is therefore warranted. In a similar manner to the eating behaviours and quality of life of patients using CSII, the literature surrounding their CM risks will also be discussed in the following literature review (see page 30) and the appropriate experimental chapter (see page 134).

In the light of these problems, the objectives of this study are therefore to investigate the eating behaviours and cardiometabolic risks of patients with T1D upon the commencement of CSII therapy and compared to those using MDI. Furthermore, the study design will also incorporate a qualitative investigation into patients lived experiences and quality of life with a view to generating hypotheses about the impact of CSII.

1.3 Organisation of the Thesis

As previously mentioned, this introduction is designed to offer the reader a broad overview of T1D and CSII therapy and the overarching problems which are tackled herein. A review of the literature, described in **chapter 2**, makes a case for the research questions in more detail and aims to give the reader an understanding of the 'state of the art' regarding these issues. A broad overview of the methods used, in particular the chosen methodology, is described in **chapter 3**. **Chapter 4** illustrates in detail the recruitment strategy and the problems which were encountered. The author feels it is important to include this as it helps to explain any irregularities which may be encountered in later chapters. An initial clinical audit which was carried out by the author prior to commencing the research can be found in **chapter 5**. The research carried out to investigate the eating behaviours, cardiometabolic risks and quality of life is presented in **chapters 6, 7 and 8**, where detailed descriptions of the research questions, the methods used, the findings and accompanying discussions can be found. **Chapter 9** outlines a series of case studies based upon a small number of patients and **Chapter 10** offers a conclusion to the thesis by synthesising the findings, outlining any general limitations and offering recommendations for future research.

1.4 Aim and Objectives

Aim:

To investigate the eating behaviours, quality of life and cardiometabolic risks of adult patients with T1D using CSII.

Objectives:

- To determine dietary intake of patients using CSII, both over time and compared to their counterparts using MDI.
- To explore the quality of life of patients using CSII, both over time and compared to those using MDI.
- To assess selected cardiometabolic risk markers of patients using CSII, both over time and compared to others using MDI.

Chapter 2

Literature review

2 - Literature Review

2.1 Introduction

Due to the continuous manner in which rapid acting insulin is administered, patients using CSII therapy have the potential to liberalise their dietary practices. This is possible as basal programmes can be quickly reduced or suspended and bolus injections can easily be adjusted in accordance with a multitude of programmes suitable for different food items and volumes. The impact dietary choices may have upon CSII (or vice-versa) is an important area which has been overlooked in the literature and is surprising given the potential influence on diabetes and wider health.

2.2 Eating Behaviours

The earliest evidence focussing specifically on the role of diet in CSII therapy is a study by Chantelau *et al.* (1982). This study investigated 10 patients with T1D who were educated in the use of CSII and who had been initiated with the therapy for 4 - 5 weeks. After this time 6 of the patients were asked to adhere to a 'conventional' diabetes diet (as recommended at the time by the ADA), consisting of 5 – 6 meals per day containing mainly unrefined CHO (50 – 60%), few saturated fats and an adequate amount of energy for the individual (Nuttall, 1979). The diet was adhered to for 2 - 3 days whilst recording CHO intake, blood glucose measurements and insulin intake. After this time patients were allowed to either remain on the conventional diet or liberalise their food intake, allowing the free choice of meal timing and number and the intake of CHO (although rapidly absorbed CHO was to be avoided in both diets). All patients chose to consume a liberalised diet. Patients were then visited at home or work where food intake was assessed for CHO consumption and blood glucose and insulin dose measurements were recorded 15 minutes before and 60 minutes after every meal. Serum lipids and body weight were also recorded and all measurements were repeated in all patients 4 - 5 months after initiating the therapy. The results showed that patients enjoying a liberalised diet consumed 3 - 4 meals per day as opposed to 5 - 6 when adhering to a conventional diet and CHO intake was reduced (from 183 ± 60 g/day to 149 ±

50 g/day respectively). Moreover, the resulting relaxed diet was largely composed of fat (51 ± 5% fat, 34 ± 5% CHO & 15 ± 2% protein). A larger variation in meal times was also observed in those using the liberalised diet; however, this did not result in any changes to glycaemic control, with the HbA_{1c} of patients on both diets remaining similar. In fact patients using both diets enjoyed an improvement in blood glucose levels upon the commencement of CSII which is in agreement with more recent evidence affirming that these changes are indeed a hallmark of the therapy (Pickup, 2002). Furthermore, dietary liberalisation also appeared to result in little change to serum lipids and body weight despite the increased consumption of dietary fats, leading the authors to hypothesise that the stabilisation of blood glucose levels resulted in a subsequent normalisation of blood lipids; a finding also described elsewhere (Vergès, 2009). In summary the findings suggest that the liberalisation of diet in those with T1D whilst using CSII does not result in any metabolic changes despite failing to meet best practice guidelines.

It should be noted that whilst shedding light for the first time on the impact of dietary liberalisation during CSII therapy the study only observed the participants for a relatively short duration (4 – 5 months). To resolve this issue the same group performed an additional study comprising of 2 parts (Chantelau, 1983). Part 1 investigated 10 patients using conventional insulin therapy (CIT) who were intending to commence CSII. These patients were asked to record their food intake for 3 days whilst using CIT. Then after using CSII for 4 weeks the patients were asked to record their diet again for 7 days. To determine the impact of dietary liberalisation over time part 2 required 15 patients already using CSII to record their food intake for 7 days after engaging with the therapy for 14 months. Both groups were educated about dietary liberalisation via a 5 day course prior to commencing CSII in a similar manner to patients who participated in the previous study. Standard clinical measurements (such as HbA_{1c} and lipid profile etc.) were collected from all participants at the same time dietary intakes were recorded. The results highlighted various similarities with the earlier study by Chantelau *et al*, with patients adopting a liberalised diet whilst using CSII and again enjoying improved HbA_{1c} (from 9.5% to 8.3% in group 1 and 7.9% in group 2) and no detrimental change in blood lipids or body weight. Furthermore, after 4 weeks patients were shown to deviate from recommendations and consume less CHO

(43% to 38%) and more fat (36% to 42%) (Nuttall, 1979). In addition to these short-term similarities the study also illustrated that after 14 months very few changes took place, thus confirming the study hypothesis that long-term liberalisation of the diet whilst using CSII would not result in any metabolic disturbances.

An additional study was also performed by Capper *et al.* (1985), focusing on the dietary practices of patients using CSII. This study was retrospective in nature and baseline HbA_{1c} data was firstly collected from 15 patients prior to commencing the therapy. After gaining experience with the device patients were then asked to complete a questionnaire designed to determine dietary intake and take part in a short interview with a nutritionist. The length of time between commencing the therapy and completing the questionnaire and interview varied between patients (mean 16.2 ± 2.3 months). The results from this study were very similar to the previous studies by Chantelau *et al*.; HbA_{1c} decreased after commencing the therapy and mealtimes appeared to be more varied in patients using CSII and patients suggested that this variability was easier to manage using the pump. Furthermore, upon commencing CSII CHO consumption was below ADA guidelines (38% of total energy intake as opposed to recommendations of 50%) and dietary fat intake was above (42% of total energy intake as opposed to recommendations of 30%) (Nuttall, 1979). Despite similarities to Chantelau *et al*. Capper's findings offered some intriguing differences. Although mealtimes were varied yet well managed, meals were actually larger and snacking was more prevalent which resulted in an average weight gain of 7.2 lb. Patients also compensated for food intake changes by raising their insulin bolus frequency to 8.8 times per month as opposed to 2.8 times on conventional injections and it was also apparent that patients tended to estimate their insulin dose more whilst using CSII rather than checking postprandial glucose levels. This subsequent relaxation of meal structure and insulin administration may be indicative of motivational benefits prevailing from the potential for dietary relaxation inferred by CSII. Indeed, an appreciation by patients for dietary liberalisation has been shown in the literature and if this can be achieved with no metabolic disturbances (as is suggested by the studies described above) illustrates an additional positive benefit associated with the therapy (Nicolucci, 2008).

Despite these studies providing valuable information there are various limitations. Primarily, the promoted dietary liberalisation in the studies mentioned above was not specifically a 'free diet' due to the prohibited intake of refined CHO and suggestions to adhere to ADA guidelines. It is therefore unlikely that food intake was truly selected at will. Furthermore, the failure to meet these guidelines by those consuming a liberalised diet was also met with concern; however, little thought was given to the wider perspective. For example, although total fat intake increased after the commencement of CSII in all studies leading to speculation about an increased CVD risk, there was a failure to consider the types of fat consumed. It was also unacknowledged that the reduced CHO intake observed may result in a decreased requirement for insulin which has been described in more recent literature which may in turn be of physiological benefit (Pickup, 2002; Wang, 2013). Moreover, it should also be noted that the studies all advised patients to restrict simple sugars in line with recommendations of the time and only reported the total CHO intake; however, distinctions between the types of CHO and their influence upon blood sugars is important (Nuttall, 1979).

It is with this specific point in mind that Venhaus (1988) performed a study to determine the impact of CHO type (refined vs unrefined) in patients using CSII. This randomised cross-over study investigated 10 patients who were well acquainted with CSII therapy and who were asked to adhere to either a refined or an unrefined CHO diet, each for a 6 week period in a random order. Those consuming an unrefined diet had a lower energy intake (2372 ± 669 kcal/day vs 2757 ± 654 kcal/day) and also consumed a lower quantity of CHO (211 ± 62 g/day vs 249 ± 59 d/day respectively). Despite this the patients on the unrefined diet consumed a considerably larger amount of dietary fibre (35.3 ± 13.0 g/day vs 17.9 ± 5.1 g/day). Although there were differences in dietary composition there were few metabolic changes. Blood glucose levels in those consuming unrefined CHO remained similar to their counterparts (7.3 ± 0.8 mmol/L vs 7.2 ± 0.5 mmol/L) and there were no changes in blood pressure, lipids and lipoproteins and HbA_{1c}. Patients consuming a diet of refined CHO experienced a slight weight gain (69.1 ± 11.0 kg to 70.2 ± 12.3 kg), but this did not reach statistical significance and there were no changes in insulin dose. These were somewhat surprising findings, particularly with regard to glycaemic control, as more recent evidence suggests

that the type of CHO does indeed modulate glycaemic response in T1D (Giacco, 2000). Despite largely neutral findings it is important to note that previous studies reporting the influence of fibre on glycaemic control generally administered unpractically large doses typically exceeding dietary recommendations and it is therefore unlikely that doses below the RNI, such as those used by Venhaus (1988), would modulate glycaemia (Giacco, 2000). Furthermore, Venhaus also suggests that the smaller total CHO amount consumed by the unrefined diet group may be reflective of a decreased intake of low glycaemic index (GI) and low glycaemic load foodstuffs which are hypothesised to have influenced results. This may be a more probable explanation for the similar glycaemic control observed between groups as a Cochrane meta-analysis concluded a low GI diet may result in HbA_{1c} decreases of up to 0.5% (Thomas, 2009). Therefore if patients decrease their intake of low GI foods (such as those approved for consumption in the unrefined group) then it may be reasonable to expect predicted improvements in glycaemic control to diminish.

Collectively these four studies provide an insight into the potential impact of dietary liberalisation at a time when CSII was a novel therapy for the treatment of T1D. Since their publication circa thirty years ago CSII has become a commonly used tool in clinical practice and the theory and practice regarding its implementation and that of diabetes in general has evolved considerably. For example, patients are now routinely informed about the importance of regular blood glucose monitoring regardless of which insulin therapy they may be using and are given the resources to do so in an effective manner. This was not the case in the study by Capper *et al*. (1985) where patients using conventional injections were not practicing the technique at all and so it is perhaps unsurprising that the CSII group enjoyed reductions in HbA_{1c}. Moreover, even though the other studies educated patients about how to self-test blood glucose it should be remembered that the equipment to carry out the tests (likely by using test strips) may have been somewhat rudimentary compared to today's standards. This again casts potential doubt on the findings and whether they could be replicated with patients using the blood monitoring equipment of today. Also, it should be noted that the insulin pumps themselves have advanced greatly, as has insulin, and again it is difficult to speculate if the dated studies described above could be replicated using the

modern pumps and insulin analogues which are now commonplace. Moreover, the studies also compare patients using CSII vs those using CIT. This was appropriate at the time of publication; however, multiple daily injections (MDI) are now recommended as a standard insulin therapy for the treatment of T1D and offer superior glycaemic control and so the therapy comparisons outlined in the previous studies may no longer be appropriate (NICE, 2015). Furthermore, it is also useful to remember that the education sessions preceding all of these studies advised patients based upon nutrition recommendations outlined at the time by the ADA. Like other areas of diabetes nutrition guidelines have also changed over the past thirty years (as previously discussed). This therefore poses the problem of patients in these studies attempting to attain dietary ideals of which some are now contentious (as discussed in more detail in chapter 6 (see page 95)). These limitations combined with those described earlier present strong doubts about how these studies represent the current diabetes topography. Furthermore, since their publication in the 1980s there has been little literature of note regarding dietary liberalisation in patients using CSII and given the limitations of existing literature outlined herein and the strong influence diet may infer upon the management of T1D presents an important gap in the research which requires filling.

2.3 Cardiometabolic Risks

In addition to a dearth of data concerning eating behaviours, the impact CSII may have upon cardiovascular risk markers is also not well understood, which is surprising given the attention bestowed upon T1D in a broader context and the ability of insulin pumps to successfully alter glycaemic control. Despite this there are a small number of studies investigating the use of CSII in patients with T2D, with Li (2004) reporting significant improvements in all traditional lipid parameters (low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), plasma or serum triglycerides and total cholesterol) after 2 weeks of CSII therapy. Also, Noh (2008) described similar effects over a longer period (30 weeks) in patients with poorly controlled T2D using CSII, as well as a decreased proportion of patients with dyslipidaemia at the end of the study (33.3% to 13.3%). Furthermore, a study by Megson (2015) investigated oxidative stress in patients

with T2D who were engaging with CSII and found oxidation of LDL lipoproteins was reduced by 10.5% after using the therapy for 16 weeks.

Despite these promising findings the evidence in those with T1D is sparse, even though CSII is both recommended for use and most often adopted by those with this form of the disease. That said, previous work by Krönert (1987) has shown that treatment with CSII therapy improved autonomic nerve dysfunction which in turn has the potential to positively impact upon cardiac function; however, this study only investigated 9 participants over a 4 week period. To improve on this similar research by Jakobsen (1988) utilised 24 patients undergoing CSII therapy and found that over 2 years improvements in autonomic nerve function were sustained. Thuesen (1986) also emphasised improvements in cardiac function in 24 patients with T1D using CSII, which translated into an increased capacity for exercise, possibly as a result of reduced cardiovascular resting state demands caused by improved glycaemic control. There have also been studies focussing directly on lipids, all showing either a normalisation or decrease of LDL, triglycerides and total cholesterol and an increase in HDL-C; in particular the HDL_2 subfraction (Falko, 1982; Helve, 1987; Pietri, 1980; Bagdade, 1991). Although this modicum of evidence highlights generally positive cardiovascular benefits associated with CSII it should be recognised that they all are small in scale and dated. Furthermore, all compare CSII vs CIT and this is no longer a relevant comparison as CIT is no longer the standard treatment of T1D.

Although it is clear that these studies suffer from a number of limitations, primarily due to their age, a small number of more modern studies exist regarding the impact CSII may have upon specific markers of CVD. Work by Tołwińska (2013) illustrated how in a group of 32 children with T1D the use of CSII resulted in a decrease in intima media thickness and an increase in flow-mediated dilation over 6 weeks. Interestingly, a similar but larger study by Rosenlund (2014) involving 601 adult patients with T1D (58 treated with CSII and 5543 treated with MDI) showed significantly lower arterial stiffness, which is again suggestive of potential benefits to the arterial wall associated with the therapy. Controversially though, these cardiovascular benefits inferred by CSII appeared to disappear. Furthermore, a study by Cetinkalp (2015) found that when comparing 25 adult patients with well-controlled T1D using either CSII or MDI against a group of 13

controls there was no difference in a host of markers associated with atherosclerosis, including oxidised LDL, C-reactive protein, homocysteine and fibrinogen. Despite these neutral findings, the study did reveal the CSII group to have significantly higher levels of HDL-C, which in turn was negatively correlated with C-reactive protein, therefore highlighting a potential degree of atheroprotection. However, caution should be taken when evaluating these results due to the cross-sectional study design and small sample size.

Despite offering valuable insights these small scale modern studies have been largely eclipsed by perhaps the most noteworthy research to date regarding the implications of CSII on CVD risk in those with T1D. This particular study by Steineck (2014) retrospectively observed 18,168 patients with T1D (2441 who were using CSII and 15,727 who were using MDI) from the Swedish National Diabetes Register between 2005 and 2012. The authors found that when using MDI as the reference group patients using CSII were at a significantly lower risk of fatal/non-fatal coronary heart disease, fatal cardiovascular disease and all-cause mortality (hazard ratios: 1.0 vs 0.55; 1.0 vs 0.58 and 1.0 vs 0.73 respectively). Despite this large scale study, which is notable in its singularity, showing favourable associations between the use of CSII and CVD risk, causation cannot be implied. The authors acknowledge this and although attempting to speculate on potential driving mechanisms behind these positive findings they make clear that further research is needed before CSII can be promoted as an effective tool for the prevention of CVD and that the underlying processes need elucidating.

Although evidence, albeit rather sparsely, exists regarding the cardiovascular scenario encountered by those using CSII, it is remarkable that there is a dearth of modern data focussing on the impact CSII may have upon plasma lipids/lipoproteins directly given their important role in CVD. Only one study of this nature appears to exist by Derosa (2009). This was longitudinal in nature and focused on 32 patients with both T1D and T2D using either CSII or MDI over a 12 month period. The study found that in those using MDI there was no change in LDL and HDL but increases in both total cholesterol and triglycerides; a trend which others suggest may also represent an increase in very low density lipoprotein cholesterol (VLDL-C) and potential shift from larger to smaller LDL particles (Krauss, 2010). The CSII group; however, displayed significant

decreases in total cholesterol and LDL after 9 months of engaging with the therapy as well as significant decreases in triglycerides and increases in HDL after 12 months, possibly as a result of steadily managed insulin administration.

Collectively these studies make up a small body of work within which many gaps exist. Particularly intriguing is the lack of research focussing on lipid abnormalities in patients who are using CSII, given that that those with well controlled T1D do not appear to be immune from changes in lipid quality, such as a predominance of small, dense LDL particles, despite improvements in lipid quantity. It could therefore be presupposed that if CSII improves glycaemic control and lipid levels improve or plateau then patients may still remain at an increased risk of CVD. Furthermore, these risks may remain undiscovered and therefore not communicated to the patient as they fall 'below the radar' of standard lipid panel tests used by physicians. This presents an interesting area for further research which needs to be probed.

2.4 Quality of Life

Although biological measures provide useful information regarding the effectiveness of treatments or the risk of complications they offer little insight into patients' experiences of living with the condition. Although patient quality of life has been previously researched in those with T1D, remarkably few detailed understandings of the lived experience have emerged. Despite this, studies conducted over the past decade, the majority of which being quantitative in nature, have had reasonable success in highlighting generalised predictors of poor quality of life. For example, complications associated with the disease have been correlated with reduced quality of life outcomes (Coffey, 2002). Also, low levels of social support to deal with these issues, combined with the emotional burden of living with T1D have been shown by Joensen (2015) to be associated with reduced quality of life in a cross-sectional survey of 2419 Danish patients. Furthermore, work by Solli (2010) indicated that in 1000 adult patients in Norway the fear of hypoglycaemic episodes remains a strong determinant of anxiety and depression. This has in turn has been shown to predispose patients to increased risks of ischemic heart disease, stroke and neuropathy, which no doubt further perpetuate reductions in quality of life (*Ibid*). Conversely, the provision of

structured education and self-management training has been shown to significantly improve quality of life outcomes, as have lifestyle factors such as participating in physical activity, abstaining from smoking and consuming a healthy diet (Cooke, 2015; Cochran, 2008; Imayama, 2011).

Unfortunately the survey-based methods used to measure these determinants serve only to quantify and tell very little of the patient perspective, which is likely to be the reason for the dearth of evidence pertaining to patients actual thoughts and feelings. Despite this, a limited number of qualitative studies do exist regarding patients with T1D and span a variety of quality of life related areas, thus offering richer insights than their quantitative counterparts. An example is work by Browne (2014) which investigated 27 patients with T1D residing in Australia and found stigma from others to be a catalyst for reduced life quality, along with being frequently compared to those with T2D by an uneducated general public. A further qualitative study by Balfe (2007) echoed quantitative research mentioned earlier showing associations between lifestyle choices and quality of life; however, this study does so in a more intimate and subtle manner than metrics can achieve. This is illustrated when patients explain how participating in sports and eating healthily is not a conscious effort to improve immediate quality of life, but rather an attempt to minimise the risks of future complications. However, the process of exercise often comes at a risk of hypoglycaemia and is often seen by patients as '*not worth it*'. These brief glimpses into patients' worlds are also seen again in a study by Rankin (2014) which investigated the effectiveness of diabetes education groups. The link between these groups and improved glycaemic control have already been previously mentioned in the introduction chapter (see page 8); however, this qualitative, longitudinal work revealed how patients who attended a DAFNE training course also reported how skills developed on the course prompted them to obtain further knowledge and social support. These nuanced understandings have culminated in arguably the most compelling and robust piece of work in this area. This is a metasynthesis by Vanstone (2015) which consolidated 31 qualitative studies regarding glycaemic variability. The authors concluded that glycaemic variation, whether it is hypo or hyperglycaemia, was responsible for great declines in patients' physical, social, emotional and practical

quality of life; primarily resulting from substantial psychological stress thus illustrating the true burden of poorly controlled diabetes.

These quantitative and qualitative studies, although offering useful insights into the risk factors which may influence quality of life in those with T1D and offering unique, humanistic glimpses into patients' lived experiences with the disease, typically do not differentiate between treatment types. Furthermore, those that exist which do discriminate between treatment principally focus on children or adolescents (presumably due to the high prevalence of T1D in this population and the known biological, emotional, psychological and social difficulties of transitioning through these life periods) (Bridgett, 2015). As such little attention is given to adult patients, which is surprising when considering that they typically form the largest category of CSII users and therefore research focussing on this specific population would be welcomed. As this forms the rationale for the present study this review will focus on literature concerning adults where possible; however, to properly evaluate the literature it would be unreasonable to totally discount those that do not.

In a similar manner to the broader spectrum of research concerning T1D, it is quantitative measures which have been largely used to determine quality of life in those using CSII. In particular, various studies have revealed that the improvements in glycaemic control enjoyed by those using CSII are often accompanied by increased quality of life, with work by Bayrakdar (2014) showing this in adolescents. These correlations were further demonstrated in adult populations by Franciosi (2010) and Hoogma (2006), who conducted large-scale studies investigating CSII patients over 43 sites in Italy and 11 European centres respectively. Other large-scale studies, such as that by Nicolucci (2008), also suggest that the flexible nature of CSII may also improve prognosis by enabling patients to feel less restricted in terms of their lifestyle choices. Despite these positive findings, they are confounded by research which has found little difference between CSII and MDI treatments and the development of quality of life issues. For example, a cross-sectional study by Birkebaek (2014) found that despite CSII showing improvements in quality of life there was no difference between CSII and MDI after using either therapy for a year or longer. Admittedly, this study only investigated an adolescent population and was cross-sectional in nature; however,

similar results were again revealed by a long-term study by van Dijk *et al.* (2014). After a follow-up period of 15 years the research group also found that there were no differences in health related quality of life between patients using either CSII or MDI. In an attempt to distinguish between this conflicting evidence Barnard (2007) performed a systematic review. This incorporated 17 studies (including 5 RCTs) and again found that much of the evidence was indeed conflicting. Additionally, many of the study designs were found to be flawed with poor methodologies that inconsistently assessed quality of life and which are likely to be responsible for the lack of reported benefits. The authors of the review therefore concluded that based upon the available evidence it is difficult to determine the superiority of CSII over MDI in terms of quality of life.

In addition to this quantitative research a series of qualitative studies have also been performed; however, these are small in number, with a proportion of these actually assessing the impact of CSII on patients' lives from the perspective of the Healthcare Professional. An example of this is a study by Lawton (2016) in which Healthcare Professionals mentioned during interviews how they felt the therapy improved the quality of patients' lives and that it is ideal for those '*with really unpredictable lifestyles where things are changing at the drop of a hat*' and active individuals such as '*sporty patients, long distance cyclists, hill climbers….*'. These comments were reiterated in a study by Shulman (2016) who found that Healthcare Professionals believed that the benefits of these improved lifestyle choices may also apply to children; which may then in turn transpire to increased levels of independence.

In addition to evaluating quality of life benefits from a Healthcare Professional perspective there is also a small body of qualitative evidence investigating this from the point of view of parents whose children are using the therapy as well as family members and significant others. Work by Barnard (2016) found that various issues were expressed, mainly related to sleep disturbances for both the patients and those around them by the noise of the pump alarms, as well as a fear of hypoglycaemia which remained from previous incidences. However, despite these issues the overall consensus was CSII was generally viewed in high regard. Positive views were again expressed in work by Rankin (2015) and Alsaleh (2014) who both found that when interviewing the parents of child patients it was often

cited that an improved ability to manage physical activity was an advantage which could lead to improved lifestyle choices and how despite the pump not being a panacea, the medical benefits of the device act as a reassurance for the parent, thus demonstrating wider quality of life implications aside from those which benefit the patient alone.

Although these studies highlight interesting aspects pertaining to quality of life from the point of view of others there are only a handful, to the author's knowledge, which relate directly to patients' experiences. An example of this is a study by Low (2005), which although focussing on children and adolescents only, again reported issues with disturbed sleep due to alarms as well as the physical size of the device causing minor body image issues. However, despite these concerns the therapy was largely viewed favourably and that the positive aspects of the treatment outweighed the negative. Positive findings were also mentioned in a small study by Todres (2010) which investigated the lived experiences of 4 adult patients switching to CSII from MDI. Additional benefits compared to MDI with relation to quality of life were found which stemmed initially from the clinical benefits inferred by the therapy, but the ultimate impact on patients' lifestyle was above and beyond. The final qualitative study focussing on CSII which is known to the author is by Barnard (2007). This larger study interviewed 80 patients and again found that the overwhelming majority reported benefits associated with the therapy, that it improved quality of life and that they were using the therapy by choice. Despite these positive findings it is interesting to point out that over half the interviewees also reported negative findings, largely regarding the device itself, with issues ranging from blocked cannulas to the physical size of the pump. However, before forming a judgement of this it should be noted the interviewers used in this study were briefly trained call centre staff from insulin pump manufacturers and the interviews were carried out when patients phoned the company to reorder consumables. The potential for bias here is clear and serve to illustrate the methodological issues which may confound findings.

The small amount of existing qualitative studies which focus both on patients' lived experiences with CSII and how the therapy has impacted upon their quality of life illustrate an area of research which is urgently in need of further exploration. Furthermore, the conflicting existing research in this area needs resolving and

together with the high rates of psychological disorders related to diabetes further perpetuate requirements for additional research investigating the patient experience.

Chapter 3

General Methods

3 - General Methods

3.1 Introduction

This chapter will firstly focus on the overall framework of the study, primarily involving the methodological paradigm. Also, the theoretical and pragmatic notions underpinning the chosen individual methods will be discussed and it is hoped that by navigating through this in detail will enlighten and clarify the process from commencement to conclusion. Furthermore, the reader will be guided through the study design and process with not only justification in mind, but also transparency with a view to ensuring reproducibility. Detailed methods pertaining to specific techniques will be outlined in the appropriate experimental chapter.

3.2 Methodological Considerations

Although a kaleidoscope of research methods exist, it is imperative the most appropriate overall methodology is chosen to address the specific research questions and ensure the successful completion of study objectives. As the research aims of the study described herein were intended to inform rather than test an existing hypothesis, the study was carried out following an inductive approach, with a view to producing new knowledge and theories about patients using CSII to subsequently inform clinical practice. Despite the inductive nature of the study the research team decided that it would have been inappropriate to adopt either a fully quantitative or qualitative stance. Although quantitative findings are useful for the objective determination of variables, such as physiological markers of risk which can then be generalised to a population, they reveal nothing of the patient experience (Flick, 2015). On the other hand, purely qualitative research, although offering insight into the thoughts and feelings of patients, above and beyond that which can be inferred from quantitative methods alone, cannot measure associations or determine causality (Ibid). Other research projects may find one or the other acceptable to address specific research aims; however, the lines between approaches may sometimes become blurred and after consideration it was decided that a multiple methods approach would be more suitable.

Multiple methods refer to the combination of at least one quantitative and one qualitative approach within the same study and have become popular over recent years; leading to what Tashakkori and Teddlie (2003) refer to as a 'third methodological movement'. This act of combining methods has been justified as a way of extending beyond constraints and introducing new dimensions which can then be connected to offer a better understanding above and beyond that which would come from the use of a single method (Somekh, 2011). Some of the specific benefits of this approach, as outlined by Brannan (2008), are that researchers may develop their skillset by being open to novel ways of addressing study questions, thus expanding their methodological horizons. Similarly, they may also find that this broad minded approach may encourage creative thinking which is outside of the traditional 'box'. This attribute, particularly in a research community where cross-disciplinary studies are now frequently encouraged, may prove to be more fruitful than simply following accepted methodological norms. An example being that scientific studies utilising a multiple methods approach may resonate with the 'political currency' of policymakers and funding bodies in ways which may be distinct from those using basic science methods alone. Similarly, with the advent of large-scale studies spanning multiple countries (such as EU funded projects), multiple methods may allow opportunities for comparative analysis above and beyond those offered by the contextualisation of quantitative data alone. In addition to these benefits, more effective dissemination of study findings may also be achieved. This is described by Brannan (2008) who suggests that the modern researcher needs to be equipped with two 'languages', consisting of a technical language to appreciate the detail of a study's principle concepts and a second language to facilitate the effective diffusion of these concepts to broad audiences. A multiple methods approach may therefore help with the explanation of these technical concepts and allow meanings to be conveyed in a straight-forward manner in situations where words may be just as important as numbers.

The combinatory approach typified by multiple methods research, despite benefits, has also aroused concerns regarding incompatibility, leading to a 'paradigm war' in which some researchers were deeply embattled during the 1980's. Although pragmatists contended that there exists a false dichotomy between methodologies, purists on the other hand maintained the assertion that there are

distinct reasons for keeping methods separate and that 'never the twain shall meet' (Cameron, 2007). Although the purist argument was largely focussed on the presumption that the differences in paradigms were too great to allow a complementary overlap to be successfully obtained, this outlook has since been shown to be somewhat short-sighted. Guba and Lincoln (2005 p.200) discuss this and conclude that methods can in fact be '*retrofitted to each other in ways that make the simultaneous practice of both possible*' and that '*at the paradigmatic, or philosophical, level, commensurability between positivist and postpositivist world views is not possible, but that within each paradigm, mixed methodologies (strategies) may make perfect sense*'.

Since this acceptance of multiple method study design in the research community various theorists have produced typographies in an attempt to categorise and classify the often abstract concepts which are involved in a specific methodology. The resulting theoretical structures are too numerous to review individually; however, one in particular by Creswell (2009) resonated with the author. This typology presents four aspects which should be considered and have been summarised in Table 3.1.

Timing	***Weighting***	***Mixing***	***Theorizing***
No Sequence concurrent	Equal	Integrating	Explicit
Sequential Qualitative first	Qualitative	Connecting	
Sequential Qualitative first	Quantitative	Embedded	Implicit

Table 3.1 - Multiple methods typology (Adapted from Creswell, 2009).

This particular typology invites the researcher to consider firstly the timing of their methodological components. In brief this refers to whether the study will use quantitative data to inform subsequent qualitative work (or vice-versa) in a 'sequential' design, or if all components will be carried out at the same time

'concurrently'. Secondly, the researcher must determine if either quantitative or qualitative elements will dominate or if the sum of both parts will be equal. Thirdly, the typology also demands that the type of 'mixing' be deliberated and whether the resulting data will be kept separate yet 'connected' (for example in a 2 phase-study using a quantitative stage to inform later qualitative stage), merged together and 'integrated', or using one (usually smaller) set of data to support another in an 'embedded' manner. The fourth and final consideration for a researcher is if the study will be guided by a larger, overarching theory which is 'explicitly' mentioned, or whether any influencing theories will be omitted, in accordance with an 'implicit' model.

In the case of the present study, a sequential model was unfeasible due to time constraints and therefore a concurrent design was followed. Furthermore, due to the nature of the research questions it was deemed more appropriate to select a number of quantitative methods to gauge the treatment outcomes associated with CSII and to utilise a smaller qualitative element to elucidate patients' lived experiences with T1D. This resulting qualitative data was then used to support the quantitative findings, from which hypotheses could be generated. Due to the inductive nature of the study theories were not outlined prior to the commencement of the study and therefore it could be said that an 'implicit' model was followed. When comparing this design with Creswell's model it is clear that the study therefore followed a 'concurrent embedded strategy'. Furthermore, it should also be noted that rather than comparing the data derived from these different paradigms directly against one another, the typological strategy will be adhered to within this thesis by sitting the results together to provide an '*overall composite assessment of the problem*' (Creswell, 2009).

3.3 Overall Study Design

The following section describes the methods used to address the study aims and objectives (see page 29). The project consisted firstly of an audit of patient medical records which was followed by the recruitment of participants to two research study designs. Firstly, there was a longitudinal study which observed CSII patients over time. This consisted of three outcome measures (eating behaviours, quality of life and cardiometabolic (CM) risks) running concurrently

over five time points (baseline, 3, 6, 9 and 12 months). Secondly, there was a cross-sectional study which compared CSII patients against those using MDI. This examined the same three outcome measures as the longitudinal study; however only one time point was used. The methods used to observe the three outcomes differed slightly between the studies and an overview is given herein.

3.3.1 Pre-study audit

The first component of the project was an audit of medical records pertaining to patients undergoing CSII therapy at the Royal Liverpool Hospital Diabetes Centre. Audits are commonly used tools within the NHS and other sectors for the evaluation and improvement of services; however, clinical audits involve more than simply gathering data alone and it is important to realise that this process is not the same as research. Although research is typically carried out to gain new knowledge a clinical audit should principally collect data in a systematic manner in accordance with agreed standards which should be then compared to certain criteria and any identified areas for change should be implemented (UHBristol Clinical Audit Team, 2009). Furthermore, an audit should not incorporate any kind of intervention or treatment and the data should not be randomised (Health Research Authority, 2013). The principle components of an audit, which in their totality should be cyclical, are illustrated below in Figure 3.1:-

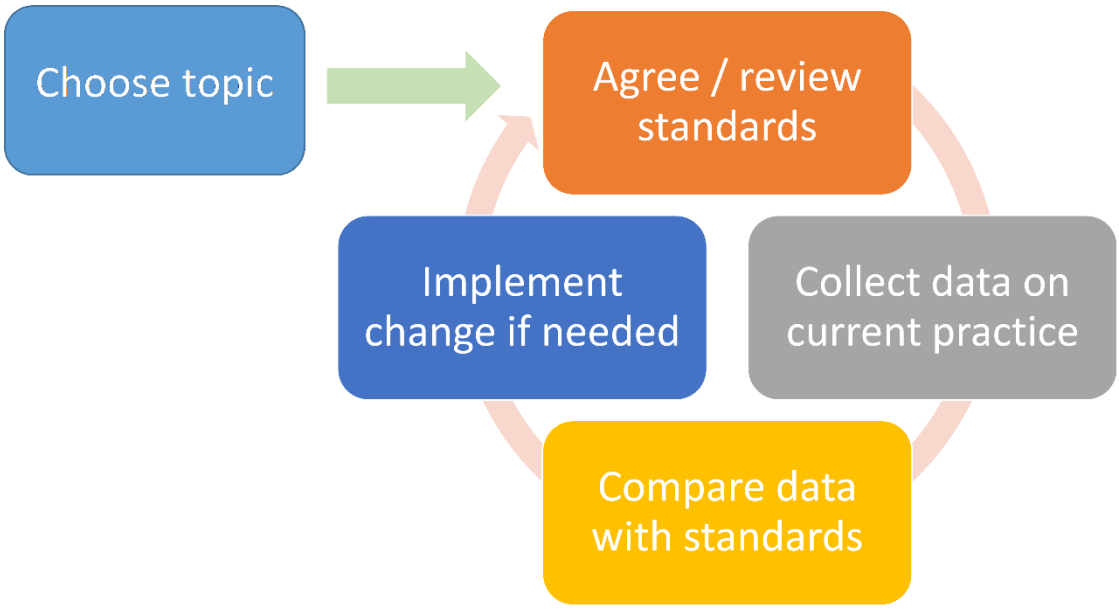


Figure 3.1 – NHS clinical audit process (Adapted from UHBristol, 2009)

After considering the attributes of an audit the research team together with colleagues at the Royal Liverpool Hospital, realised that it was unknown if CSII patients in particular were meeting the current clinical care standards for patients with T1D with regards to traditional markers of cardiovascular disease (i.e. lipids, lipoproteins and blood pressure). It was therefore decided that it would be useful for an audit to be performed focussing on these markers together with other standard markers of risk for those with the disease. Details regarding the audit method will be clarified in the appropriate chapter.

3.3.2 Research Study Participants

Whilst data for the audit collection was underway the author also recruited participants to take part in the two research studies from the Diabetes Centre at the Royal Liverpool Hospital. Participants taking part in the longitudinal study had all recently been approved for CSII therapy and were pending the supply of an insulin pump. Participants taking part in the cross-sectional study had been using either CSII or MDI for over 1 year. All participants were aged 18 years or over and lived in Liverpool or the surrounding areas. A note was also taken if a participant was taking any kind of medication which could alter lipid/glycaemic control to inform any statistical corrections which may need to be made during data analysis. Furthermore, participants were told that they may be excluded if they did not give permission for their healthcare professional to be contacted, or if they had been involved in any other research over the previous 3 months which may affect lipid/glycaemic control.

3.3.3 Research Study Sample Size

Due to the nature of this single-site study, the clinic dictated the sample size. The study therefore acted as a pilot; however, the findings may potentially lead to more robust multi-site studies using appropriately powered sample sizes at a later date.

A sample size of 20-25 was originally estimated for the longitudinal study. This was determined from forecasts expecting approximately 50 patients to be offered CSII therapy at the Royal Liverpool Hospital over 12 months. The recruitment period for this study lasted for 6 months meaning a convenience sample of approximately 25 patients should have been potentially accessible. It was taken

into account that not all patients would meet the inclusion criteria and that some would be unwilling to take part in the study; however, all suitable patients were approached.

A subsample of around 5-8 participants were also required for qualitative interviews and were selected via convenience sampling from the existing study population as participants had already met all inclusion criteria and given consent. Each participant was informed that they would be interviewed after recruitment 5 times in 3 month intervals, producing a total of 25-40 interviews. The work of Hancock suggests theoretical saturation may be achieved by performing 20-60 interviews using a constant comparison approach, therefore a sample size of approximately 5-8 participants was deemed appropriate (Hancock, 2009).

For the cross-sectional study a convenience sample of 30 patients using CSII and 30 using MDI was agreed based upon the pilot nature of the study and the small clinic size. A subsample of approximately 10 patients using CSII and 10 using MDI was also considered appropriate to take part in additional optional activities such as food diaries and interviews. These activities will be explained in more detail in the following section and in the respective experimental chapters. Again, due to the pilot, exploratory nature of this study and the limitations of the clinic this small subsample size was thought to be appropriate. The recruitment process is discussed in more detail in the Recruitment Feasibility chapter (see page 65).

3.3.4 Research Study Data Collection

Longitudinal Study

To investigate participants' eating behaviours weighed food diaries were employed.

This is a commonly used method which involves participants recording the mass or volume of all food and drink items at the time of consumption in a diary booklet along with any waste. This technique has been used extensively throughout the literature and is a cheap and easy to produce and distribute method of assessing dietary intake. That said the method is not without limitations. Although some authors regard the open-ended nature of food diaries to be a benefit which assists with the reduction of recall bias, there are those who are in disagreement

(Thompson, 2008). These disparities in opinion result from evidence demonstrating how food diaries may be prone to underreporting and urge vigilance to be taken when analysing findings (Bingham, 2001). Although these concerns are not unfounded it is important to note that underreporting is a commonly encountered issue with dietary assessment methods in general, with the OPEN study illustrating how both males and females routinely underreport energy intake when using a variety of assessment methods (Subar, 2003). Furthermore, Livingstone (1990) demonstrated how the sample population may in fact be a better indicator of underreporting than assessment method per se by highlighting incidence specifically in adolescents and the obese. Moreover, food diaries have shown agreement against the 'gold standard' doubly labelled water method of determining energy intake when used in an adult parent population, thus demonstrating their reliability when used in appropriate circumstances (Livingstone, 1990). Although methodological issues such as underreporting should of course be acknowledged it is important to note that they are no more prevalent in food diaries than when using other methods of retrospective nutritional assessment (Lentjes, 2014). This has likely contributed towards their common use throughout nutrition research and together with pragmatic reasons is why the author chose to use food diaries as a method of determining dietary intake.

Patients taking part in the longitudinal study were required to complete a food diary (see appendix 12.7) at each of the five study points (every three months) and to fill in each diary for five days; ensuring two of the days were over a weekend. This strategy was chosen to not only provide a suitable timespan to capture typical eating behaviour changes in participants' weekly routines, but also to compromise with evidence illustrating potential participant fatigue and motivation issues (de Castro, 2007; Livingstone, 1990). The diaries were given out at routine clinic sessions or posted to participants' home addresses at each of the study time points previously mentioned. To enhance accuracy participants were required to weigh all consumed food. Where this was not possible participants were asked to provide the type of food and brand name or label which could be later checked against supermarket websites. They were also asked to provide a portion size comparison made in conjunction with a food atlas. This involved associating portion size with colour photographs printed inside the cover of the diary (Turconi,

2005). To further ensure details were correctly entered the participants were also briefly interviewed.

As previously mentioned, a small number of patients (5 - 8) were invited to participate in quality of life interviews. These were ‘semi-structured’ in nature, meaning that a series of open questions were loosely adhered to which formed the ‘structure’ of the interview; however, unlike survey based methods or ‘fully-structured interviews’ the participants were given freedom to discuss and elaborate upon their answers (Bryman, 2004). Although this method typically requires considerably more post-interview transcribing and processing than fully-structured interviews or surveys it is arguably a superior way of understanding the lived experience due to the lack of constraints regarding the responses participants may give (Flick, 2015). From a practical standpoint interviews are also relatively cheap, straightforward and easy to organise and given the time constraints of the study these were important aspects to consider. Aside from interviews the reader may initially consider that other qualitative methods could also have been employed. Indeed focus groups in particular have been widely used throughout health research to develop an understanding of participants’ thoughts and feelings and may appear to be a complimentary method (Somekh, 2011). This could be argued as the group dynamic is often regarded as a useful tool to enable participants to feel comfortable and to assist with the generation of ideas; however, it should be noted that depending on the members of the group strong personalities can overshadow others meaning some may be left feeling unable to voice personal issues (Bryman, 2004). It is for this reason specifically that the author felt a focus group, rather than encouraging free discussion, may actually have hindered it, particularly regarding sensitive matters; therefore individual interviews were deemed to be more appropriate.

Prior to commencing the study the author devised a brief interview outline (which is typical in qualitative research) to highlight the areas of discussion which were to be covered with each patient (see appendix 12.6). The structure of this interview outline followed suggestions made in the literature and the preliminary questions were designed to initially build rapport with the patient and develop a picture of their life history living with the disease (Leech, 2002). The next questions which followed were more specific to quality of life itself and whilst being based around

the main study objectives were also designed to provoke elaborative responses. Four main themes were covered by these questions, the first three were ‘activities’ (i.e. leisure activities, mobility etc.), ‘health’ (i.e. general health, self-help, self-esteem etc.) and ‘relationships’ (i.e. partner, healthcare professional, family etc.). These particular questions were directly related to quality of life and were inspired by the University of Toronto’s quality of life model, which after reviewing alternative definitions of the term the author felt was the most appropriate to apply. This particular model defines quality of life as being ‘*the degree to which a person enjoys the important possibilities of his or her life*’ and can be further refined into a conceptual framework of 3 categories each consisting of 3 subcategories as shown in Table 3.2 (Quality of Life Research Unit, 2016). The overarching categories of ‘*being*’, ‘*belonging*’ and ‘*becoming*’ provided an anchor from which the interviews were grounded and which the chosen themes were ultimately based upon.

Being	Who one is
Physical Being	physical health personal hygiene nutrition exercise grooming and clothing general physical appearance
Psychological Being	psychological health and adjustment cognitions feelings self-esteem, self-concept and self-control
Spiritual Being	personal values personal standards of conduct spiritual beliefs
Belonging	**Connections with one's environments**
Physical Belonging	home workplace/school neighbourhood community
Social Belonging	intimate others family friends co-workers neighbourhood and community
Community Belonging	adequate income health and social services employment educational programs recreational programs community events and activities
Becoming	**Achieving personal goals, hopes, and aspirations**
Physical Belonging	home workplace/school neighbourhood community
Social Belonging	intimate others family friends co-workers neighbourhood and community
Community Belonging	adequate income health and social services

Table 3.2 - Conceptual quality of life framework (Adapted from Quality of Life Research Unit, 2016)

The fourth and final theme which was discussed during the interviews involved the 'diets' (i.e. eating behaviours, appetite etc.) of patients. The author felt that it was essential to discuss this in more detail as the primary objective of the study was to investigate the impact of CSII upon patients' eating behaviours. Furthermore, investigation using a qualitative paradigm is likely to reveal data and subsequent understandings which may otherwise have been 'missed'. It should also be noted that all questions were formed in an open manner to encourage thoughtful responses and probing questions were occasionally used to provoke further discussion. The author used active listening techniques throughout to ensure rapport was built and maintained with each patient.

Although quality of life was assessed qualitatively through semi-structured interviews it was also quantitatively measured using Euroqol EQ-5D questionnaires (Euroqol, 2016). This questionnaire is a standardised measure of health outcomes and consists of a series of brief descriptive questions concerning 5 dimensions (mobility, self-care, anxiety/depression, pain/discomfort and usual activities), with each dimension having 3 levels (no problems, some problems and extreme problems). Additionally the questionnaire also contains a visual analogue scale which asks participants to self-rate their health. An example can be seen in appendix 12.4. The questionnaire has been fully validated and has been used extensively throughout the literature and in populations with T1D (Solli, 2010). All participants were asked to complete the survey and the responses were triangulated with the findings from the interviews.

In addition to eating behaviours and quality of life the final study objective was to investigate CM risk. Although standard definitions of CM risk are in their infancy, the literature often associates specific clustered markers with increased risks of CM diseases (Van der Meer, 2013). To determine patients' risks the study compared various markers falling under the 'CM risk' umbrella, both before and after the commencement of CSII therapy at the time points previously described. These risk factors consisted of age, sex, anthropometrics, HbA_{1c} level, blood pressure and the standard lipid profile. This information was found within participants' medical records which are continually updated after every hospital appointment and a note was taken of these measurements at each designated study visit. In addition to medical record access, a 20 ml volume of blood was also

required from participants after 12 hours of fasting. This sample was required for the additional analysis of lipoprotein subclasses (Davies, 2003). General information pertaining to this analysis can be found later in this chapter and the methods used are described in detail in chapter 3 (see page 45).

The reader should note that there were various recruitment issues for this longitudinal study which resulted in the findings being instead presented as a series of brief case studies. This is explained in more detail in the 'Recruitment Feasibility' chapter (see page 65).

Cross-Sectional Study

To examine the eating behaviours of patients taking part in the cross-sectional study food frequency questionnaires (FFQ) were used. A FFQ is a method of describing food consumption patterns over a reference period using standardised responses, which in turn allow data to be inexpensively collected and quickly analysed (MRC, 2013). Despite these advantages, FFQ's have been shown in the literature to be less reliable than other dietary assessment methods, such as food diaries and although they provide an important overview of dietary habits, it should be acknowledged that under or over reporting may occur (Day, 2001). The author appreciates this limitation; however, the pragmatic issues associated with using tools such as food diaries on a larger population were deemed too great for a study of this nature. It was therefore decided that a small subsample of participants would be asked to complete food diaries, whereas all participants will be asked to complete a compulsory FFQ. The FFQ chosen was the European Prospective Investigation of Cancer (EPIC) FFQ (see appendix 12.5), which was designed to measure participants' food intake over the previous year and may also be used to determine food group data (University of Cambridge, 2014). It is a fully validated questionnaire and has been extensively used in previous studies incorporating a variety of populations, including patients with T1D (Matteucci, 2004). The FFQs were mailed out to potential participants, along with a cover letter, information sheet, informed consent form and quality of life questionnaire. It should be noted that patients taking part in the longitudinal study were not required to complete a FFQ as it is felt that adequate eating behaviour data will already be

collected using the food diary alone and that the study may become too burdensome with the incorporation of additional data collection tools.

Participants were also asked to complete the EQ-5D quality of life questionnaire mentioned previously. This only needed to be completed once after consent. Furthermore, to take part in the study the participants had to allow the research team access to their medical records so risk factors could be recorded in the same way described previously for the longitudinal study; however, measurements were only recorded once when consent was given, rather than over numerous time points.

Participants in the cross-sectional study were also able to ‘opt in’ during the consent procedure to participate in various additional tasks. These tasks consisted of completing weighed food diaries, taking part in semi-structured interviews and giving a sample of blood. The requirements for patients participating in these tasks was the same as those previously described for the longitudinal study, but only took place once after giving consent rather than at various time points. It should also be noted that the patients using MDI therapy were asked slightly different questions during their semi-structured interviews to determine their opinion of CSII therapy rather than their experience using it; however, the key interview themes remained the same. Examples of the interview questions can be seen in appendix 12.6.

The following flow charts present the process each participant went through upon consenting in a visual form. Figure 3.2 illustrates a general overview of the studies and Figures 3.3 and 3.4 clarify the processes in more detail for both cross-sectional and longitudinal studies.

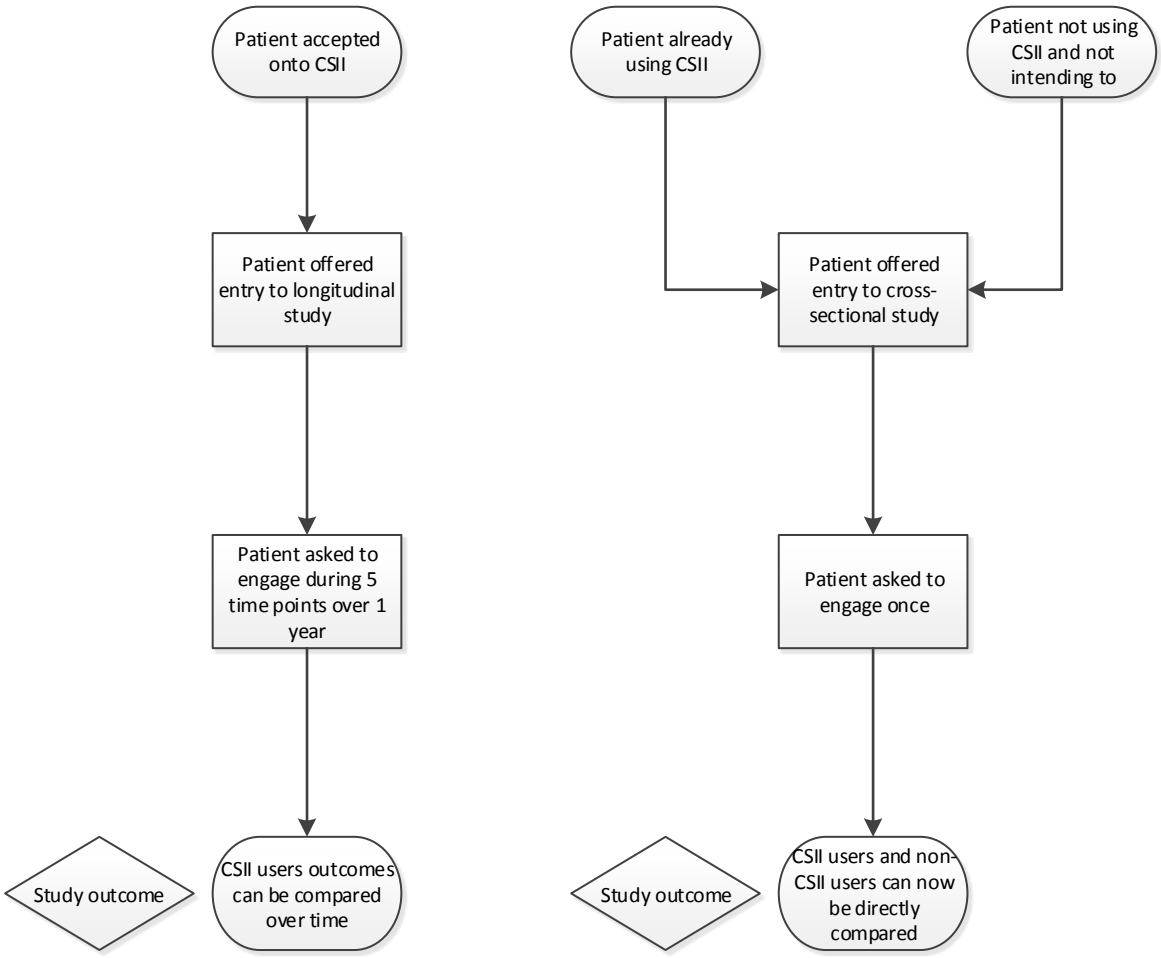


Figure 3.2 – Flow chart outlining the general study procedure for longitudinal and cross-sectional studies.

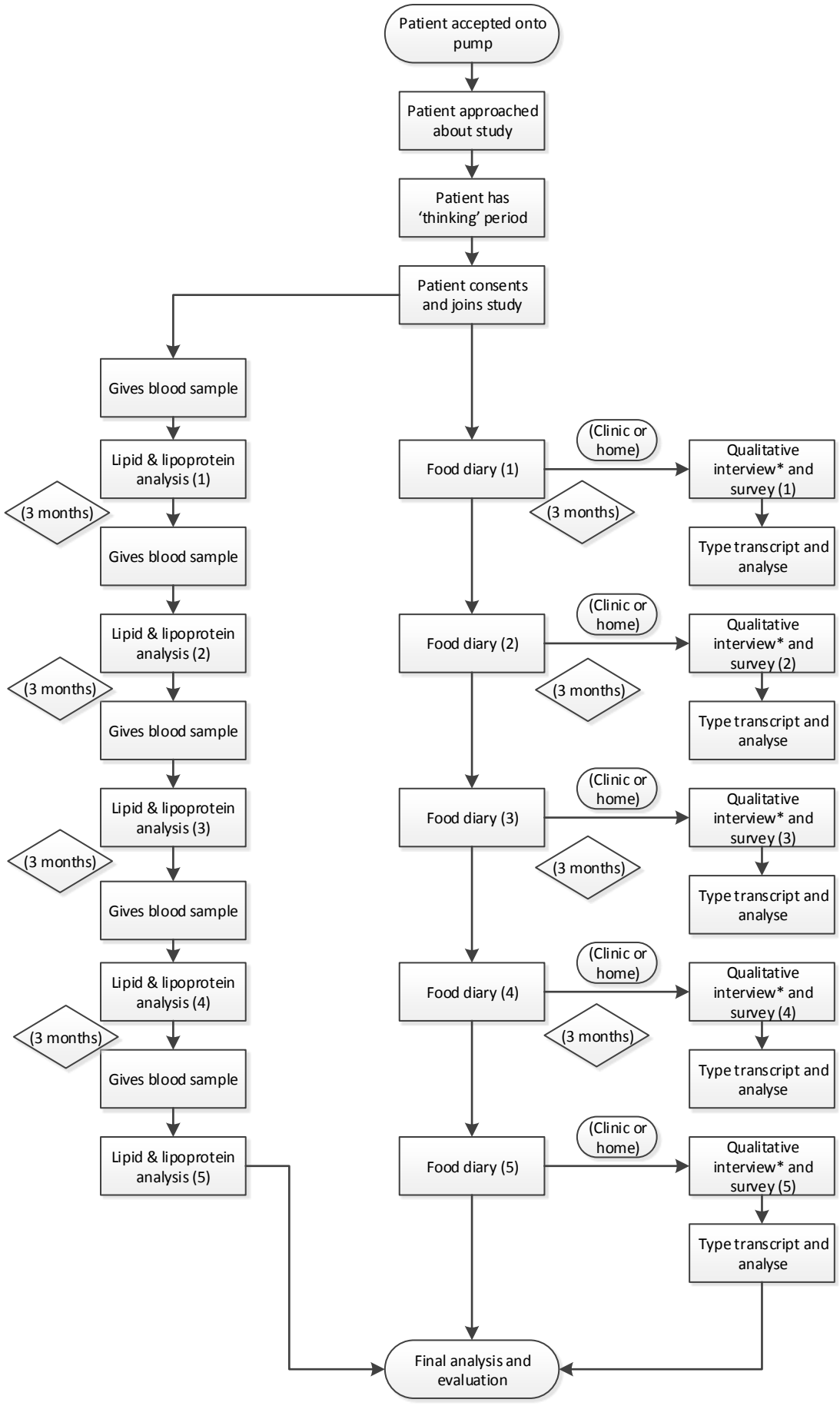


Figure 3.3 – Flow chart detailing the procedures for the longitudinal study

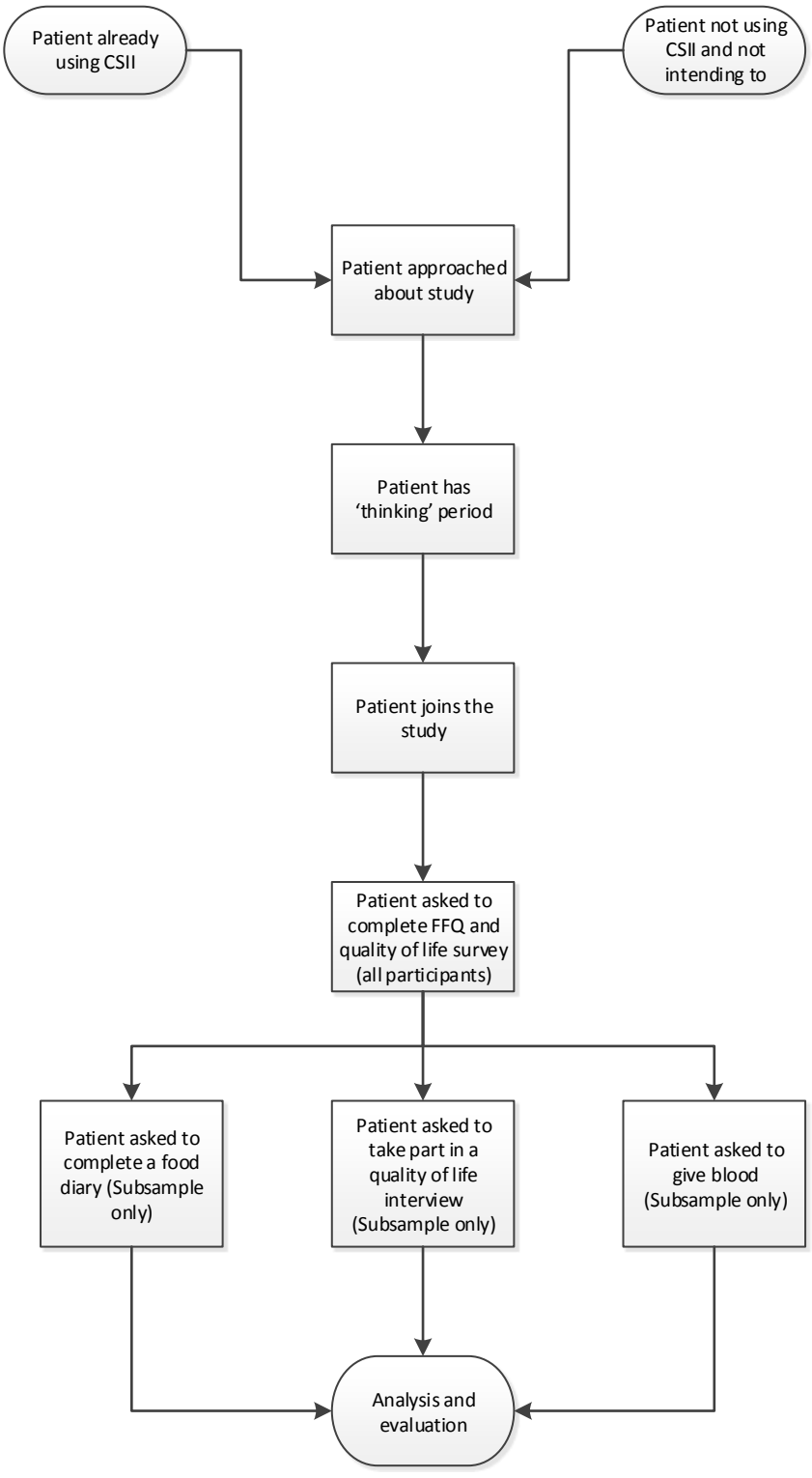


Figure 3.4 – Flow chart detailing the procedures for the cross-sectional study

3.3.5 Research Study Data Analysis

All data were analysed after each study time point (baseline, 3, 6, 9 and 12 months for participants in the longitudinal study and immediately after data collection for the cross-sectional study) and were summarised upon the completion of both studies.

Dietplan 6 software (Forestfield Software Ltd., West Sussex, UK) using standard McCance and Widdowson food tables was used to analyse dietary intake data obtained from food diaries (Food Standards Agency, 2002). Data obtained from the FFQ's employed in the cross-sectional study was analysed using FFQ EPIC Tool for Analysis (FETA) software (University of Cambridge, 2014).

Fasting plasma from venous blood samples was prepared for analysis by low-speed centrifugation. The resulting plasma was aliquoted equally into two samples. One portion of aliquoted plasma was rapidly separated into LDL and HDL subclasses using ultracentrifugation and then divided into fractions (Davies, 2004; Harman, 2013). Each fraction was then analysed for lipid content and categorised into different density classes and atherogenic phenotypes. The second portion of whole plasma was also analysed for lipid content. More details of these procedures are described in chapter 7 (see page 134).

Statistical analysis

Descriptive and inferential statistics were used to describe all quantitative data obtained. Descriptive statistical analysis was carried out on data obtained from blood samples, food diaries and risk markers found in participants' medical records, as well as data collected from food frequency questionnaires and the Euroqol EQ-5D questionnaires. Frequencies and percentages were calculated for categorical variables. Furthermore, continuous variables were tested for normality using Q – Q plots and the Shapiro-Wilks test and any non-normal data was then transformed logarithmically prior to further analysis using either Student's *t*-tests or Mann-Whitney *U* tests. Correlations between variables pertaining to CM risk derived from the analysis of plasma samples were established using the non-parametric Spearman's rank correlation coefficient. Linear repeated measure models were also used when analysing the clinical audit data to determine the

influence of CSII therapy over time. Statistical Package for Social Sciences (SPSS) (v.21) was used for all quantitative data analysis throughout the study.

Qualitative data analysis

Qualitative data generated during interviews was subjected to a thematic analysis as described by Gubrium and Holstein (2009), Riessman (2008), and Sparkes and Smith (2014). This involved transcribing the anonymous interview data into a Microsoft Word 2010 document. The data then underwent a number of readings prior to being broken down into categories of meaning. This led to the development of key themes both within and between the participants as individual cases and allowed for the theoretical elaboration of data to occur. NVivo 10 software was used to assist this analytical process.

Chapter 4

Recruitment Feasibility

4 - Recruitment Feasibility

Effective participant recruitment is greatly important for the success of any human-based study and this section will give an overview of the recruitment issues pertaining to studies in general and those involving patients with diabetes along with potential remedies. It will also explain in detail the recruitment process for the present study from its commencement to its conclusion. In doing so the author hopes that the reader will gain a sense of the challenges which were faced throughout the study and that this may help to explain some of the irregularities which may appear in the following chapters. Furthermore, it may also offer hints at how the study may have been improved and how future similar studies may be more effective; however, these issues will be discussed in more detail in later chapters.

4.1 Introduction

Given the importance of effective recruitment and the weight of significance relying upon this fundamental process the literature regarding the recruitment of study participants is remarkably scarce. This is both surprising and concerning, especially when much research is funded by public money and its success is of great importance to society as a whole.

Despite this it is reassuring that the few existing studies have generally been conducted in a robust manner and the available reviews are extensive. Although this literature offers promise it is important to note that much of the research tends to focus largely on the recruitment of participants to randomised control trials (RCTs). These highlight various issues, in particular concerning the frequent failure of studies to meet proposed recruitment rates. For example, Copeland (2016) attempted to recruit participants to a large physical activity trial and found that only 47% of the target sample was ultimately enlisted. These disappointing figures were echoed by Carter (2015) who also found that when recruiting for a multiple sclerosis RCT only 120 patients from a possible 369 actually took part, thus producing a recruitment rate of only 32.5%. Additionally, work by Campbell (2007) assessing a database of trials which took place between 1994 to 2003

highlighted that even those in the UK which benefited from the assistance of a clinical trial centre failed to recruit successfully, with approximately half being unable to recruit 100% or more of the original target and 45% failing to recruit within 80% of their original target.

The reasons for these shortcomings appear to be multifaceted with commonly cited issues often being associated with a lack of staff and resources as well as frequent difficulties both communicating and maintaining relationships with participants after randomisation (Copeland, 2016; Carter, 2015; Campbell, 2007). Furthermore, research staff being unprepared and untrained in how to deal with problems arising from the complexities of carrying out human-based studies also appears to be a problem (*Ibid*). A qualitative study by Newington (2014) attempted to further unpick these issues through interviews with research workers and found there were four reoccurring themes regarding recruitment. Firstly, a suitable 'infrastructure' has to be in place to ensure recruitment is organised rather than a secondary thought. Secondly, the 'nature of the research' must be considered. For example, clinical trials have been shown to be more difficult to recruit for than observational studies due to the extra commitment required by participants and as such measures should be considered to compensate for this, such as incentives etc. Thirdly, adequate thought should be given to the 'recruiter characteristics'. For example, patients are more likely to consent to take part in a study when approached by a doctor rather than a research nurse and the recruiter should therefore be considered in the design phase. The final point discovered by Newington (2014) was regarding the 'participant characteristics'. For example, patients are more likely to participate in a study when they are likely to gain a clinical benefit from doing so. Interestingly, in the present study it also became apparent that the reason for patient participation, from the researchers' perspective, was typically and perhaps unsurprisingly altruism and conversely logistical considerations appeared to be the most important catalyst for not taking part. To determine optimum strategies of dealing with complex recruitment issues such as these a meta-analysis by Treweek (2013) was performed, investigating 45 trials with over 43,000 participants. This study revealed that there are in fact promising methods which can be used to increase both recruitment and retention, such as the use of open-trial designs, opt out strategies and telephone reminders;

however, the authors emphasise that there remains a large gap in the knowledge in this area and that there is little evidence surrounding commonly used alternatives, such as financial incentives.

Despite the majority of existing research in this area focussing specifically on RCTs, it is incorrect to say that this is absolute. Observational studies also get a degree of attention by authors, although this is often of a smaller magnitude than their RCT counterparts. For example, work by Pickering (2010) which focused on recruitment to three observational studies, all involving patients with stroke, found that the recruitment rates after screening for all studies varied between 10% and 50% and that all were significantly lower than expectations. Furthermore, in one study where a history of stroke was the only required eligibility criteria recruitment was still found to be only 50%, illustrating how even studies with few design barriers may still find recruitment a challenging process. Large and multicentre studies also appear to suffer from the same issues but on a greater scale. This was illustrated in research conducted by Stone (2013), which investigated recruitment to a palliative care study and revealed that only 8.2% of referral patients who were originally deemed eligible to participate actually ended up taking part in the study. This was found to be due to a variety of reasons, similar to those discussed previously by Newington (2014), and fell under three main themes involving patient ‘availability’, ‘accessibility’ and ‘consent’ and concluded by stating that recruitment ‘bottlenecks’ such as these need acknowledging to ensure effective study outcomes.

Although this evidence is useful, research specifically focussing on recruitment to diabetes studies is rare. Despite this a diminutive collection of literature does exist and in particular a ‘rapid review’ by Cooper (2015) offers a useful example to highlight some of the unique issues pertaining to the recruitment of participants with diabetes. This review shows how those studies which offer a treatment (such as drug trials) tend to have higher rates of recruitment than those which offer some form of prevention (for example dietary and exercise interventions). Furthermore, Herbert (2015) showed that in a paediatric population with Type 1 diabetes (T1D), even after consenting to a longitudinal study (lasting 6 months) there were reductions in the retention of patients ranging from 58 – 90% and that there were variations within patients. In particular those who were older, had worse glycaemic

control, lower household income and who belonged to families with unmarried parents were associated with a higher chance of failing to complete the study. To ensure that recruitment is maximised in studies involving patients with diabetes there have been various attempts to produce databases of patient details forming clinical research networks which researchers can then use to contact potential relevant participants. An example of this is the TrialNet programme which originated from the US, but now has registrants with T1D from 21 centres based in many countries including the UK (TrialNet, 2016). Furthermore, there has also been the creation of the Diabetes Research Registry which is a similar endeavour; however, despite being a smaller venture it has still managed to enrol 5000 patients with both T1D and T2D residing in the US and over the past 5 years has facilitated the recruitment of participants for 31 studies (Tan, 2016).

Although the literature suggests there are many recruitment related issues associated with most human-based studies, not least those involving patients with diabetes, there also appear to be pitfalls which can also be avoided through proper planning and ensuring the study is designed appropriately. The following section will describe the recruitment process for the present study in detail and will conclude by explaining the potential issues which arose, how they may have been prevented and their implications for the study moving forward.

4.2 Recruitment Process and response rates

Clinical Audit

As previously mentioned, a clinical audit was performed whilst preparations were being made for the subsequent research studies. This audit was approved by the NHS and data was collected retrospectively by examining patients' medical records. More details can be found about this audit in chapter 5 (see page 79); however, it should be noted that the NHS audit approval gave the author access to the medical records of every patient using CSII at the Royal Liverpool Hospital. As data was retrieved from 100% of the patients using the therapy at the Trust at that particular time with no issues no further attention is required regarding recruitment and hence the audit will not be referred to again throughout this chapter.

Longitudinal Study

As mentioned in the General Methodology chapter, the author was initially aiming for the longitudinal study to obtain a sample size of 20 – 25 CSII patients. This was deemed both reasonable and attainable after considering the pilot nature of the study and data from previous years suggesting approximately 50 patients are typically offered the therapy at the hospital over the course of a year.

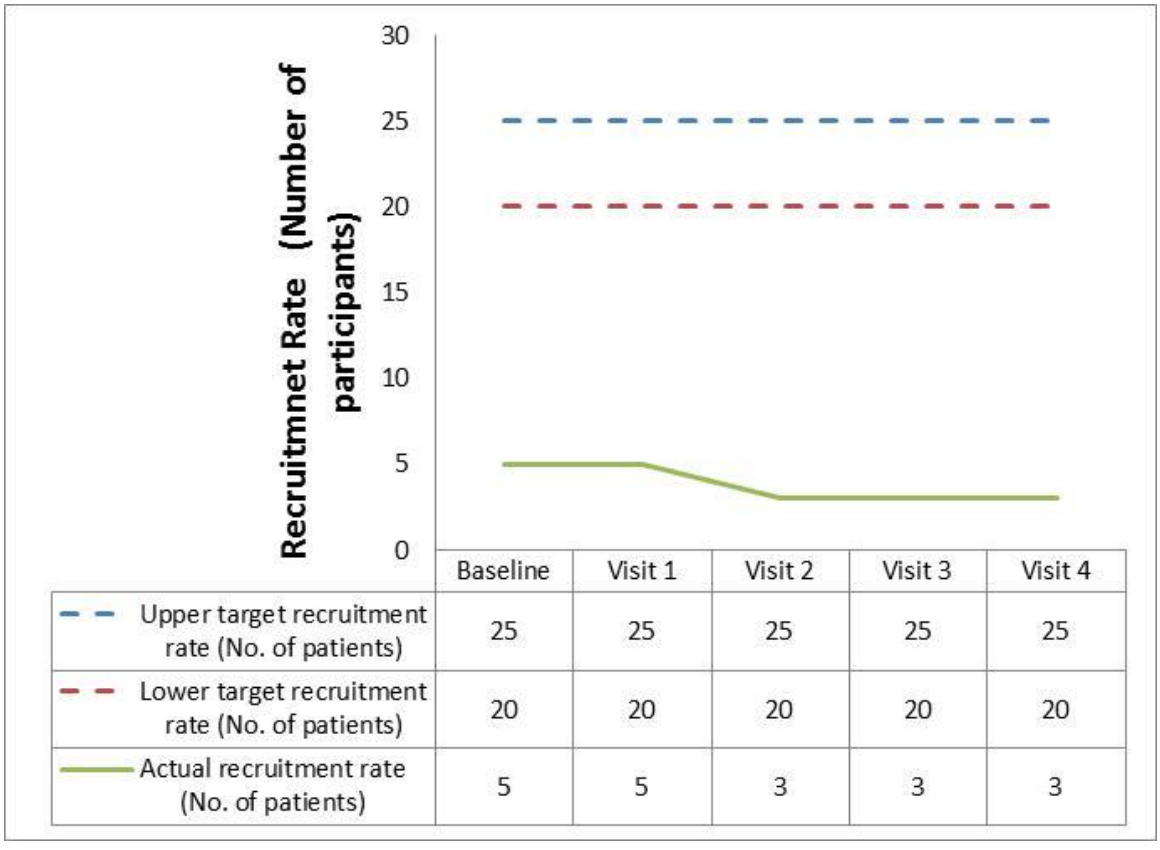
Unfortunately immediately after NRES NHS ethical approval was granted for this study and recruitment was about to begin a key member of hospital staff fell ill. The implications of this were that no new patients were offered CSII treatment and therefore recruitment was stopped. After waiting for a number of months for the individual to return to work and for recruitment to resume it became apparent that this would be unlikely. In response to this the author and research team decided that a different strategy would be required and thus the idea for a cross-sectional study was formed which would recruit patients well established with either CSII or MDI for comparison. It was planned that this would run concurrently with the longitudinal study which patients could be recruited to at a later date should new patients start to be offered CSII again.

As patients eligible for CSII have to attend a compulsory, week long, intensive education session prior to them being given the device recruitment for the longitudinal study was relatively straightforward. This consisted firstly of the Consultant Diabetologist informing the author of the next scheduled education session. Before this took place the author then delivered the appropriate number of recruitment ‘packs’ (containing participant information sheets and consent forms etc.) to the CSII specialist nurse who would be facilitating the education sessions. The nurse then verbally informed patients during the sessions about the study and handed out the packs to any interested patients. If a patient decided they would like to take part or find out some more information they could then contact the author directly using the contact details contained within the pack. Recruitment using this method meant that the author did not know any patient details unless they decided to make contact first.

Unfortunately, due to the hospital staffing issues described above the education sessions became consultant-led and were significantly less frequent than usual.

As a result during the course of the study only two sessions took place, each consisting of five patients. Out of these 10 patients who commenced CSII therapy only five agreed to take part in the longitudinal study. When using the recruitment target of 20 patients this indicates that there was a recruitment success rate of only 25%. Furthermore, during the course of the study one patient withdrew for personal reasons and another became uncontactable. The recruitment rates and retention over time can be seen in Figure 4.1.

In the light of this it is obvious that the data which was collected would not be statistically meaningful; however, it was decided that some of the results may still be of interest and that they may instead lend themselves better to being used as case studies. These are described in more detail in the 'Case Studies' chapter (see page 206).



	Baseline	Visit 1	Visit 2	Visit 3	Visit 4
Upper target recruitment rate (No. of patients)	25	25	25	25	25
Lower target recruitment rate (No. of patients)	20	20	20	20	20
Actual recruitment rate (No. of patients)	5	5	3	3	3

Figure 4.1 –Recruitment rate to longitudinal study and participant retention over time.

Cross-Sectional Study

As mentioned previously, the cross-sectional study was devised partly in response to staffing issues at the hospital which prevented initial recruitment to the longitudinal study. This therefore meant that NRES NHS ethical approval again had to be sought to allow this new study to take place. This was eventually approved and recruitment began immediately.

In a similar manner to the longitudinal study the author was prevented from knowing the patients identity until they had agreed to take part and as this study was targeting patients who had been using either CSII or MDI for a year or longer and who may only have annual check-ups it was unfeasible to ask the healthcare professionals to approach the patients during their clinic appointments. The recruitment process therefore involved the author instructing an IT technician responsible for managing the Diabetes Register at the hospital to filter the database according to the studies inclusion and exclusion criteria. The resulting patient contact details were then emailed to the Consultant Diabetologist's secretary. At this point the author delivered the appropriate number of blank recruitment packs to the secretary who then labelled and posted each pack to the patients' homes. If a patient then decided they would like to take part or find out some more information they were free to contact the author. This method, although slightly convoluted, enabled the identity of any patient who did not want to take part to remain anonymous and for all patient details to remain within the hospital.

Given the small amount of available patients imposed by the single clinic and the pilot nature of the study described previously, a sample size of 30 patients using CSII and 30 using MDI was thought appropriate and agreed. It should also be noted that a small subsample of approximately 10 CSII and 10 MDI patients were required to take part in further optional activities such as food diaries and interviews. These activities are explained in the General Methods chapter (see page 45) and will be explained in more detail again in later chapters. Again, due to the pilot, exploratory nature of this study and the limitations of the clinic this small subsample size was thought to be appropriate.

A total of 50 patients using CSII and 50 using MDI were initially approached during a first mailshot. These patients were chosen at random from the list produced from the Diabetes Register. The randomisation process involved potential participants from each treatment group being assigned a numerical code. These codes were then ordered randomly using the Microsoft Excel 'random' function and the first 50 from each group were then contacted. Unfortunately it quickly became clear that this mailshot had not been successful. During the month following the mailshot only 7 patients returned consent (6 of these were using CSII and 1 was using MDI). The research team then decided that recruitment should be significantly increased and an amendment was submitted and approved by the NRES ethics committee allowing the author to approach a further 255 patients using CSII (which when including the 50 already approached made up the entire population of patients using CSII at the hospital). This was then matched by an equal amount of packs sent out to appropriate patients using MDI (whose identities were chosen at random using the procedure previously outlined from the filtered list derived from the Diabetes Register). The packs were sent out in the same manner as previously described in order to preserve patient identity.

This second mailshot was far more successful and a total of 60 responses offering informed consent were ultimately received. These came from 40 patients using CSII and 20 patients using MDI. This equated to 133% of the target CSII patients being recruited and 67% of the target for MDI patients being recruited and is illustrated in Figure 4.2. These patients all completed a food frequency questionnaire and a quality of life questionnaire which were included in the final analysis. Unfortunately, 16 of the patients that initially gave consent did not go on to take part in the rest of the study as they were lost to follow up. This equated to 20% of consented patients using CSII and 40% patients using MDI and is shown in Figure 4.3. The questionnaire data for these participants remained in the final analysis. There were also a number of participants who did not agree to take part in some of the optional aspects of the study. It should also be noted that as soon as a patient gave consent to take part in the study the author sent a letter to their G.P. along with a participant information sheet to explain what they had agreed to. No G.P. replied to object to their patient taking part in the study. After the subsample of 10 CSII and 10 MDI patients had been reached interested

participants were then only offered the opportunity to take part in the donation of a blood sample. The reason for this was that whilst the author had a valuable opportunity to receive more food diary and interview data, the analysis of this excess data would be both out of the remit of this study and the scope of feasibility for the author to manage alone and was therefore deemed an unnecessary burden for the participants.

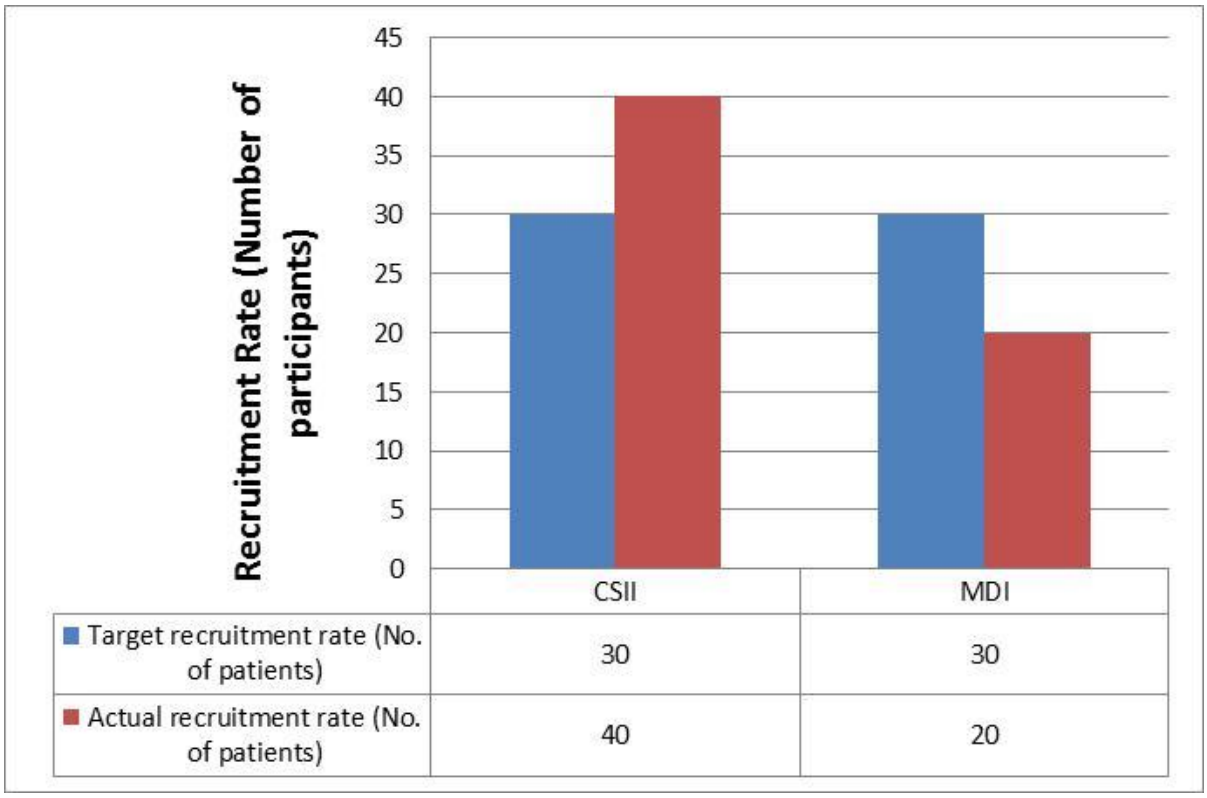


Figure 4.2 – Cross-sectional study recruitment rates by treatment type.

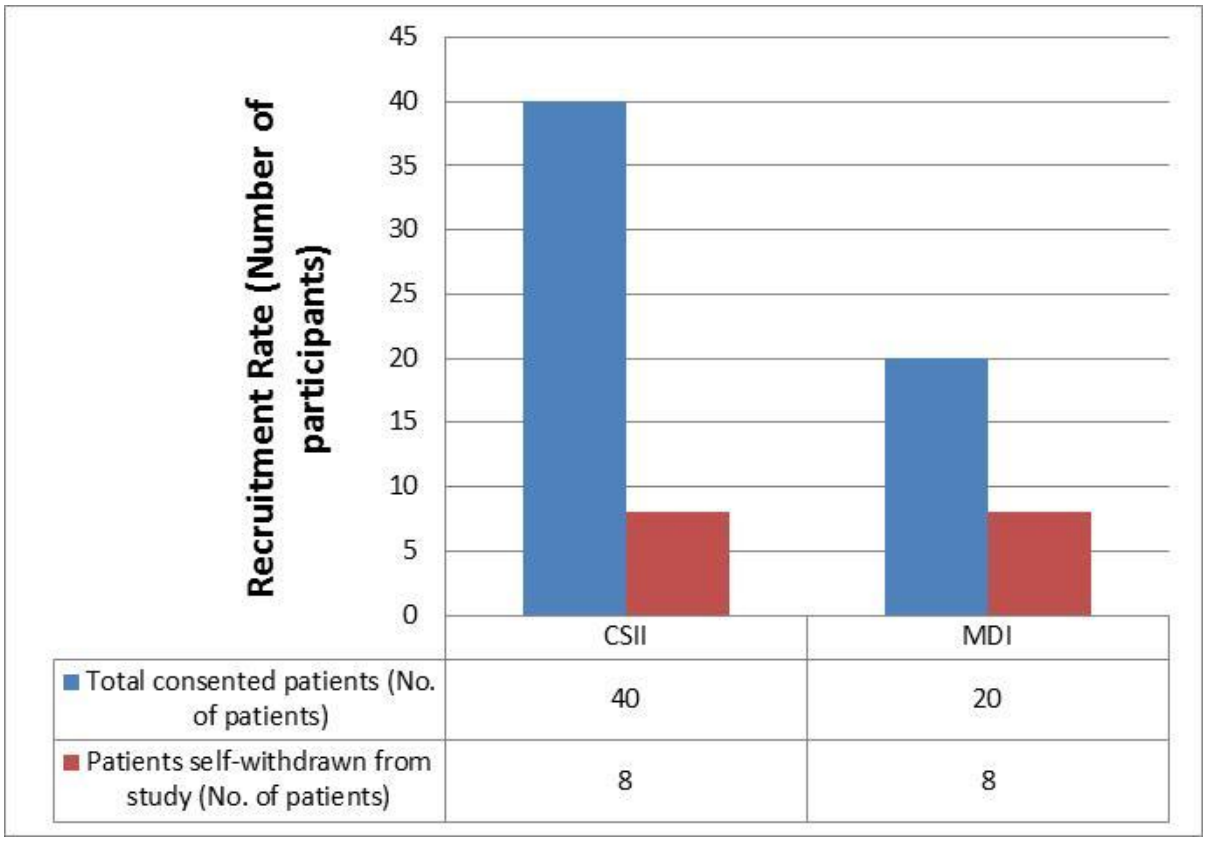


Figure 4.3 – Graph showing cross-sectional study withdrawal rates after consent by treatment

4.3 Discussion

Although the recruitment strategy was in some ways successful, with 133% percent of the recruitment target for patients using CSII being achieved, there remained various issues in other areas. For example, the recruitment of MDI patients was less impressive, with only 67% of the target sample size being met. Furthermore, when considering that a significant amount of patients had to be approached through the mailshot the effectiveness of the strategy leaves a lot to be desired. The mailshot reached 305 patients with CSII and an equal number of patients using MDI. This equates to only 13% of those using CSII who were initially contacted offering consent and just 7% of those using MDI. These rather disappointing figures are followed by poor retention rates, with 20% of those using CSII and 40% of those using MDI subsequently either withdrawing from the study or becoming uncontactable after offering consent.

Furthermore, with respect to the longitudinal study it can be seen that the recruitment rates were also poor; however, it is clear that this is largely down to uncontrollable and unusual staffing issues which could not have been forecasted by the research team. Unfortunately, the reasons for poor recruitment remain elusive as the identities of patients were blinded from the author until consent was given and no follow-up was proposed to determine why some were unwilling to take part. It can be hypothesised; however, that the patients perhaps may have had issues akin to those found by Newington (2014) and Stone (2013) which may have prevented or discouraged them from taking part. Also, it is interesting to note that the study is observational in nature and would not be offering any form of treatment, which Herbert (2013) found often plays a role in deterring patients with diabetes from participating. Furthermore, a lack of monetary incentive may also have contributed towards patients feeling unmotivated to take part, although this remains speculative as the influence a financial reward may have is debatable, with altruism often cited as a more prominent driving force for participation (Treweek, 2013; Newington, 2014). It is also interesting to note that despite the amount of patients consenting being relatively low compared to the overall amount approached, it is clear that those using CSII appeared to be far more willing to participate and were less inclined to withdraw. It is difficult to say with certainty why this could be, but patients offered CSII have to meet strict criteria and evidence of working together with a healthcare professional to improve their health must be shown. In short it could be said that because of this eligibility criteria patients using CSII may on average typically be more disciplined and health-conscious group than their MDI counterparts and as such potentially more motivated to take part in research studies.

Although these reasons are purely hypothetical there were various pragmatic issues which almost certainly contributed towards recruitment problems. The clinic size was an important influencing factor with recruitment bound by this limitation. Although patient numbers are dynamic the Royal Liverpool Hospital consistently has one of the largest populations of patients with T1D using CSII in the UK. Despite this all eligible patients using CSII (n = 305) were contacted and the only way this could have been expanded would have been to recruit from multiple centres. To pursue this would have been troublesome, primarily because a

consequence of the hospital's large CSII clinic is that the remaining local pump centres only support small numbers of patients. The next largest clinics are based in Harrogate and Cambridge and recruiting from these centres would have been unfeasible for a small pilot study of this nature. Furthermore, even if staff were in place to recruit from these sites the resources needed to pursue this were unavailable; for example, the costs of carrying out a larger mailshot etc. These issues embody comments made by Campbell (2007) that common problems with recruitment are often associated with a lack of research staff and resources needed to carry out the process effectively.

Despite these issues it is also important to acknowledge that there were ways in which the study could have recruited patients more effectively using the existing resources and staff. In hindsight asking healthcare professionals to assist with vocalising the existence of the study to patients in clinics may have helped to improve awareness. The evidence suggests that this may have proved to be an effective method as shown in work by Carter (2015) who found that when performing a trial involving patients with multiple sclerosis 60% were recruited from clinic appointments as opposed to 29.2% from a mailshot. Furthermore, the use of posters in clinics may also have further improved numbers. Finally, the use of a purpose made recruitment database may also have helped; however, examples such as TrialNet which was discussed earlier in this chapter, despite being affiliated with centres in the UK, are not yet available for use by the Royal Liverpool Hospital, but an NHS equivalent is currently being rolled out.

In summary similar future studies in this area may therefore benefit from expanding their recruitment strategy to incorporate various other opportunities aside from a mailshot alone and take advantage of the increased scope. Also, attempting to gain access to a purpose-made clinical research network may help to identify patients already willing to take part in studies. Furthermore, it is imperative that researchers attempt to understand their proposed sample population before study recruitment commences so that nuances can be recognised and exploited. For example, in the present study it is now clear that patients using MDI may be more difficult to recruit than their CSII counterparts, therefore perhaps more effort should have been made to find creative ways of reaching out to them. Despite an initial struggle to recruit participants the research

team feel that the final sample size for the cross-sectional study is appropriate for the purposes of a pilot study. The team also feel that the small number of recruited patients to the longitudinal study, although not statistically meaningful, still make for interesting and valuable case studies and offer an original contribution to the existing literature.

Chapter 5

Clinical Audit

5 - Clinical Audit

5.1 Abstract

The long-term effects of continuous subcutaneous insulin infusion (CSII) therapy on traditional clinical markers of risk such as glycated haemoglobin (HbA_{1c}), insulin dose, lipid profile, blood pressure and body mass index (BMI) is under-researched. An evaluation of 260 patients (33.8% male; 66.2% female) engaging with CSII therapy at the Royal Liverpool Hospital was carried out. Medical records spanning 8 years were interrogated and analysed. Over 4 years significant reductions were seen in systolic blood pressure from borderline hypertension to within the normotensive range (128.2 to 122.1 mmHg; p = 0.003). This was also shown in diastolic blood pressure (75.2 to 72.0 mmHg; p = 0.027). HbA_{1c} and insulin dose also decreased upon commencing the therapy (from 8.3 to 7.9%; p = <0.001 and 54.5 to 45.0 IU; p = <0.001 respectively), reflecting previously reported data. There was little change in BMI (from 26.1 to 26.0 kg/m^2; p = 0.288) and lipid profile, with total cholesterol and triglycerides decreasing slightly (4.3 to 4.2 mmol/L; p = 0.440 and 1.1 to 1.0 mmol/L; p = 0.018 respectively) and HDL-C and LDL-C remaining static (1.7 mmol/L; p = 0.639 and 2.1 mmol/L; p = 0.990 respectively). The results illustrate patients undergoing CSII therapy enjoy improvements in glycaemic control and blood pressure whilst using less insulin and that these changes have little or no adverse impact upon BMI or lipid profile. In fact, from a lipoprotein perspective patients appear to be well protected against cardiovascular disease. Despite these positive findings further work remains to be done to elucidate their validity, the mechanistic components which may be driving them and potential improvements to enhance patient outcomes.

5.2 Introduction

It is well known that patients with Type 1 diabetes (T1D) are at an increased risk of macrovascular complications compared to the general population, with cardiovascular disease accounting for 44% of fatalities in the UK (Diabetes UK, 2015). Furthermore, increased microvascular risks are also apparent, such as nephropathy which accounts for 21% of deaths in those with T1D; retinopathy

which presents in nearly all patients within 20 years of disease onset and neuropathy (Morrish, 2001; Scanlon, 2008). Fortunately, the progression of these microvascular risks may be slowed or prevented through attaining optimal glycaemic control (The Diabetes Control and Complications Trial Research Group, 1993). Similarly, more effective insulin treatments have also been associated with reductions in cardiovascular disease (CVD) risk, with Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) data highlighting incidence rates of 14% in those using a conventional injections compared to 9% in those using an intensive therapy (Nathan, 2009).

One such intensive treatment is continuous subcutaneous insulin infusion (CSII), which has been shown to be an effective method of achieving glycaemic control in those with T1D (Pickup, 2002). Since its introduction in the 1970's the therapy has undergone many changes with modern pumps offering the ability to set multiple basal rates, bolus profiles and temporary insulin delivery programmes, which may all potentially contribute towards further glycaemic improvements (Skyler, 2010). Opportunities to disconnect the pump, the introduction of waterproof cases and the advent of patch pumps may too impact upon long-term overall health through improved lifestyle (Ibid). There have also been significant advances in both T1D and CSII knowledge and education. As such patients are now frequently offered skills courses to enable effective carbohydrate counting and the appropriate management of diet and lifestyle, as well as structured CSII education sessions delivered by specialist healthcare professionals (NICE, 2008). Improvements in insulin quality have also occurred with new analogues being produced together with better patient access to these innovations (Owens, 2014; Woo, 2015). The sum of these advancements mean patients can now enjoy an improved state of health which was neither previously available nor accounted for in past studies.

Despite this progress there is a dearth of literature focusing on the long-term effects the therapy may have upon routine markers of CVD risk. Existing studies typically focus on children or adolescents and are frequently performed over short time periods with few robust studies following up adult patients for 24 months or more (Jeitler, 2008). Furthermore, they are often dated and therefore do not take

into account the technological advancements of insulin pumps over recent years and the benefits these may have upon patient health.

Although rare, there are important exceptions to this scarcity of literature. A study by Melidonis (2016) investigating 94 Greek patients using CSII over a 3 year period found that in addition to improved glycaemic control the therapy was also associated with a reduction in hypoglycaemic episodes whilst inferring a neutral effect on BMI. Furthermore, work by Rosenlund (2015) illustrated that over 4 years a cohort of 193 patients utilising CSII compared to 386 patients using MDI displayed a significantly improved urinary albumin/creatinine ratio. As this measure is associated with the production of microalbuminuria these findings may therefore be suggestive of reductions in kidney and cardiovascular disease risk. This potential for CSII to reduce cardiovascular risk was further investigated by Steineck et al. (2015) in the largest existing long-term study regarding this population. This observational study, spanning nearly 7 years, revealed that in 18,168 Swedish patients using CSII the therapy was associated with significantly lower adjusted hazard ratios for fatal cardiovascular disease, fatal coronary heart disease and all-cause mortality compared to MDI.

Despite this modicum of studies suggesting favourable long-term benefits associated with CSII there are none, to the authors' knowledge, which focus specifically on a UK adult population. Furthermore, recent evidence revealing how many patients with T1D do not receive adequate care and that only 15% of these under the age of 65 meet HbA_{1c}, blood pressure, and cholesterol treatment targets compound the need for an evaluation of both historical and present outcomes, particularly at a Trust level (NHS England, 2015; Diabetes UK, 2015). It was therefore decided that carrying out an audit of CSII patients' medical records at the Royal Liverpool Hospital would be beneficial. Clinical audits are useful to determine whether healthcare is being provided in line with standards and in this case would also offer an overview of standard clinical markers of risk within the sample population prior to the commencement of the research study (UHBristol Clinical Audit Team, 2009). This report therefore describes the aforementioned audit with a view to elucidating the long-term impact CSII may have upon standard clinical markers pertaining to the the whole population of patients using CSII at the

Royal Liverpool Hospital, thus enabling informed changes to be implemented (if needed) and to improve future care.

5.3 Aims and Objectives

Aim

To evaluate the long-term impact CSII may have upon routinely taken clinical measures of risk.

Objectives

To perform a clinical audit of medical records belonging to adult patients with T1D who are using CSII under the care of the Royal Liverpool Hospital.

5.4 Methods

After gaining NHS audit approval the medical records of 260 patients using CSII therapy at the Royal Liverpool Hospital were interrogated. Data from these patients spanning 8 years (4 years prior to the commencement of CSII and the subsequent 4 years after) were collected and comprised of total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C). Additional body mass index (BMI), HbA_{1c}, insulin dose and systolic and diastolic blood pressure information was also recorded; however, data for these risk markers were only available for the 4 years after patients commenced the therapy. The age and gender of each patient was also noted. All identifying patient details were anonymised.

Statistical Analysis

Data was inputted between January 2013 and November 2014 and descriptive statistics were used to initially scrutinise the data. Normality was determined using Q - Q plots and Shapiro-Wilks tests and a linear mixed model analysis was then employed, using SPSS version 21 (SPSS, Chicago, IL, USA). This statistical method was chosen specifically as a number of data points were found to be missing throughout the dataset. Although repeated measures tests are typically used to determine differences between time points in longitudinal data this may have been problematic as each participant with missing data would be

automatically excluded (thus severely minimising the sample size). A linear mixed model was therefore chosen due to its ability to retain every participant and account for missing data in the analysis. This test was used to determine differences between baseline measurements (taken upon the commencement of CSII) and measurements taken after 12 and 48 months of treatment. Additionally, the relationship between insulin dose and other variables was also determined using Spearman's rank correlation coefficient. A p-value <0.05 was used to denote statistical significance in all tests and correlation strength was determined using r-value criteria devised by Evans (1996), as shown in Table 5.1.

Table 5.1 – Correlation r-values and their corresponding levels of association (adapted from Evans, 1996).

5.5 Results

Patients

From the 260 patients' interrogated data 33.8% were male and 66.2% were female with a mean age of 45 ± 14 years and all patients were using CSII therapy. It should be noted that after examining the medical records it became clear that there was a significant amount of missing data as clinic appointments were often unattended. This may possibly be due to patients disengaging with the service for periods of time or clinic appointments being fully booked. Additionally, it was also found that variables of interest to the audit were not always habitually measured for each patient during each clinic appointment. In the light of this sample sizes (n) have been given in Table 5.2 concerning every variable at each time point.

The observed course of treatment parameters are presented in Table 5.2 and the estimated clinical parameters for 0 - 12 months and 0 - 48 months using linear mixed models analysis are presented in Table 5.2.

HbA_{1c}, Insulin Dose and BMI

Mean HbA_{1c} decreased significantly from 8.3 to 7.6% 12 months after the commencement of CSII [mean difference: -0.7%; 95%CI: 0.5-1.0; $p < 0.001$] and was maintained until month 48 where it slightly increased to 7.9%. Mean insulin dose also decreased significantly from 54.5 to 46.4 IU during the 48 months which followed the commencement of CSII [-8.1 IU; 95%CI: 2.7-13.5; $p < 0.001$]. These trends are illustrated in Figure 5.1. Upon engaging with CSII very little change in patients' BMI was observed over the following 48 month period [-0.3 kg/m^2; 95%CI: 1.0-1.1; $p = 0.288$].

Blood pressure

Statistically significant reductions in systolic blood pressure were observed during 48 months of engaging with CSII from 128.2 to 122.1 mmHg [-6.1 mmHg; 95%CI: 1.9-10.3; $p = 0.003$]. Significant reductions from 75.2 to 72.0 mmHg were also observed in the diastolic blood pressure of patients who engaged with CSII over a 48 month period [-3.2 mmHg; 95%CI: 0.3-6.0; $p = 0.027$]. These trends are illustrated in Figure 5.2.

Lipid profile

There were few changes in patients' total cholesterol [-0.1 mmol/L; 95%CI: -0.2-0.5; $p = 0.771$] and LDL-C [0.0 mmol/L; 95%CI: -0.3-0.3; $p = 0.990$] after 48 months of CSII therapy. Triglycerides, however, significantly decreased over 48 months of CSII use [-0.1 mmol/L; 95%CI -0.1-0.4; $p = 0.018$] and HDL-C showed a significant increase from 1.7 - 1.8 mmol/L [0.1 mmol/L; 95%CI: -0.2-0.1; $p = 0.025$] during the first 12 months of CSII use and this was maintained for a further 36 months as shown in Figure 5.3. The total cholesterol/HDL-C ratio remained largely static during 48 months of commencing CSII [0.0; 95%CI: -1.0-1.0; $p = 0.978$].

Data was also collected for lipids and lipoproteins covering the 48 months prior to initiating with the therapy. This illustrated no significant changes with: total cholesterol increasing from 4.0 to 4.3 mmol/L, LDL-C increasing from 1.9 to 2.1 mmol/L, HDL-C remaining between 1.6 and 1.7 mmol/L and triglycerides increasing from 1.0 to 1.1 mmol/L. The total cholesterol/HDL ratio increased from 2.5 to 2.7 during this period.

Insulin Dose Correlations

When looking at Table 5.3 it can be seen that insulin dose was significantly correlated with BMI; however, this positive relationship was weak [baseline: r = 0.443, p < 0.001; 12 months: r = 0.434, p < 0.001; 48 months: r = 0.252, p = 0.022]. There was also a significant negative relationship with HDL, the strength of which grew from weak to moderate as the treatment time progressed [baseline: r = -0.262, p = 0.014; 12 months: r = -0.472, p < 0.001; 48 months: r = -0.575, p = 0.001]. A significant but weak positive relationship between insulin dose and triglycerides was also demonstrated at baseline and after using the therapy for 48 months a moderate yet significant association was seen [baseline: r = 0.291, p = 0.006; 48 months: r = 0.513, p = 0.004].

Variables	Month -48	Month -36	Month -24	Month - 12	Month 0	Month 12	Month 24	Month 36	Month 48	Change between months 0–12	*P*-value (Months 0–12) (* = sig)	Change between months 0–48	*P*-value (Months 0–48) (* = sig)
HbA_{1c} (%)	N/A	N/A	N/A	N/A	8.3 (8.2, 8.5) (n=222)	7.6 (7.4, 7.8) (n=160)	7.8 (7.6, 8.0) (n=134)	7.7 (7.5, 7.9) (n=119)	7.9 (7.7, 8.2) (n=94)	-0.7 (0.5, 1.0)	**<0.001***	-0.4 (0.1, 0.7)	**<0.001***
HbA_{1c} (mmol/mol)	N/A	N/A	N/A	N/A	67.3 (65.5, 69.1) (n=170)	59.5 (57.8, 61.2) (n=160)	61.8 (59.8, 63.8) (n=133)	60.3 (58.1, 62.6) (n=119)	63.5 (61.1, 66.0) (n=93)	-7.8 (5.3, 10.3)	**<0.001***	-3.8 (0.7, 6.9)	**<0.001***
Insulin Dose (IU)	N/A	N/A	N/A	N/A	54.5 (50.8, 58.3) (n=207)	46.4 (42.7, 50.2) (n=151)	46.6 (42.1, 51.2) (n=135)	44.7 (40.8, 48.5) (n=117)	45.0 (42.2, 48.8) (n=102)	-8.1 (2.7, 13.5)	**<0.001***	-9.5 (3.6, 15.5)	**<0.001***
Systolic B.P. (mmHg)	N/A	N/A	N/A	N/A	128.2 (125.8, 130.5) (n=189)	128.0 (125.6, 130.5) (n=147)	126.1 (123.0, 129.1) (n=123)	125.2 (122.0, 128.3) (n=105)	122.1 (119.1, 125.1) (n=74)	-0.1 (-3.3, 3.5)	**0.812**	-6.1 (1.9, 10.3)	**0.003***
Diastolic B.P. (mmHg)	N/A	N/A	N/A	N/A	75.2 (73.7, 76.7) (n=189)	76 (74.4, 77.7) (n=147)	72.9 (70.9, 74.9) (n=123)	72.3 (70.0, 74.6) (n=105)	72 (69.4, 74.6) (n=74)	0.9 (-3.1, 1.3)	**0.451**	-3.2 (0.3, 6.0)	**0.027***
Total Cholesterol (mmol/L)	4.0 (3.7, 4.4) (n=14)	4.3 (3.8, 4.8) (n=21)	4.3 (3.9, 4.7) (n=18)	4.2 (3.9, 4.5) (n=45)	4.3 (4.1, 4.5) (n=139)	4.4 (4.2, 4.6) (n=90)	4.2 (4.0, 4.4) (n=75)	4.3 (4.08, 4.54) (n=64)	4.2 (4.1, 4.5) (n=47)	0.1 (-0.3, 0.2)	**0.771**	-0.1(-0.2, 0.5)	**0.440**
Triglycerides (mmol/L)	1.0 (0.5, 1.5) (n=13)	1.4 (0.8, 2.1) (n=16)	1.4 (1.0, 1.8) (n=14)	1.2 (1.0, 1.4) (n=39)	1.1 (1.0, 1.2) (n=92)	1.1 (0.9, 1.3) (n=66)	1.1 (0.8, 1.3) (n=58)	1.0 (0.9, 1.2) (n=43)	1.0 (0.8, 1.1) (n=38)	0.0 (-0.2, 0.2)	**0.655**	-0.1 (-0.1, 0.4)	**0.018***
LDL-C (mmol/L)	1.9 (1.7, 2.2) (n=13)	2.3 (1.7, 2.7) (n=15)	2.0 (1.6, 2.5) (n=14)	2.1 (1.8, 2.4) (n=40)	2.1 (1.9, 2.2) (n=92)	2.2 (2.0, 2.4) (n=65)	2.0 (1.8, 2.2) (n=55)	2.1 (1.9, 2.4) (n=43)	2.1 (1.8, 2.3) (n=38)	0.1 (-0.4, 0.1)	**0.353**	0.0 (-0.3, 0.3)	**0.990**
HDL-C (mmol/L)	1.7 (1.5, 2.0) (n=13)	1.6 (1.3, 1.8) (n=16)	1.6 (1.3, 1.9) (n=14)	1.6 (1.4, 1.7) (n=40)	1.7 (1.6, 1.8) (n=92)	1.8 (1.6, 1.9) (n=66)	1.7 (1.6, 1.9) (n=57)	1.9 (1.7, 2.1) (n=45)	1.7 (1.5, 1.8) (n=38)	0.1 (-0.2, 0.1)	**0.025***	0.0 (-0.2, 0.2)	**0.639**
TC/HDL-C ratio	2.5 (2.0, 3.0) (n=13)	3.0 (2.4, 3.7) (n=16)	2.9 (2.4, 3.5) (n=14)	2.8 (2.5, 3.1) (n=40)	2.7 (2.5, 2.8) (n=92)	2.7 (2.4, 2.9) (n=66)	2.7 (2.4, 3.0) (n=57)	2.6 (2.3, 2.8) (n=45)	2.7 (2.4, 2.9) (n=38)	0.0 (-0.9, 0.9)	**0.090**	0.0 (-1.0, 1.0)	**0.978**
BMI (kg/m^2)	N/A	N/A	N/A	N/A	26.1 (25.4, 26.8) (n=207)	25.8 (25.1, 26.6) (n=155)	25.9 (25.2, 26.7) (n=139)	26.2 (25.3, 27.0) (n=118)	26 (24.8, 26.7) (n=107)	-0.3 (-0.7, 1.3)	**0.107**	-0.3 (1.0, 1.1)	**0.288**

Table 5.2 - Clinical characteristics before and after the commencement of CSII (Data are presented as means with 95%CI and the appropriate n values)

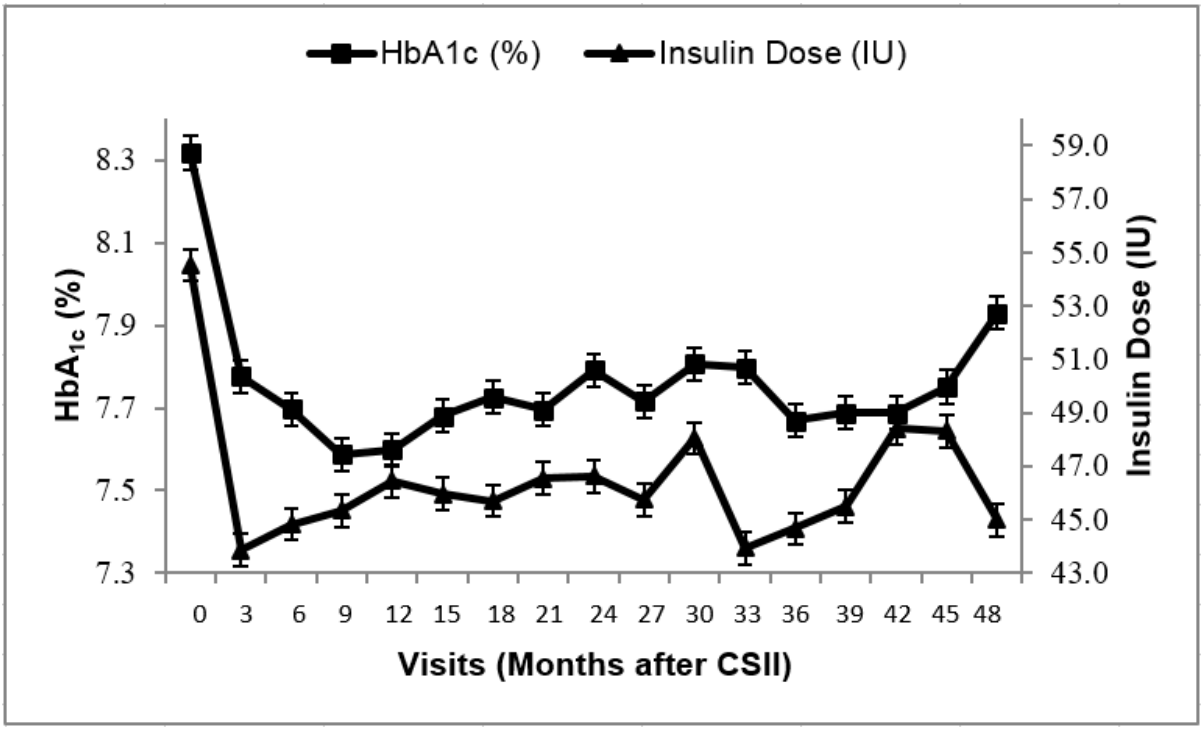


Figure 5.1 – HbA_{1c} (%) and insulin dose (IU) over a 48 month period after the commencement of CSII therapy.

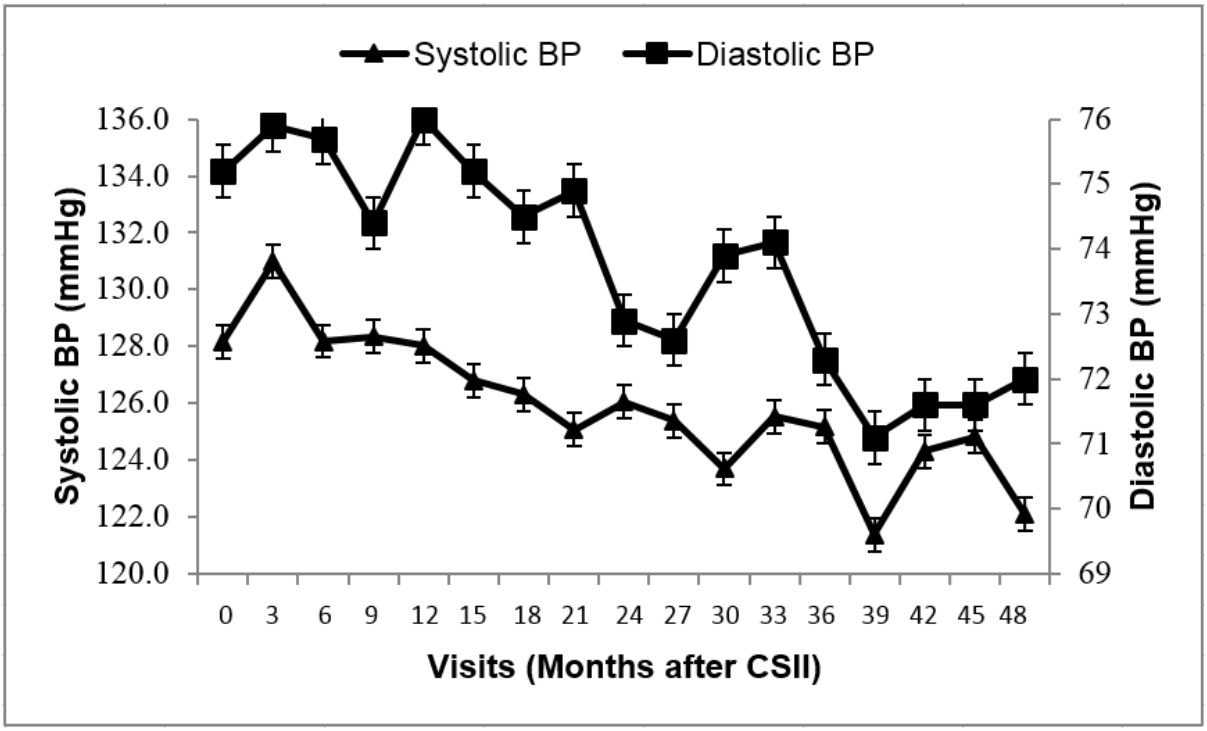


Figure 5.2 – Systolic and diastolic blood pressure (mmHg) over a 48 month period after the commencement of CSII therapy.

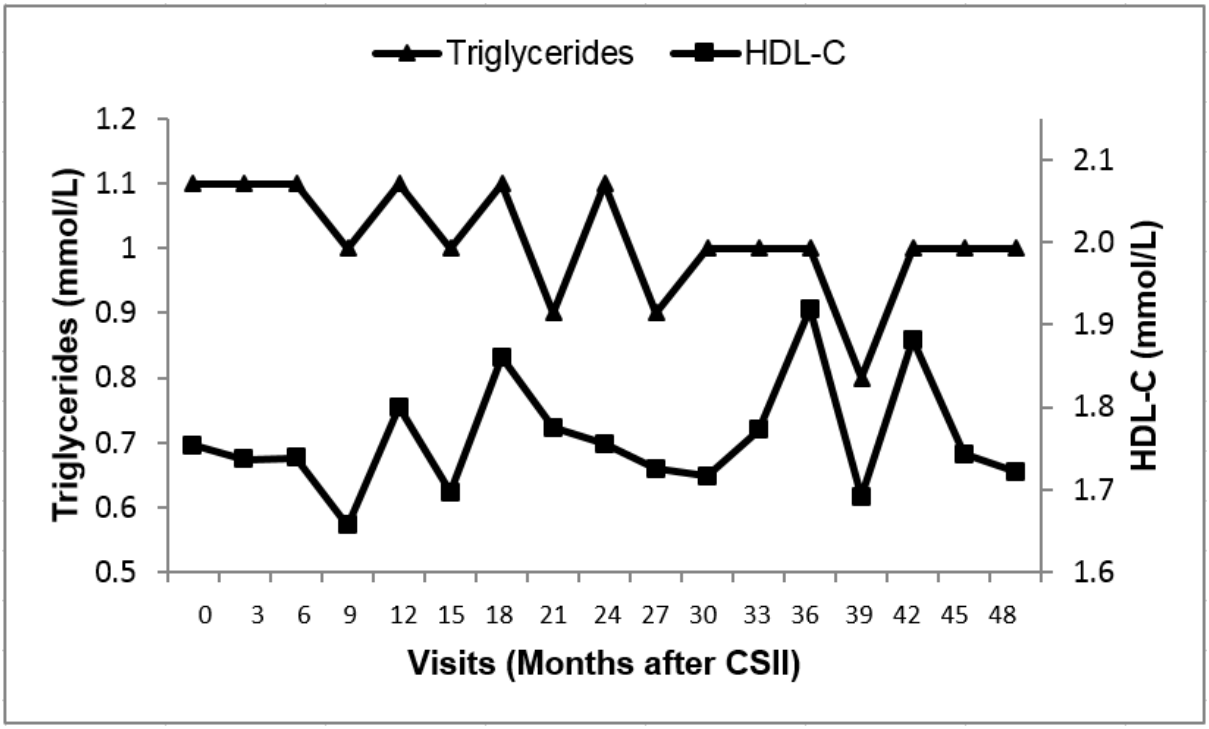


Figure 5.3 – Triglycerides (mmol/L) and HDL-C (mmol/L) over a 48 month period after the commencement of CSII therapy.

Variable	Baseline		12 months		48 months	
	r-value	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value
BMI	0.443	<0.001*	0.434	<0.001*	0.252	0.022*
Total Cholesterol	0.158	0.076	-0.165	0.152	0.009	0.958
LDL-C	0.211	0.050	0.084	0.544	0.259	0.175
HDL-C	-0.262	0.014*	-0.472	<0.001*	-0.575	0.001*
TC/HDL-C Ratio	0.357	0.001*	0.341	0.015*	0.176	0.298
Triglycerides	0.291	0.006*	0.148	0.275	0.513	0.004*
HbA_{1c}	0.035	0.620	0.085	0.324	-0.039	0.749
Systolic blood pressure	0.178	0.020*	0.160	0.079	0.193	0.155
Diastolic blood pressure	-0.019	0.807	0.068	0.461	0.097	0.476

Table 5.3 – Correlations of standard clinical measures against insulin dose at baseline and after 12 months and 4 months of CSII use (Spearman correlation used for all tests and significance <0.05 denoted by *).

5.6 Discussion

This audit is one of the few pieces of evidence focussing on clinical parameters of risk in patients with T1D using CSII over an extended time period. Our findings indicate HbA_{1c} is significantly reduced within the first 12 months of engaging with the therapy and that this is maintained throughout the majority of the treatment (Figure 5.1). Despite these positive improvements mean HbA_{1c} remained marginally above the national treatment target of between 6.5 and 7.5%. It is debateable whether this is a failure or an achievement when considering only 27.3% of UK hospitals documented the average HbA_{1c} of their patients with T1D to be <7.5% (HSCIC, 2014). Furthermore, only 7.5% recorded an average of <6.5%, with the Royal Liverpool Hospital narrowly missing these targets for patients with T1D in general, and according to this data, those using CSII (*Ibid*). That said, the improvements shown may still transpire to clinical benefits such as reductions in microvascular disease, with previous research from the Diabetes Control and Complications Trial suggesting a 10% lower HbA_{1c} may relate to a 43% reduction in retinopathy risk (DCCT Research Group, 1995).

In addition to HbA_{1c} reductions, the amount of insulin used by patients also significantly decreased during the anterior 12 months of CSII therapy and was maintained thereafter (Figure 5.1). This is a welcome finding as the large insulin doses typically used by patients with T1D are often regarded as above physiological norms and potentially detrimental (Unger, 2010). Although reductions in both HbA_{1c} and insulin dose upon commencing the therapy are positive findings they are somewhat unsurprising as initial improvements are well documented (Pickup, 2002). Furthermore, the long-term maintenance of these parameters is in agreement with more recent literature also showing a sustained plateau of improved glycaemic control and insulin requirements over 3 - 4 years (Rosenlund, 2015; Melidonis, 2016).

These reductions in insulin dose may potentially lead to decreased fat deposition and subsequent weight loss and this postulate has been demonstrated in previous studies examining patients using CSII therapy (Bode, 2002; Pickup, 2005; Morrison, 2008). Unfortunately, our findings were not in agreement, with data at 48 months highlighting how CSII patients' BMI remained persistently above 25 kg/m^2

throughout, indicating that the majority of patients were either overweight or obese. Similar findings have also been shown by Melidonis (2016) who reported no change in BMI over 4 years of CSII use; however, mean BMI also remained consistently >25. Although the patients in the current study did not gain weight upon commencing the therapy the findings are still of concern due to the risks associated with raised BMI; with some of which, such as CVD, being further exacerbated by T1D (Redondo, 2015). Furthermore, it should also be noted that our findings give little insight into patients' lean mass status and it is possible that although BMI remained static lean mass may have altered as this is insulin mediated (Umegaki, 2015). In fact the correlations shown in Table 5.3 illustrate a weak/moderate, positive relationship between insulin dose and BMI which was statistically significant and although not demonstrating a causal link still serve to illustrate a potential avenue for future research in this population.

In addition to quantitative reductions in patients' HbA_{1c} and insulin dose, the findings also demonstrate significant improvements in blood pressure after the commencement of CSII. As previously mentioned, the majority of patients were overweight or obese and their acceptance onto CSII may be suggestive of their inability to achieve glycaemic control, which could imply many may be suffering from metabolic syndrome (Chillarón, 2010). If this is the case the results suggest that prior to the commencement of the therapy the majority of patients were borderline hypertensive (according to NICE guidelines of 130/80mmHg); however, over the subsequent 48 months gradual reductions in blood pressure can be seen into the normal range (NICE, 2015). These significant decreases in both systolic and diastolic blood pressure, which can be seen in Table 5.2 and Figure 5.2, are favourable findings when considering that only 73.4% of patients with T1D achieve targets of 140/90mmHg and the associations of blood pressure with micro and macro-vascular diseases (HSCIC, 2014; Maahs, 2005). Despite this it should be noted that these long-term changes in blood pressure are atypical and have not been previously reported elsewhere. Furthermore, it is difficult to accurately hypothesise an influencing mechanism. Medication would usually appear an obvious candidate to facilitate such a decrease in blood pressure; however, pharmacologically driven changes would typically be expected to occur over a much shorter time period than 48 months and would almost certainly be more

dramatic than the gradual demonstrated decline. Moreover, correlation tests were carried out to determine if the reduced insulin requirements of CSII therapy were associated any of these changes. The findings from these tests, shown in Table 5.3, revealed that only the relationship between insulin dose and systolic blood pressure at baseline reached statistical significance and that the relationship was weak. The deleterious effect of hypoglycaemia upon blood pressure has also been previously shown in the literature; therefore, another reasonable proposition may be that any reduction in hypoglycaemia mediated by the blood sugar stabilising effect of CSII may too be contributing towards these improvements in blood pressure (Sommerfield, 2007). Other potential influencing factors may be lifestyle improvements such as increased physical activity and positive dietary change together with increased education and more contact with healthcare professionals; however, none of these were measured but their possible influence justifies additional attention.

On examination of the patients' lipid profiles it can be seen that for 48 months prior to the initiation of CSII total cholesterol, LDL-C, total cholesterol/HDL-C ratio and triglycerides changed very little (although the change in triglycerides was statistically significant). Likewise, these levels were maintained throughout the initiation of the therapy, indicating a generally well-managed group in this respect. This profile was further accentuated by data, illustrated in Figure 5.3, showing that both before and after the commencement of CSII levels of HDL-C were much higher than current recommendations of >1.0 mmol/L, possibly suggestive of a group somewhat protected against CVD. Furthermore, Table 5.3 shows an initially weak but significant negative relationship between insulin dose and HDL-C and positive relationship between insulin dose and triglycerides. These relationships both became moderate after 48 months of treatment, possibly suggesting that the reduced insulin requirements of CSII may have a positive mediating effect. A weak yet significant positive association between insulin dose and total cholesterol/HDL-C ratio further implies this. Despite these perceived positive findings research shows patients with T1D remain at an increased risk from CVD disorders (Brindisi, 2010). Furthermore, this is not the first time raised levels of HDL-C have been reported in this population, with other authors highlighting its occurrence and how it is often observed in tandem with elevated levels of the atheroprotective HDL_2

subfraction, therefore adding further substance to this unusual yet frequently observed clinical conundrum (Vergès, 2009). Recent efforts to investigate the mechanisms driving this phenomenon have revealed that not all HDL particles are the same and that interestingly in patients with T1D these particles often undergo glycoxidative changes causing abnormalities rendering them dysfunctional, thus reducing or abolishing their potential for reverse cholesterol transport, cholesterol efflux and in particular HDL's antioxidant capabilities (Denimal, 2015). This leaves concern that these findings, despite presenting a positive depiction of patients' cardiovascular state, may not be as they initially seem and warrant further investigation.

Despite offering some interesting findings this audit is not without its issues. Patients' medication data in particular would have been most useful to determine the role of pharmacological agents in the changes described herein; however, details were stored at patients' G.P. surgeries and collection of these was out of the remit of this exercise. This was in part one of the main limitations of this audit as the authors only had access to data which was collected retrospectively and with little thought given to its future analysis. As such the conditions during which the original measurements were carried out are unclear and may therefore cast doubt over the quality of the results. A particularly palpable example is the measurement of blood pressure which is well known to be affected by various external influences (Pickering, 2005). In addition to this patients also invariably missed appointments, moved from the area, died or simply 'disappeared' for periods of time. The substantial amounts of missing data therefore explain the disparity in sample size before and after the commencement of CSII. Also, as structured education and increased contact with healthcare professionals was offered alongside the initial commencement of CSII the sample size can be seen to substantially increase; however, measurements taken for all markers diminished over the following years. Despite this caution should be taken before assuming specific causes for sample size variabilities and it may be useful to consider that this data reflects an intensive period of diabetes management which involves the fine tuning of insulin doses to ensure optimal care. Also, when comparing the findings to results from the National Diabetes Audit, which highlighted how only 49.8% of patients attending the Liverpool CCG achieved screening for all care

processes (which is nevertheless above the national average of 41.3%) perhaps indicates that work must be done to investigate the reasons behind this reduced follow-up attendance and find ways of reducing future attrition (HSCIC, 2014). Furthermore, it should also be noted that the findings are from one trust and as such cannot be extrapolated to others.

Despite these limitations the findings illustrate that patients undergoing CSII therapy can achieve improvements in glycaemic control and blood pressure whilst using less insulin and that these changes may be accompanied with little or no adverse impact upon BMI or lipid profile. It should also be made clear that regardless of these positive findings further work remains to be done to elucidate the validity of these trends, the mechanistic components which may be driving them and improvements to enhance patient outcomes.

Chapter 6

Eating Behaviours

6 - Eating Behaviours

6.1 Abstract

Continuous subcutaneous insulin infusion (CSII) offers patients the potential to liberalise their dietary behaviours; however, research investigating this is sparse and dated. To remedy this food frequency questionnaires (FFQs) were given to patients from the Royal Liverpool hospital who had been using either CSII (n = 40) or MDI (n = 20) for a year or longer. A subgroup of CSII (n = 11) and MDI (n = 9) patients were also asked to complete a 5 day food diary. All patients gave permission for the author to examine their medical records to document their basic clinical parameters. After analysis, the findings showed that some nutrients such as fibre and iron in females failed to meet the RNI and that there were subtle differences between the treatment groups. For example, the results from the FFQ showed that mean energy intake was below the estimated average requirement (EAR) for both CSII and MDI groups (1717.7 kcal/day vs. 1886.4 kcal.day; p = 0.416). This finding was also shown in the food diaries and given that both the majority of CSII and MDI patients were either overweight or obese (27.1 kg/m^2 vs. 25.9 kg/m^2 respectively) suggests the occurrence of underreporting; which was confirmed by the Goldberg equations. Total carbohydrate (CHO) consumption was shown by both the FFQs and food diaries to be below the RNI of 50%, however it should be noted that consumption of total sugars was above the RNI for males and female using both CSII and MDI. This may be partly explained by the consumption of fruit which was also higher in those using CSII. Despite these differences the diets between the two groups were largely homogenous, with no statistically significant variables. This suggests that patients using CSII chose not to take advantage of the flexibility the device infers and did not change their diet to one more detrimental to health upon commencing the therapy.

6.2 Introduction

Role of diet for the treatment of T1D

Along with insulin, nutrition is delicately entwined in the management of T1D and the implication of diet in the quest for normoglycaemia is far reaching. On one hand the consumption of food and drink provides a complex 'package' of nutrition required for human survival and health, yet on the other foodstuffs are often a prominent source of carbohydrates (CHO); the component of food which most affects blood glucose and the management of which is of chief concern for patients with the disease.

Although diabetes is not a recently discovered phenomenon, with Egyptian records of cases dating back to 1500BC, it was not until 1797 that a Scottish physician with an interest in diabetes named John Rolo had the pioneering notion that a diet high in fat and protein and low in vegetables and grains could be used to limit the symptoms of the disease (Stylianou, 2008). This was a success and this principle was elaborated on by L. Traube who confirmed in 1816 that it was indeed the dietary intake of CHO and its subsequent digestion which results in the increased amounts of sugar typically seen in the urine of patients with diabetes and that reducing CHO consumption can alleviate this (Guthrie, 2009). Over the following century this concept bloomed and a number of dubious 'fad' diets ensued, including the 'milk diet' and the 'oatmeal cure' (Moran, 2004). Little explanation is required to describe the substance of these diets and the fact that their use was relatively short-lived is perhaps an indication of the quality of their results (*Ibid*).

Despite the obvious failure of many of these unconventional dietary approaches in 1915 Frederick Allen, a diabetes specialist from the U.S., together with a physician named Elliott P. Joslin devised perhaps the most severe dietary approach to date for the treatment of diabetes. This consisted of extreme calorie restriction; often referred to as a starvation diet. Modern recalculations suggest that 70% of calories consumed by patients undergoing the diet were derived from fat, 10% from CHO and 20% from protein and although not providing a cure the pair had initial success in prolonging the lives of patients (Westman, 2006). Despite offering some respite from diabetes, the patients were instead condemned to the myriad of

new hazards associated with malnutrition and the obvious risk of death by starvation (Mazur, 2011). Adherence to the diet was understandably difficult and physicians (including Allen and Joslin) and patients alike resented the brutality of the therapy; however, it had a moderate amount of success in extending life and allowed many patients to survive, albeit miserably, until insulin came into production (Sawyer, 2009).

After the treatment of diabetes with insulin became commonplace the medical community were slow to realise that dietary CHO could be increased without immediate risk of hyperglycaemia. Dr William Sansum took note of this and in 1926 proceeded to increase the CHO intake of his patients to great effect (Tompkins, 1977). His patients appreciated the increased dietary flexibility and the ability to lead a conventional life (*Ibid*). This was further enhanced in 1930 when Karl Stolte developed a clear and easy to understand method of insulin therapy consisting of 3 or more injections before meals and in return patients were allowed to consume a 'free diet' which was recommended to be high in CHO (Howorka, 1991).

In the following years confusion reigned regarding the superiority of different dietary approaches for the treatment of T1D, with the ADA initially suggesting that a low CHO diet was an integral part of diabetes care which could not be avoided; yet 12 years later in 1971, based upon evidence implicating dietary fat in heart disease, the advice was changed to the promotion of a high CHO, low fat diet (Sawyer, 2009). These shifting recommendations were typical of the era and as the use of insulin became more established and patients routinely enjoyed longer lives it became clear that although mortality caused directly as a result of diabetes was decreasing, patients were now dying from complications; namely vascular disease (*Ibid*). This presented important questions regarding nutrition. What is the best diet for the treatment of T1D and what dietary advice should patients receive? Although over the years many combinations of macronutrient proportions have been tested, the stark reality remained. For the first time evidence based dietary guidelines were required with a view to improving not only glycaemic control, but also reducing the risks of mortality from these complications. This resulted in a series of guidelines developed by different agencies which have evolved over the

years as evidence has become available; however, rather than converging to a consensus these recommendations may have created even more confusion.

Nutritional Guidelines

Although the ADA had been producing dietary guidelines since 1971 it was not until 1982 that Diabetes UK (then known as the British Diabetic Association) developed the first evidence based dietary recommendations for those with diabetes (Nuttall, 1979; British Diabetic Association, 1982). Over the following years both organisations, along with the European Association for the Study of Diabetes (EASD), released subsequent 'best practice' guidelines as more research became available (Lean, 1991; DNSG Study Group, 2000; ADA, 2002; Connor, 2003; Mann, 2004; Bantle, 2008; Evert, 2013; Evert, 2014; ADA, 2015). Although this review will not describe the differences between each of these historical guidelines in detail a summary from the last 15 years can be seen in Table 6.1 – 6.3.

Diet Component	ADA (2002)	ADA (2003)	ADA (2004)	ADA (2008)	ADA (2013)	ADA (2014)	ADA (2015)
Sucrose	No restriction. Sucrose should be substituted for other CHO sources	No restriction. Sucrose should be substituted for other CHO sources	No restriction. Sucrose should be substituted for other CHO sources	Sucrose should be substituted for other CHO sources. Care should be taken to avoid excess energy intake	Sucrose should be substituted for other CHO sources and consumption minimised	Sucrose should be substituted for other CHO sources and consumption minimised	Sucrose should be substituted for other CHO sources and consumption minimised
Fat							25 – 35%
Saturated fat	<10% total energy, <7% total energy if dyslipidaemia	<10% total energy, <7% total energy if dyslipidaemia	<10% total energy, <7% total energy if dyslipidaemia	<7% total energy and trans fat intake should be minimised	<10% total energy intake and trans fat intake should be minimised	<10% total energy intake and trans fat intake should be minimised	<10% total energy intake and trans fat intake should be minimised
PUFA	<10% total energy	<10% total energy	<10% total energy				
n-3 PUFA	Two to three portions of oily fish per week	Two to three portions of oily fish per week	Two to three portions of oily fish per week	Two or more servings of oily fish per week	At least two servings per week	At least two servings per week	At least two servings per week
MUFA	60 – 70% total energy	60 – 70% total energy	60 – 70% total energy				
Cholesterol	<300 mg/d, <200 mg/d if dyslipidaemia	<300 mg/d, <200 mg/d if dyslipidaemia	<300 mg/d, <200 mg/d if dyslipidaemia	<200 mg/d	<300 mg/d	<300 mg/d	<300 mg/d
Fibre	A variety of fibre containing foods should be chosen.	A variety of fibre containing foods should be chosen.	≥5 g per serving (14 g/1000 kcal)	14 g/1000 kcal	14 g/1000 kcal	14 g/1000 kcal	14 g/1000 kcal
Plant stanol & sterol	~2 g/d	~2 g/d	~2 g/d	~2 g/d	1.6 – 3g per day	1.6 – 3g per day	
Protein	15 – 20% total energy, 0.8 g/kg in overt nephropathy	15 – 20% total energy, 0.8 g/kg in overt nephropathy	15 – 20% total energy, 0.8 g/kg in overt nephropathy	15 – 20% total energy, 0.8 g/kg in overt nephropathy			

Table 6.1 – USA Dietary guidelines from the last 15 years devised by the ADA

Diet Component	ADA (2002)	ADA (2003)	ADA (2004)	ADA (2008)	ADA (2013)	ADA (2014)	ADA (2015)
Alcohol	Max 1 drink per day for women, max 2 drinks per day for men	Max 1 drink per day for women, max 2 drinks per day for men	Max 1 drink per day for women, Max 2 drinks per day for men	Max 1 drink per day for women, max 2 drinks per day for men	Max 1 drink per day for women, max 2 drinks per day for men	Max 1 drink per day for women, max 2 drinks per day for men	Max 1 drink per day for women, max 2 drinks per day for men
Ca	1000 – 1500 mg/d	1000 – 1500 mg/d	1000 – 1500 mg/d				
Na (Table salt & Nacl)	2400 mg/day (100 mmol) or 6 g/d	2400 mg/day (100 mmol) or 6 g/d	2400 mg/day (100 mmol) or 6 g/d	<2300 mg/day	<2300 mg/day	<2300 mg/day	<2300 mg/day

Table 6.1 (Con't)

Diet Component	EASD (2000)	EASD (2004)
CHO	40 – 60% total energy	45 – 60% total energy
Sucrose	<10% total energy	<10% total energy
Fat	25 – 35% total energy	<35% total energy
MUFA	10 – 20% total energy	10 to 20% total energy
Saturated fat	<10% total energy	<10 % total energy
PUFA	<10% total energy	<10% total energy
n-6 PUFA		<10% total energy
n-3 PUFA	Oily fish once per week. Olive, rapeseed or soybean oil. Nuts & some green vegetables	Two to three servings of oily fish per week. Rapeseed or soybean oil, nuts and green leafy vegetables
MUFA	60 – 70% total energy	
Cholesterol	<300mg/d	<300 mg/d
Fibre	CHO containing foods which are rich in fibre are recommended	>40 g/d (or 20 g/1000 Kcal/day)
Protein	10 – 20% total energy. 0.8g/kg per day	10 – 20% total energy. 0.8 g/kg per day
Antioxidants	Vitamins A, C and E & flavonoids. Not in pharmaceutical quantities	Vitamins C, flavonoids, polyphenols, phytic acid and trace elements are encouraged
Folate	Regular consumption of foods high in folate	
Alcohol	<15 g/day for women and <30 g/day for men	<10 g/day for women and <20 g/day for men
Na (Table salt & Nacl)	<6 g/day table salt	<6 g/day table salt

Table 6.2 – European Dietary guidelines devised by the EASD

Diet Component	DUK (1982)	DUK (1991)	DUK (2003)	DUK (2011)
CHO	No recommendations, although CHO should not be 'regulated at an unduly low level' and the 'majority should be polysaccharides'	50 – 55% total energy	40 – 60% total energy	
Sucrose	No specific recommendations, although 'avoidance of rapidly absorbed CHO' is recommended	<25 g/day	10% total energy eaten in the context of a healthy diet	
Fat	<35% total energy	30 – 35% total energy	<35% total energy	35 – 40% total energy
MUFA		10 – 15% total energy	10 – 20% total energy	
Saturated fat	No recommendations, but consumption should be reduced	<10% total energy	<10% total energy	
PUFA		<10% total energy	<10% total energy	
n-3 PUFA		Marine fatty acids are not recommended. Intake of oily fish is reasonable as a substitute for meat and cheese products	Oily fish one to two times weekly. Fish supplements not recommended	Oily fish twice weekly. Supplements of up to 3g per day is Type 2 diabetes
MUFA			60 – 70% total energy	
Cholesterol		<300 mg/day		
Fibre	A 'high fibre diet' is recommended	<30 g/day		
Plant stanol & sterol			2 g/d	2 – 3g/day
Protein		10 – 15% total energy	≤1 g/kg, May benefit from <1 g/kg with nephropathy	
Antioxidants			Encourage foods naturally high in vitamins & antioxidants	
Alcohol	Acceptable to drink, although moderation is recommended	<3 units per day for men; <2 units per day for women	Moderate intake (one to three units daily)	Moderate intake (one to two units daily)
Na (Table salt & Nacl)	Should not consume 'more sodium than consumed by a non-diabetic'	<6 g/day	<6 g/d	<6 g/day

Table 6.3 – UK Dietary guidelines devised by Diabetes UK

The most recent UK nutrition recommendations for patients with diabetes were outlined in 2011 by Diabetes UK (Dyson, 2011). These took into account the evidence which had accumulated since the publication of the previous 2003 document. These guidelines are currently being used to inform best practice in the UK and as such it is important that some of the most prominent recommendations receive a more detailed description so the reader might understand the current guidelines in relation to the broader treatment of T1D.

Carbohydrates

CHO is often thought of as the nutritional mainstay of glycaemic control and ever since the first set of evidenced-based dietary guidelines by Diabetes UK were issued in 1982 the benefits of consuming a diet rich in CHO have been at the fore. Previous recommendations in 2003 suggested that 40 - 60% of total energy intake should comprise of the macronutrient; a challenging target to achieve which signified the end of guidelines advocating CHO restricted diets and instead represented a shift in focus towards recommendations similar to those offered to the general population. The recent guidelines from 2011 are no different; however, specific numerical recommendations were abandoned due to a lack of confirmative evidence, with intervention studies suggesting the dietary manipulation of CHO intake actually has little effect on glycaemic control (Dyson, 2011). Despite this it is clear that the actual amount ingested very much determines post-prandial blood glucose and therefore the insulin required to metabolise this should be carefully considered; ideally through the use of an appropriate CHO counting strategy (*Ibid*). Additionally, it is also clear that the type of CHO is an important factor for glycaemic control and as such the guidelines suggest patients consume a diet rich in both low glycaemic index (GI) foods and fibre (Dyson, 2011). Furthermore, the recommendations also highlight that sucrose has no different effect on glycaemic control than other types of CHO and that fructose may be used as a replacement to decrease post-prandial glycaemia and sweeteners to reduce $HbA_{1c,}$ if consumed within the daily intake levels (*Ibid*).

Fat

The intake of fat for patients with diabetes is recommended to comprise of 35 - 40% of total energy intake and that reductions in saturated and trans fats and their

replacement with monounsaturated fats is thought to be beneficial for minimising cardiovascular disease (CVD) risk (Dyson, 2011). Furthermore, previous recommendations for polyunsaturated fat intake to comprise of 10 – 20% total energy have been omitted from the most recent guidelines due to a meta-analyses by Ramsden (2010) suggesting that an increase in n-6 fatty acids without a corresponding increase in n-3 fatty acids is associated with increased mortality from CVD (Connor, 2003). Consequentially recommendations for the consumption of oily fish, high in n-3 fatty acids, has increased from 1 to 2 portions per week to at least twice per week and that despite conflicting evidence regarding adverse effects these oils may have on blood lipids the benefits are currently thought to outweigh the risks (Dyson, 2011). Despite recommendations it should be noted that this is an ongoing debate, with some research suggesting that the only adverse effects of n-3 fatty acids may be an increase in LDL-C; however, the particles have been shown to be less prone to oxidative modifications and therefore likely to be less atherogenic (De Caterina, 2007). Furthermore, fewer risks may also be posed if these changes are accompanied by an increase in particle size and without a corresponding increase in particle number; however, the evidence is still emerging regarding these aspects (Sneiderman, 2014).

Protein

As mentioned previously, the authors explain that there is no true consensus regarding the ideal proportions of macronutrients in the diet to achieve optimal glycaemic control and there is some evidence suggesting that excessive protein intake in the form of meat may be associated with an increased risk of T2D and CVD (Dyson, 2011). Therefore the protein recommendations offered by Diabetes UK have remained in a state of flux, with each set of updated guidelines differing as new evidence becomes available (British Diabetic Association, 1982; Lean, 1991; Connor, 2003). The most recent 2011 recommendations do not deviate from this trend and rather than suggesting an optimal intake of protein instead opt to omit a recommendation altogether (Dyson, 2011).

Fibre

Although the health benefits of fibre upon lipid profile, gastrointestinal health and CVD risk are well documented there is little conclusive evidence to suggest a

beneficial effect on glycaemic control; as such there are no specific quantitative recommendations for those with diabetes (Dyson, 2011). The authors of the most recent Diabetes UK guidelines instead advise that efforts should be made for patients to attempt to meet the dietary reference values (DRV) for the general population (*Ibid*).

Salt

Diabetes UK stand by their long-standing recommendation of <6 g salt per day in the 2011 guidelines (Dyson, 2011) This has been a permanent fixture in the document since 1991 and the blood pressure lowering effects associated with decreasing salt intake are well documented (*Ibid*; He, 2007). In fact evidence suggests that reducing salt intake to <3 g per day would have further benefits, but the guideline authors illustrate that this would require significant contributions from the food industry (*Ibid*). Furthermore, recent National Diet and Nutrition Survey (NDNS) data highlighting how the UK population are still consuming an average of 7.2 g salt per day and despite the beneficial effects, illustrates how recommendations of 6 g per day may not be an optimum target, but rather a more realistically achievable aim (NDNS, 2014).

Implications of CSII upon diet

Although a critical appraisal of the evidence concerning CSII and diet has already been presented in the Literature Review chapter (see page 30), it is important to briefly reiterate some of the most contentious points as these form the rationale for the present study. The introduction of CSII may be associated with the opportunity for patients to relax their diet and there is dated evidence to suggest that patients take advantage of this without detrimental effects; however, the treatment methods and technology used throughout these studies is now antiquated. Therefore it is unknown if commencing the therapy using modern CSII treatment regimens and technology has any impact upon the eating behaviours of patients.

6.3 Aims and Objectives

Aim

This aim of this section of the study is to determine if the use of CSII has any impact upon eating behaviours when compared to those using MDI.

Objectives

- To determine basic patient characteristics through an assessment of participant medical records.

- To assess the eating behaviours of patients using either CSII or MDI therapy using food frequency questionnaires and food diaries.

6.4 Methods

An overview of the methods used to determine the eating behaviours of patients who participated in the cross-sectional study are described in the General Methods chapter (see page 45). In brief, food frequency questionnaires (FFQs) and 5 day weighed food diaries were used to elucidate the diets of patients using either CSII or MDI (Examples can be seen in appendices 12.5). The data resulting from these dietary assessment methods allowed the author to determine the mean dietary intake of a variety of macro and micronutrients which were then compared by treatment group against percentage energy intake and/or appropriate dietary reference values (DRV). Furthermore, data resulting from the FFQs enabled food items to be separated into discreet categories, allowing comparisons of consumed food types to be made between treatment groups.

In addition to dietary information, basic characteristics (i.e. age and sex) of the participants were recorded from their medical records. This data allowed the author to not only recognise the attributes of the sample, but also split the dietary assessment data by gender to reveal any gender-specific differences.

Written consent was taken from all participants who took part in this section of the study. It should also be noted this chapter will only describe the dietary findings from the cross-sectional study. Longitudinal dietary data will be described later on in this the in the ‘case studies’ chapter (see page 206).

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences (SPSS) (v.21). Initially the data was subjected to descriptive statistics; after which normality was determined by using the Shapiro-Wilks test. Any data which could be normalised using a log10 transformation was then analysed using Student's *t*-test (the assumption of homogeneity of variance was also tested in this instance). Any data which could not be normalised was subjected to non-parametric Mann-Whitney *U* tests. All findings with a *p*-value <0.05 were deemed to be statistically significant.

To discover if any underreporting was occurring the Goldberg equations were used. The outcome of these equations were then used to determine if the ratio of reported energy intake compared to basal metabolic rate fell within or outside predefined cut-off values. Any ratios which fell outside these parameters indicated either under or over reporting.

The formulas used to produce the cut-off values are shown in Figures 6.1 and 6.2:-

$$\mathrm{EI_{rep}{:}BMR} > \mathrm{PAL} \times \exp\left[\mathrm{s.d._{min}} \times \frac{(S/100)}{\sqrt{n}}\right]$$

$$\mathrm{EI_{rep}{:}BMR} < \mathrm{PAL} \times \exp\left[\mathrm{s.d._{max}} \times \frac{(S/100)}{\sqrt{n}}\right]$$

Figure 6.1 – Goldberg equations (adapted from Black, 2000)

Before these formulas could be used the following values had to be determined and some assumptions made.

EI_{rep} - Energy intake (derived from findings).

BMR - Basal metabolic rate (estimated using the Schofield equations) (Schofield, 1985).

PAL - Physical activity level (estimated at 1.55 for light activity as the actual value was not known; however, this is an acceptable substitute) (Black, 2000).

exp - Exponential function.

s.d.$_{min}$ - -2 for 95% C.I. or -3 for 99.7% C.I.

s.d.$_{max}$ - +2 for 95% C.I. or +3 for 99.7% C.I.

n - Sample size.

S – *S*-factor is calculated using the following equation:-

$$S = \sqrt{\frac{CV^2_{wEI}}{d} + CV^2_{wB} + CV^2_{tP}}$$

Figure 6.2 – *S* factor equation (adapted from Black, 2000)

Before this formula could be used the following values had to be determined and some assumptions made.

CV^2_{wEI} - Within-subject coefficient of variation in energy intake (estimated at 23% which is an acceptable approximation) (Black, 2000).

CV^2_{wB} - Coefficient of variation of repeated BMR measurements of precision of estimated compared with measured BMR (estimated at 8.5% which is an acceptable approximation) (Black, 2000).

CV^2_{tP} - The coefficient of variation derived from the mean and standard deviation of a study and includes true between subject variation, an element of within-subject variation and methodological errors (estimated at 15% which is an acceptable approximation) (Black, 2000).

d – Number of days of dietary assessment.

6.5 Results

Sample Characteristics

All patients (n = 60) (40 using CSII vs 20 using MDI) agreed to complete an FFQ. A subsample (n = 20) patients (11 using CSII vs 9 using MDI) agreed to complete a food diary. Selected sample characteristics are described in the tables below (see Tables 6.4 and 6.5).

	CSII (n = 40)	**MDI (n = 20)**
Sex	13 male / 27 female	7 male / 13 female
Age (Years)	49.4 (± 14.9)	44.9 (± 17.3)
BMI (kg/m^2)	27.1 (± 4.7)	25.9 (± 3.4)
HbA_{1c} (%)	7.7 (± 1.3)	8.5 (± 1.6)

Table 6.4 – Basic sample characteristics of participants who completed FFQs. (Data is either presented as frequencies or mean averages with standard deviation).

	CSII (n = 11)	**MDI (n = 9)**
Sex	4 male / 7 female	3 male / 6 female
Age (Years)	42.8 (± 16.5)	56.1 (± 11.3)
BMI (kg/m^2)	28.0 (± 6.0)	27.0 (± 3.3)
HbA_{1c} (%)	8.6 (± 1.9)	7.7 (± 0.9)

Table 6.5 – Basic sample characteristics of participants who completed food diaries. (Data is either presented as frequencies or mean averages with standard deviation).

Food Frequency Questionnaire

The macronutrient intake of patients who completed the FFQ can be seen in Table 6.6 and the principle findings are as follows.

Energy intakes for groups using both CSII and MDI were found to be below the estimated average requirements (EAR) (2550 kcal/day for males and 1940 kcal/day for females) regardless of gender (COMA, 1991), although males using CSII in particular failed to meet recommendations by consuming only 61.6% of the EAR.

The dietary intake of CHO for both CSII and MDI groups were marginally below the general population RNI guidelines of 50% energy intake per day (COMA, 1991). This was not gender specific as males using CSII and MDI consumed

42.3% and 39.8% respectively and females using CSII and MDI consumed 44.4% and 44.3%. Despite this, the recommended RNI for total sugar currently suggests that it should not contribute to more than 90 g/day yet both groups exceeded this with those using CSII consuming 102.0 g/day and those with MDI consuming 96.0 g/day (European Food Safety Authority, 2009). Both groups, irrelevant of gender, consumed less than the recommended consumption of 30 g of fibre per day, with the mean average consumed by those using CSII therapy being 15.9 g/day and 16.2 g/day by those using MDI.

Protein intake was slightly higher in those using MDI (89.7 g/day) compared to those using CSII (79.7 g/day) and when looking at the contribution this made to average energy intake it can be seen that the differences were not gender specific and non-significant (p = 0.802).

	Mean Values (CSII)	% Energy Intake (or DRV) (CSII Males)	% Energy Intake (or DRV) (CSII Females)	Mean Values (MDI)	% Energy Intake (or DRV) (MDI Males)	% Energy Intake (or DRV) (MDI Females)	*p*-value
Energy (kcal)	1717.7 (1536.1, 1899.4)	61.6[1]	91.01[1]	1886.4 (1505.9, 2266.9)	85.6[1]	89.0[1]	0.416
Energy (kJ)	7227.0 (6464.9, 7989.2)	61.9[1]	91.5[1]	7931.7 (6334.3, 9529.1)	85.9[1]	89.5[1]	0.421
CHO (Total) (g)	199.9 (177.4, 222.4)	42.3	44.4	213.6 (168.6, 258.5)	39.8	44.3	0.724
Total sugar (g)	102.0 (88.4, 115.7)	21.0	22.7	96.0 (72.6, 119.4)	17.5	20.1	0.706
Starch (g)	93.7 (81.7, 105.8)	N/A	N/A	114.4 (87.6, 141.1)	N/A	N/A	0.185
Sucrose (g)	39.4 (30.2, 42.6)	N/A	N/A	35.6 (24.1, 47.1)	N/A	N/A	0.846
Glucose (g)	19.5 (16.3, 22.8)	N/A	N/A	16.3 (11.3, 21.3)	N/A	N/A	0.280
Fructose (g)	21.9 (18.2, 25.5)	N/A	N/A	17.5 (12.3, 22.6)	N/A	N/A	0.204
Galactose (g)	0.6 (0.4, 0.8)	N/A	N/A	0.5 (0.2, 0.8)	N/A	N/A	0.442
Lactose (g)	20.0 (17.1, 23.0)	N/A	N/A	20.9 (17.1, 24.8)	N/A	N/A	0.745
Maltose (g)	1.8 (1.4, 2.2)	N/A	N/A	2.3 (1.3, 3.2)	N/A	N/A	0.378
NSP (g)	15.9 (13.9, 17.9)	56.3[2]	50.5[2]	16.2 (13.7, 18.7)	55.1[2]	53.4[2]	0.775
Protein (g)	79.7 (71.8, 87.5)	21.1	17.5	89.7 (66.6, 112.8)	20.0	18.4	0.802
Nitrogen (g)	12.8 (11.5, 14.1)	N/A	N/A	14.5 (10.8, 18.2)	N/A	N/A	0.257
Fat total (g)	68.7 (59.4, 78.0)	33.3	36.8	76.4 (58.0, 94.7)	39.2	34.5	0.347
SFA (g)	26.2 (22.2, 30.1)	12.5	14.1	27.9 (20.8, 35.0)	14.4	12.6	0.550
PUFA (g)	12.8 (10.8, 14.7)	6.2	6.8	14.0 (10.7, 17.2)	7.1	6.4	0.341
MUFA (g)	23.8 (20.5, 27.2)	11.7	12.8	27.9 (21.0, 34.7)	14.4	12.5	0.201
Alcohol (g)	4.8 (3.0, 6.5)	3.4	1.4	5.8 (3.0, 8.7)	1.1	2.9	0.507

[1] - percentage of daily EAR

[2] - percentage of daily RNI

Table 6.6 – Mean intake of macronutrients (with 95% CI) of patients who completed a FFQ, percentage energy intake (those which are instead based upon DRVs are indicated) and *p*-values derived from Student's *t*-test (or Mann-Whitney *U* test if data was non-normal).

The intake of total fat was close to Diabetes UK recommendations, which suggest the macronutrient should not contribute to more than 35-40% average energy intake per day (Dyson, 2011). This was shown to be regardless of treatment or gender, with males using CSII and MDI consuming 33.3% and 39.2% of their average energy intake respectively, whereas females using CSII and MDI consumed 36.8% and 34.5%. When looking at the intake of saturated fat it can be seen that consumption was slightly higher than the RNI which suggests it should contribute to no more than 11% of average energy intake. Males using CSII and MDI were shown to consume 12.5% and 14.4% respectively (Dyson, 2011). This was also shown in females using both CSII and MDI, with consumption being 14.1% and 12.6%.

None of the differences in macronutrient consumption between treatment groups reported by the FFQ were found to be statistically significant. To better visualise the differences of macronutrient consumption between treatment groups and gender in relation to average daily energy intake the findings have been consolidated into a graph (Figure 6.3).

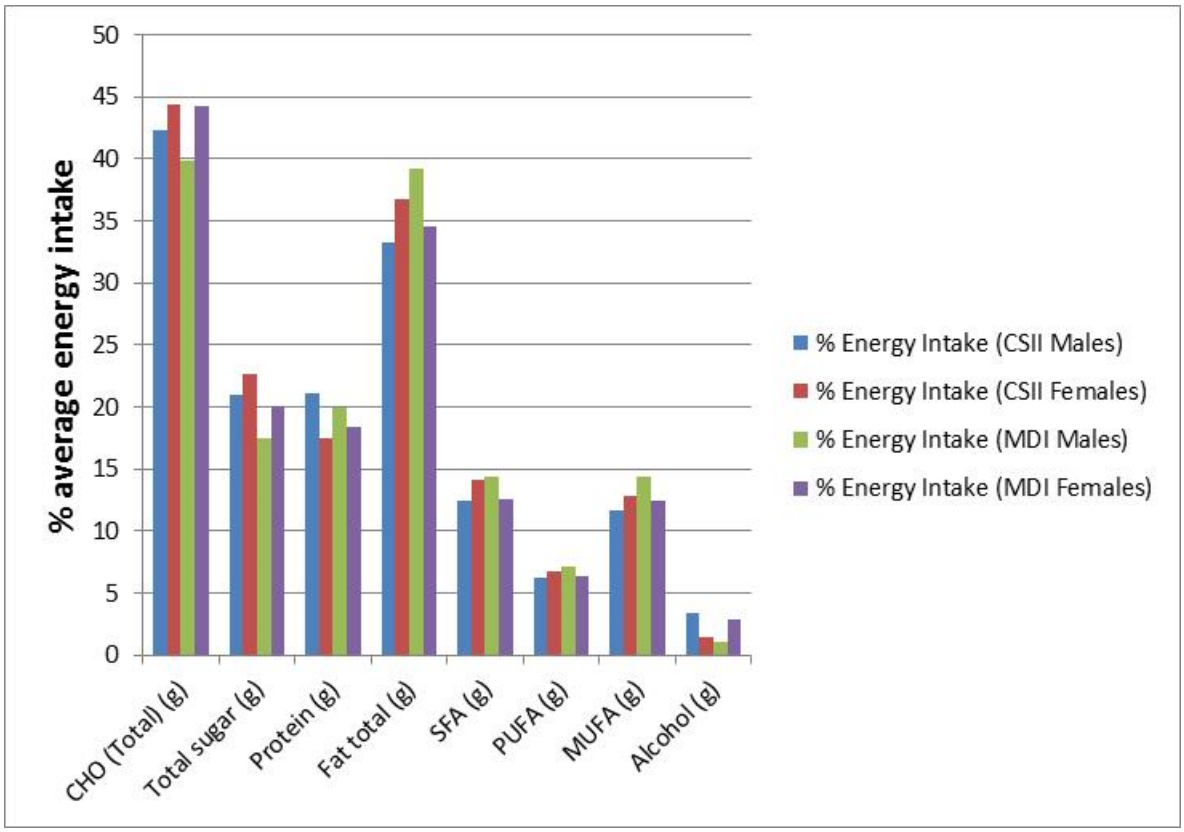


Figure 6.3 – Macronutrient consumption derived from FFQ data split by treatment and gender in relation to percentage energy intake.

The micronutrient intake of participants who completed the FFQ can be seen in Table 6.7 and please see Figure 6.4 for a visual comparison.

When looking at the intake of sodium the data showed that both treatment groups were consuming considerably more sodium than RNI suggestions of 1600 mg/day, with those using CSII consuming 2684.5 mg/day and those using MDI consuming 2927.3 mg/day. These findings were irrelevant of gender.

Furthermore, all patients were shown to meet the RNI for calcium consumption with those using CSII on average consuming 928.7 mg/day and those using MDI consuming 974.8 mg/day. This was again not gender specific, with both groups consuming slightly above the RNI.

Iron consumption, on average initially appears to meet the RNIs of 8.7 mg/day for males and 14.8 mg/day for females. However, a closer look at the gender differences reveal that the consumption of iron by males using both CSII and MDI was in excess of the RNI (by consuming 124.2% and 145.3% of the RNI respectively) and conversely female participants using both CSII and MDI failed to meet the RNI by consuming only 67.9% and 76.9%.

The consumption of Vitamin C was found to be over double RNI suggestions of 40 mg/day for adults, with those using CSII consuming on average 109.5 mg/day and those using MDI consuming 104.5 mg/day.

This trend of excess consumption can also be seen in all B vitamins; however, it is Vitamin B12 which is perhaps the most striking due to the unusually high consumption throughout all treatment groups and across genders. For example, those using CSII consumed on average 6.8 µg/day and those using MDI consumed on average 7.7 µg/day, both of which far exceed recommendations of 1.5 µg/day.

None of the differences between micronutrient variables were statistically significant between the different treatment groups.

	CSII	% RNI (Males)	% RNI (Females)	MDI	% RNI (Males)	% RNI (Females)	*p*-value
Cholesterol (mg)	278.4 (242.8, 314.0)	N/A	N/A	349.7 (182.5, 516.9)	N/A	N/A	0.227
Sodium (mg)	2684.5 (2370.2, 2998.8)	156.8	169.8	2927.3 (2405.7, 3448.9)	197.6	175.1	0.323
Potassium (mg)	3547.4 (3201.9, 3896.8)	100.5	100.2	3532.3 (3.012.4, 4052.2)	109.6	96.2	0.939
Calcium (mg)	928.7 (829.2, 1028.1)	125.8	133.2	974.8 (774.5, 1175.0)	150.9	133.0	0.541
Magnesium (mg)	312.0 (279.8, 344.1)	102.9	114.4	322.3 (262.8, 381.7)	121.8	110.7	0.658
Iron (mg)	10.3 (9.3, 11.4)	124.2	67.9	11.8 (9.3, 14.3)	145.3	76.9	0.572
Zinc (mg)	9.0 (8.1, 9.9)	100.1	124.9	9.8 (7.6, 12.1)	121.3	127.7	0.368
Vitamin A (µg)	472.1 (331.0, 613.2)	62.9	75.9	608.1 (84.0, 1132.2)	162.9	53.6	0.435
Vitamin C (mg)	109.5 (93.3, 125.7)	278.4	266.6	104.5 (76.6, 129.3)	284.1	248.9	0.797
Vitamin D (µg)	3.1 (2.5, 3.7)	N/A	N/A	3.6 (2.6, 4.7)	N/A	N/A	0.276
Vitamin E (mg)	11.9 (10.0, 13.8)	N/A	N/A	12.3 (10.0, 14.7)	N/A	N/A	0.616
Vitamin B1 (Thiamin) (mg)	1.4 (1.3, 1.5)	149.5	169.0	1.6 (1.2, 1.9)	148.9	199.8	0.288
Vitamin B2 (Riboflavin) (mg)	2.0 (1.8, 2.2)	156.9	173.8	2.0 (1.6, 2.4)	181.6	169.0	0.678
Vitamin B6 (pyridoxine) (mg)	2.1 (1.9, 2.3)	163.8	169.0	2.2 (1.8, 2.6)	176.9	176.9	0.499
Vitamin B9 (Folate) (µg)	266.6 (241.5, 291.7)	144.2	126.5	282.6 (222.0, 343.2)	148.9	137.2	0.507
Vitamin B12 (cobalamin) (µg)	6.8 (5.8, 7.9)	516.3	409.9	7.7 (4.9, 10.5)	684.0	422.3	0.376

Table 6.7 – Mean micronutrient intake (with 98% CI) of participants who completed an FFQ, percentage comparisons against daily RNI and *p*-values resulting from Student's *t*-test or Mann-Whitney *U* test for any non-normal data.

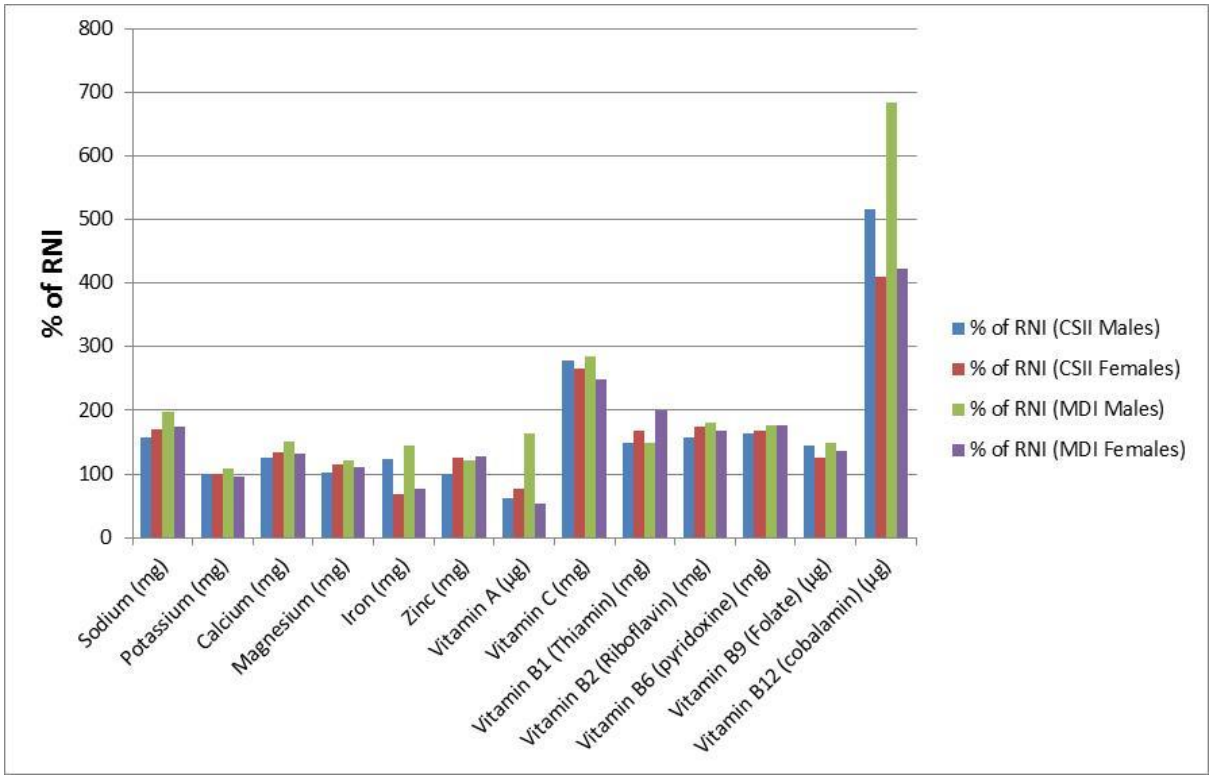


Figure 6.4 – Micronutrient consumption derived from FFQ data split by treatment and gender in relation to percentage RNI.

In addition to macronutrient and micronutrient intake the output from the FFQ also estimates the type of food products consumed. These are split into broad categories and are summarised in Table 6.8 and have been consolidated into a graph (see Figure 6.5).

The findings from this illustrate how although many of the variables were largely homogenous there were distinct differences with some food items. In particular the consumption of cereal and meat products was less in those using CSII compared to those using MDI (195.5 g/day vs 240.2 g/day and 99.0 g/day vs 129.9 g/day respectively). Also, the consumption of fruit was higher in those using CSII, with 234.2 g/day being consumed, as opposed to 160.0 g/day by those using MDI. Furthermore, the consumption of vegetables was also shown to contribute greatly to the diets of both treatment groups, with 242.9 g/day being consumed by those using CSII and 247.9 g/day by those using MDI.

Despite differences between groups none of the variables met statistical significance.

	CSII	MDI	*p*-value
Alcoholic beverages (g)	66.7 (39.6, 93.9)	82.5 (45.0, 120.0)	0.305
Cereal products (g)	195.5 (161.4, 229.5)	240.2 (162.7, 317.8)	0.235
Eggs and egg products (g)	23.2 (18.2, 28.2)	29.6 (-0.7, 59.9)	0.163
Fats and oils (g)	20.6 (14.7, 26.6)	20.6 (11.3, 29.8)	0.631
Fish and fish products (g)	43.7 (32.3, 55.0)	42.6 (26.4, 58.8)	0.925
Fruit (g)	234.2 (180.6, 287.8)	160.0 (105.9, 214.1)	0.114
Meat and meat products (g)	99.0 (83.1, 114.9)	129.9 (78.5, 181.2)	0.583
Milk and milk products (g)	408.5 (351.1, 465.8)	407.8 (333.2, 482.4)	0.981
Non-alcoholic beverages (g)	1080.0 (901.6, 1258.3)	938.1 (692.5, 1183.7)	0.517
Nuts and seeds (g)	6.1 (3.3, 9.0)	6.1 (0.8, 11.4)	0.710
Potatoes (g)	74.3 (61.7, 86.9)	79.0 (51.9, 106.0)	0.913
Soups and sauces (g)	82.8 (56.4, 109.1)	83.5 (52.4, 114.7)	0.655
Sugars, preserves and snacks (g)	35.8 (26.9, 44.6)	44.1 (27.3, 60.8)	0.500
Vegetables (g)	242.9 (207.2, 278.5)	247.9 (86.6, 309.3)	0.790

Table 6.8 – Food item consumption between treatment groups (with 95% CI) and *p*-values resulting from Student's *t*-test or Mann-Whitney *U* test for any non-normal data.

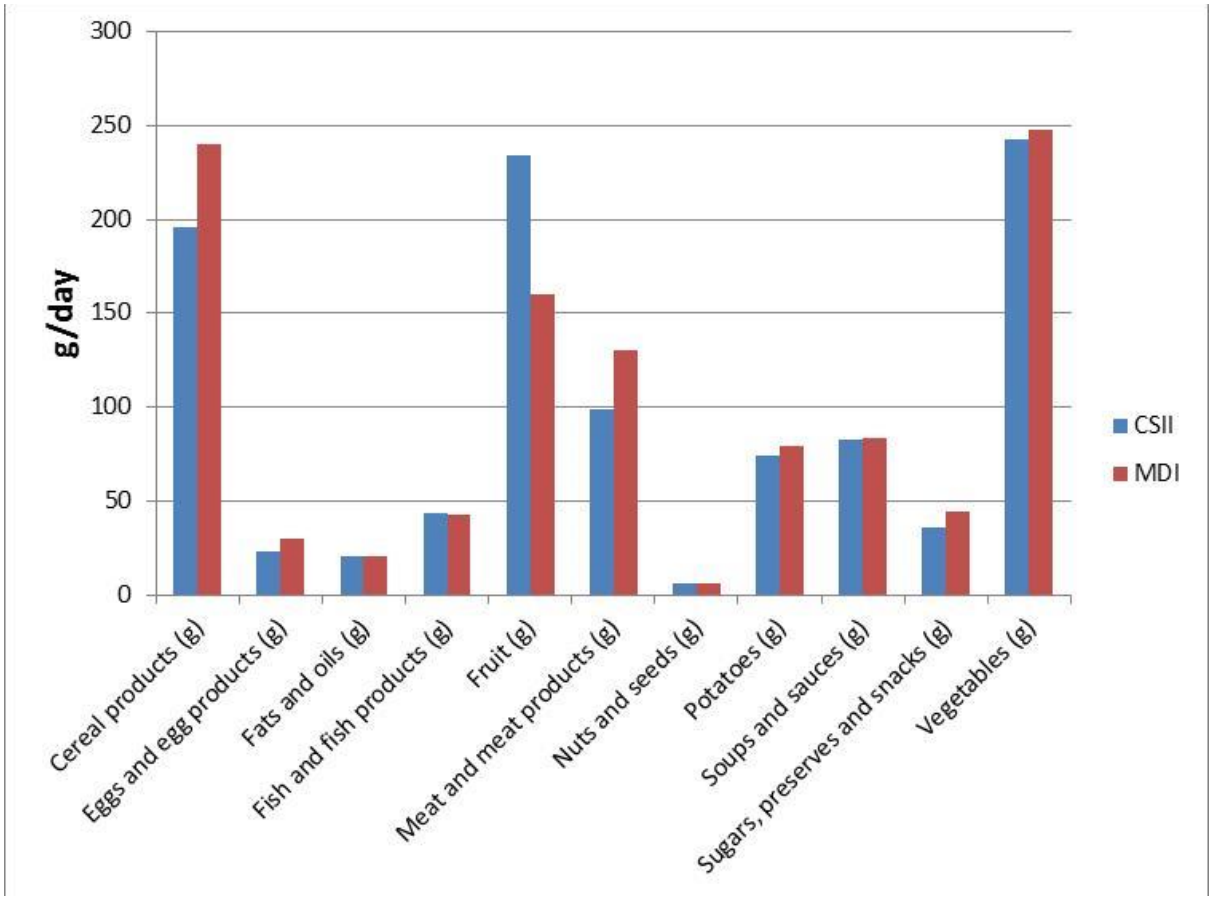


Figure 6.5 – Food items consumed by participants using either CSII or MDI as described by FFQ.

Food Diaries

The macronutrient intake of patients who completed the food diaries can be seen in Table 6.9 and to better visualise the differences between treatment groups and gender in relation to average daily energy intake the findings have also been consolidated onto a graph (Figure 6.6). The principle findings are as follows.

The reported energy intake derived from the food diaries indicates that participants using CSII were consuming below the EAR (2500 kcal for males and 1940 kcal for females), with their average energy intake being 1866.6 kcal/day (COMA, 1991). When looking at the data in terms of gender it can be seen that whereas females using either CSII or MDI virtually met the EAR (by consuming 94.4% and 101.5% of the EAR respectively), the males using CSII failed to meet the recommended guidelines by consuming only 75.7% of the EAR.

The reported consumption of CHO was shown to be slightly short of meeting RNIs suggesting that the macronutrient contribute towards 50% of average energy intake (COMA, 1991). Males using CSII and MDI consumed 49.3% and 44.3% respectively and females using CSII and MDI consumed 45.1% and 45.0%. In a similar manner, although daily recommendations of total sugar are 90 g/day the data revealed by both the FFQ and food diaries suggest that this may be exceeded by those in the CSII group and may be potentially suggestive of dietary relaxation (European Food Safety Authority, 2009). Those using CSII were shown to consume 99.8 g/day and those using MDI were shown to consume 88.6 g/day. Also similar to findings previously shown by the FFQ, the consumption of fibre was less than the RNI of 30 g/day, with those using CSII on average consuming 11.4 g/day and those using MDI consuming 20.3 g/day. This difference was shown to be highly significant (p = 0.001).

	Mean Values (CSII)	% Energy Intake (or DRV) (CSII Males)	% Energy Intake (or DRV) (CSII Females)	Mean Values (MDI)	% Energy Intake (or DRV) (MDI Males)	% Energy Intake (or DRV) (MDI Females)	*p*-value
Energy (kcal)	1866.6 (1490.7, 2242.5)	75.7[1]	94.4[1]	2110.5 (1628.7, 2592.3)	93.9[1]	101.5[1]	0.370
Energy (kJ)	7846.9 (6261.8, 9431.9,)	85.6[1]	94.6[1]	8876.0 (6857.2, 10894.7)	94.3[1]	102.1[1]	0.368
CHO (Total) (g)	232.3 (165.2, 299.4)	49.3	45.1	251.8 (197.3, 306.2)	44.3	45.0	0.628
Total sugar (g)	99.8 (58.4, 141.2)	20.6	19.7	88.6 (62.1, 115.1)	14.9	16.2	0.634
Starch (g)	103.6 (60.0, 147.1)	N/A	N/A	128.3 (96.4, 160.2)	N/A	N/A	0.336
Sucrose (g)	36.9 (9.8, 64.1)	N/A	N/A	24.6 (13.4, 35.8)	N/A	N/A	0.710
Glucose (g)	12.5 (6.6, 18.3)	N/A	N/A	11.6 (5.9, 17.3)	N/A	N/A	0.941
Fructose (g)	11.9 (6.1, 17.7)	N/A	N/A	12.2 (6.4, 18.0)	N/A	N/A	0.824
Maltose (g)	2.4 (0.8, 4.1)	N/A	N/A	2.5 (0.8, 4.1)	N/A	N/A	0.882
Lactose (g)	10.9 (7.9, 13.9)	N/A	N/A	13.5 (8.6, 18.4)	N/A	N/A	0.305
NSP (g)	11.4 (8.4, 13.9)	41.1[2]	34.9[2]	20.3 (15.7, 24.8)	65.4[2]	67.8[2]	0.001*
Protein (g)	69.0 (53.1, 85.0)	14.8	14.8	89.9 (72.4, 107.4)	15.0	18.3	0.062
Nitrogen (g)	12.4 (9.3, 15.4)	N/A	N/A	19.2 (14.0, 24.5)	N/A	N/A	0.016*
Fat total (g)	73.5 (58.0, 89.0)	31.4	37.9	80.1 (57.4, 102.9)	34.6	33.9	0.582
SFA (g)	31.6 (21.0, 42.3)	12.1	17.1	29.8 (21.8, 37.8)	14.0	11.9	0.777
PUFA (g)	8.8 (5.4, 12.1)	4.2	4.2	9.6 (7.0, 12.3)	3.3	4.6	0.659
MUFA(g)	19.6 (13.5, 25.8)	10.8	8.7	21.6 (16.0, 27.2)	8.9	9.4	0.609
Trans fat (g)	1.4 (0.9, 2.0)	0.7	0.7	1.4 (0.7, 12.3)	0.6	0.6	0.977

[1] - percentage of daily EAR

[2] - percentage of daily RNI

Table 6.9 – Mean intake of macronutrients (with 95% CI) of patients who completed a food diary, percentage energy intake (those which are instead based upon DRVs are indicated) and *p*-values derived from Student's *t*-test (or Mann-Whitney *U* test if data was non-normal).

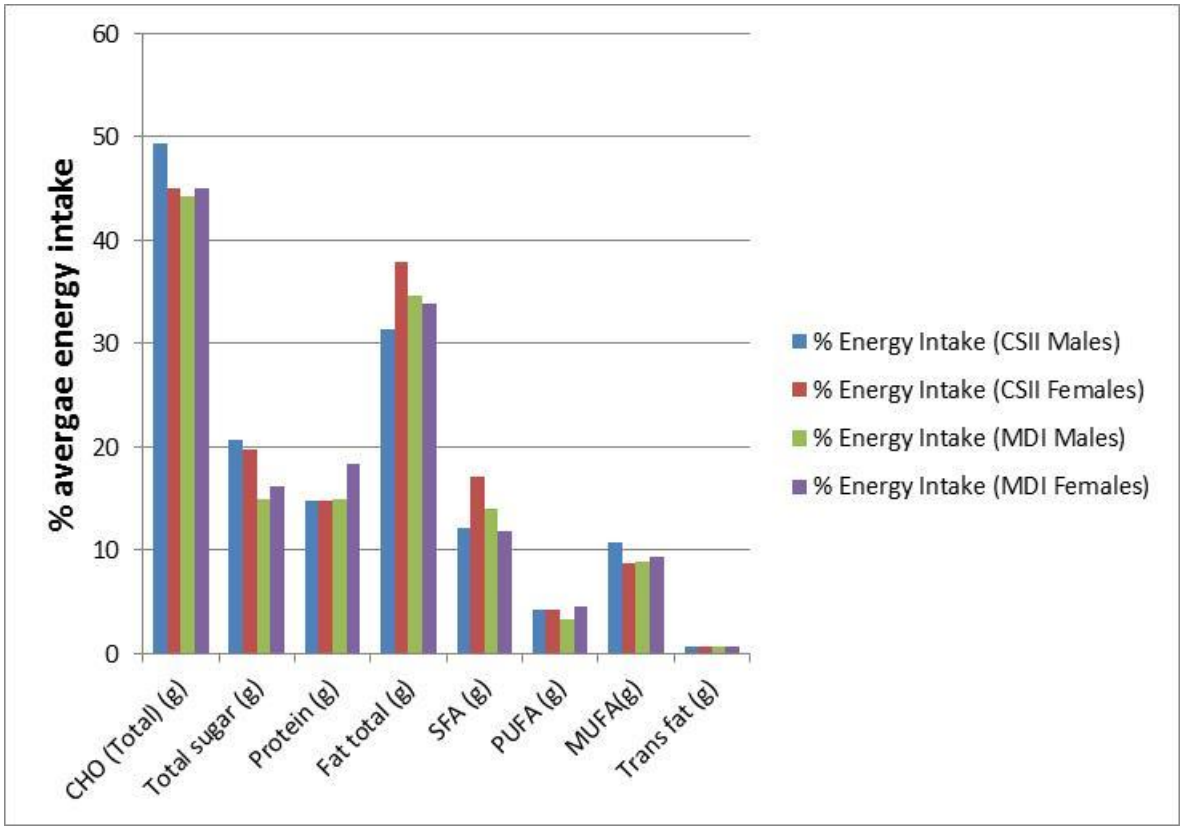


Figure 6.6 – Macronutrient consumption derived from food diary data split by treatment and gender in relation to percentage energy intake.

The consumption of protein was shown to be higher in the MDI group, who consumed on average 89.9 g/day compared to the CSII group who consumed 69.0 g/day; however, these differences were not gender specific. When focussing on the nitrogen content it can also be seen that similar differences were again shown, with those using CSII consuming 12.4 g/day compared to 19.2 g/day being consumed by those using MDI and this was shown to be statistically significant (p = 0.016).

The consumption of total fat was in virtual agreement with Diabetes UK dietary guidelines suggesting that it contribute to no more than 35 – 40% of average daily energy intake, with males using CSII and MDI consuming 31.4% and 34.6% average daily energy intake respectively and females using CSII and MDI consuming 37.9% and 33.9% (Dyson, 2011). When looking at the consumption of saturated fat it can be seen that males using CSII and MDI slightly exceeded recommendations suggesting the nutrient contribute to no more than 11% of the average daily energy intake. The consumption was 12.1% and 14.0% respectively. Females using MDI consumed 11.9%; however, it should be noted that females

using CSII consumed considerably more than recommendations as their dietary intake contributed to 17.1% of their average daily energy intake.

Similarly to the results previously described from the FFQ, the majority of differences regarding macronutrient consumption between treatment groups were found not to be statistically significant (apart from those previously described).

The micronutrient intake of participants who completed the food diaries can be seen in Table 6.10 and Figure 6.7 offers a visual comparison.

The dietary intake of sodium exceeded the RNI of 1600 mg/day in a similar manner to findings revealed by the FFQ. Those using CSII consumed on average 2724.1 mg/day and those using MDI consumed 3287.0 mg/day. Even though both groups exceeded the RNI by a high percentage, males consumed more than females in both the CSII group (204.85% vs 150.5% respectively) and MDI group (242.4% vs 186.9% respectively).

When looking at the intake of potassium it can be seen regardless of treatment less than the RNI (of 3500 mg/day) was consumed (COMA, 1991). This was particularly true in those using CSII and the difference between treatments was deemed statistically significant ($p = 0.040$). In particular it can be seen that females using CSII only consumed 58.7% of the RNI and are therefore are likely to be driving the reduced consumption in the CSII group.

The findings also highlighted that both CSII and MDI groups exceeded the RNI for calcium intake; however, a closer inspection reveals that whilst males using both CSII and MDI may be driving this by considerably exceeding the RNI (with intakes of 152.0% and 128.6% respectively), females using CSII are failing to meet the recommendations with 85.2% of the RNI being consumed.

The findings regarding magnesium consumption also present gender specific findings. Although both genders using CSII MDI meet the RNI it can be seen that females using CSII only achieve 63.1% of the RNI of 270 mg/day. The difference between groups is also statistically significant ($p = 0.046$); however, it is likely to be this female consumption which is promoting this difference.

When looking at the consumption of iron it can be seen that there were again gender specific differences. Females using CSII and MDI consumed considerably less (42.6% vs 79.1% of RNI) and males considerably more (182.8% vs 141.0% of RNI) than recommendations of 8.7 mg/day for males and 14.8 mg/day for females (COMA, 1991).

Vitamin A data also shows that the regardless of treatment or gender there was a general failure to meet RNI suggestions of 700 µg/day for males and 600 µg/day for females (COMA, 1991). Males using CSII and MDI consumed only 30.8% and 36.4% of the RNI respectively and females using CSII and MDI consumed 37.6% and 35.8% of the RNI. These differences were not shown in the data described previously from the FFQs.

In a similar manner to findings from the FFQ, the food diary results show that the consumption of vitamin C was excessive when compared to the RNI of 40 mg/day, with those using CSII consuming 62.8 mg/day and those using MDI consuming 71.0 mg/day.

These excessive intakes were also seen throughout findings pertaining to the B vitamins, with consumption generally exceeding RNIs. In particular it is noteworthy that intake of vitamin B12 was more than double the RNI of 1.5 µg/day and is similar to findings previously shown from the FFQ data.

Again, in a similar manner to findings from the FFQ, consumption of vitamin C also appeared to be excessive when compared to the RNI of 40 mg/day, with those using CSII consuming an average intake of 62.8 mg/day and those using MDI consuming on average 71.0 mg/day.

	CSII	% RNI (Males)	% RNI (Females)	MDI	% RNI (Males)	% RNI (Females)	*p*-value
Cholesterol (mg)	197.3 (120.6, 274.0)	N/A	N/A	208.2 (143.8, 272.6)	N/A	N/A	0.815
Sodium (mg)	2724.1 (2077.6, 3370.6)	204.85	150.5	3287.0 (2456.3, 4117.7)	242.4	186.9	0.234
Potassium (mg)	2315.1 (1647.2, 2982.9)	79.2	58.7	3273.9 (2564.3, 3982.7)	81.8	99.4	0.040*
Calcium (mg)	766.2 (478.3, 1054.2)	152.0	85.2	853.6 (652.9, 1054.3)	128.6	118.6	0.600
Magnesium (mg)	211.4 (146.2, 276.5)	94.4	63.1	300.1 (234.7, 365.5)	100.0	111.1	0.046*
Iron (mg)	9.8 (5.1, 14.5)	182.8	42.6	11.9 (7.3, 16.5)	141.0	79.1	0.484
Zinc (mg)	6.4 (4.1, 8.8)	87.4	77.0	7.9 (5.9, 10.0)	81.4	115.1	0.306
Vitamin A (µg)	221.9 (123.9, 319.9)	30.8	37.6	228.0 (141.9, 314.1)	36.4	35.8	0.919
Vitamin C (mg)	62.8 (23.3, 102.4)	146.6	162.9	71.0 (50.3, 91.6)	108.0	212.1	0.178
Vitamin D (µg)	1.5 (0.7, 2.3)	N/A	N/A	1.6 (0.8, 2.3)	N/A	N/A	0.868
Vitamin E (mg)	5.8 (3.5, 8.1)	N/A	N/A	6.3 (3.8, 8.8)	N/A	N/A	0.730
Vitamin B1 (Thiamin) (mg)	1.6 (0.5, 2.6)	262.0	118.9	1.5 (1.1, 2.0)	159.4	188.5	0.428
Vitamin B2 (Riboflavin) (mg)	1.6 (0.9, 2.3)	192.9	103.0	1.8 (1.2, 2.4)	149.5	157.9	0.449
Vitamin B6 (Pyridoxine) (mg)	2.2 (0.7, 3.6)	254.6	113.0	2.1 (1.5, 2.7)	135.6	185.9	0.434
Vitamin B9 (Folate) (µg)	200.9 (116.1, 285.7)	155.1	69.3	262.0 (188.6, 335.5)	126.6	133.2	0.175
Vitamin B12 (cobalamin) (µg)	4.2 (2.6, 5.9)	308.7	267.6	3.6 (2.6, 4.6)	198.2	264.2	0.456

Table 6.10 – Micronutrient intake (with 98% CI) of participants who completed a food diary, percentage comparisons against daily RNI and *p*-values resulting from Student's *t*-test or Mann-Whitney *U* test for any non-normal data.

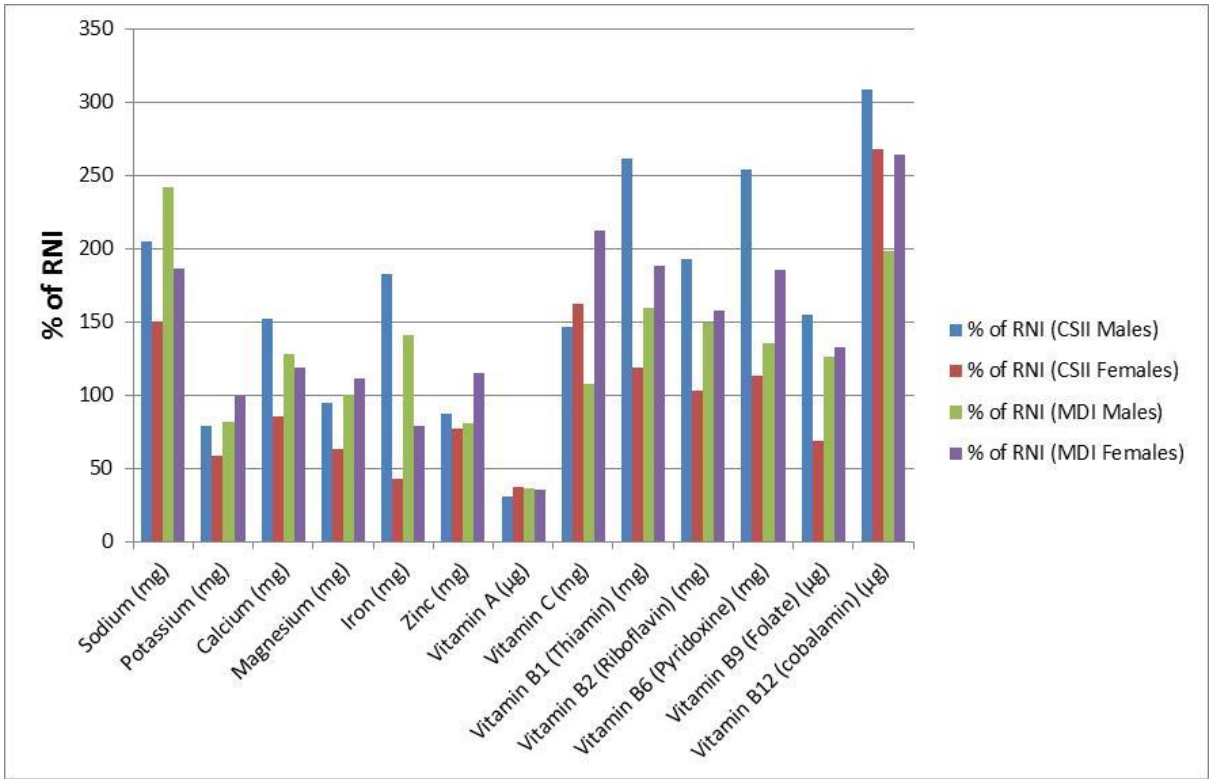


Figure 6.7 – Micronutrient consumption derived from food diary data split by treatment and gender in relation to percentage RNI.

Goldberg Equations

As a number of participants have a BMI >25 and energy intakes were often reported as being below the EAR it is reasonable to suspect that a degree of underreporting may have occurred. Therefore the Goldberg equations were used to determine if this was the case. The findings can be seen in Table 6.11.

	EI_{rep} : BMR within cut-off parameters? (%)		
	Yes	**No**	**Missing**
FFQ	66.7	23.3	10.0
Food Diary	75.0	20.0	5.0

Table 6.11 – Percentage participant EI_{rep} : BMR ratios defined from FFQ and food diary responses which fall inside and outside predefined Goldberg cut-off parameters.

As can be seen in Table 6.11, 23.3% of participants who completed the FFQ and 20.0% of participants who completed the food diary were outside of the parameters (all below minimum cut-off) and therefore classed as under reporters. In both groups 50% of under reporters were males and 50% were female.

Goldberg equations could not be applied to 10.0% of participants who completed the FFQ and 5.0% of participants who completed the food diary due to a lack of appropriate weight data.

6.6 Discussion

The findings from both dietary assessment methods, although in many ways largely homogenous, serve to provide useful insights into the eating behaviours of patients using CSII therapy compared to those using MDI. Also, despite the general similarities it would be disingenuous to say that no differences exist at all. Between the two groups one can note a number of subtle yet interesting variances and an even smaller proportion of these which are unexplainable by the author.

An example of this can be seen when looking at the average energy intake of the participants, where the majority were failing to meet the EAR for energy intake and that it was males using CSII in particular who were consuming the least calories of all. This was shown in data derived from both the FFQ and food diaries and the rationale behind this unexpected finding is unclear. It is interesting to note; however, a disparity between this failure to meet the EAR and a BMI >25 which was recorded for the majority of participants. This is suggestive of underreporting; a phenomenon widely cited in the literature, particularly in those who are overweight or obese and is a potential issue which required addressing (Black, 2000). In response to this the author employed the Goldberg equations to determine any incidence of bias and discovered that there was indeed evidence of underreporting in 20.0 - 23.3% of responses. The implications of this are that the findings for energy intake may be conservative at best or unrepresentatively low at worst. Interestingly, when this incidence of underreporting was split by gender exactly 50% of biased respondents were found to be from males and 50% from females, which offers little insight into the curiously low energy intakes for male participants using CSII therapy.

Total energy aside, the intake of CHO was found to occur in greater quantities than any other dietary variable and regardless of treatment the macronutrient contributed towards approximately 50% of the participants' average daily energy intake; a figure recommended as being ideal for the general public (COMA, 1991).

This may initially appear favourable; however, it says little about the quality of CHO and closer inspection reveals that the consumption of total sugars, particularly in those using CSII, was above the RNI of 90 g/day (European Food Safety Authority, 2009). Interestingly, when looking at the types of CHO consumed it can be seen that the group using CSII ate substantially more fruit than both the public and those using MDI, who although preferring sugary foods consumed these in lower quantities. This high intake of fruit may have potential glycaemic implications and it is noteworthy that the participants using CSII who completed the food diary actually had higher HbA_{1c} than the group using MDI. Despite this it remains difficult to say with certainty the impact this increased fruit intake had upon glycaemia as the sugars in these foods are generally prevented from rapid absorption by cell walls (unless destroyed in products such as smoothies etc.). Indeed, one wonders the effectiveness a dietary approach may have in patients such as these who are having issues with glycaemic control. After all, restricting the intake of dietary CHO results in the decreased requirement of insulin required to metabolise net glucose, thus improving glycaemia. This is not a new strategy, with examples discussed previously in the introduction of this chapter, and proponents gaining momentum within the modern literature, with studies showing rapid improvements in the blood sugar of patients with T2D who adhere to the diet (Yancy, 2005; Gannon, 2004; Boden, 2005). Despite these findings there is a dearth of literature focussing specifically on those with T1D, with the majority of evidence and indeed the guidelines citing that the manipulation of CHO has little impact upon HbA_{1c} (Dyson, 2011). There are exceptions though; an example being a study by Nielsen (2012) which investigated 48 patients with T1D who were instructed to consume a CHO restricted diet (<75 g/day with a correspondingly adapted insulin dose) and to attend a supportive education course. The authors found that only half remained on the diet after 4 years, but those that did experienced improved glycaemic control and modestly decreased insulin requirements. In addition to adherence issues it should be noted that the appropriateness of a low CHO approach is a fiercely debated topic with potential adverse effects being cited, such as increased risk of CVD, liver and kidney damage and osteoporosis which supposedly result from an excess intake of fats and protein, often from animal sources (Bilsborough, 2003). In actual fact the evidence for the occurrence of these issues is dubious and existing studies

investigating this are sparse (*Ibid*; Feinman, 2015). If anything this dearth of research together with segments of patients such as those described in the present study that consume a diet high in total sugars and present unfavourable HbA_{1c} levels illustrate the need for robust studies clarifying the risks or benefits of dietary approaches such as these which may improve treatment. Furthermore, it should also be remembered that individuals do not generally consume single nutrients and that the complex 'food matrix', consisting of an array of high and low GI foods, will have an overall impact upon glycaemic load and subsequent ability to control hyperglycaemia.

As well as the increased consumption of sugars it is also interesting to note that the intake of fibre was only half the RNI of 30 g/day in patients using both treatments regardless of gender. Although previous data focussing on those with T1D is lacking, NDNS findings suggest the average fibre consumption by adults in the UK is only 13.7 – 13.9 g/day, which is far below recommendations that could be said are unrealistically high and potentially setting people up to fail (NDNS, 2014; SACN, 2015). These low intakes may also be indicative of the types of food items consumed, in which fibre is not a naturally integrated component, with Bates *et al.* (2014) illustrating that the majority of dietary fibre is obtained from the consumption of cereals and vegetables. That said it is curious that the dietary intake of fibre was not only close to that achieved by the general population, but that the overall diet was also high in fruits and vegetables, with participants on average consuming far more of these food groups than the public. Furthermore, the participants' diet also contained a large cereal component (although admittedly the types of cereal products were not specified in the FFQ). Despite this the issue of low fibre intake remains and questions regarding the quality of these fruit, vegetable and cereal products therefore spring to mind. Furthermore, it is well documented that the consumption of a fibre rich diet is associated with decreased risks of colorectal cancer, rectal cancer and T2D, whilst inferring no impact on body weight (*Ibid*). A number of RCTs also demonstrate a reduction in risk of CVD (although the majority use doses >30 g/day, which although being in line with recommendations far exceeds typical daily intake) (Van Horn, 2010). The particularly low consumption of fibre seen in the participants is therefore

concerning, particularly with regards to the inherent risks of complications bestowed upon those with T1D.

In a similar manner to the total CHO findings described previously, total fat also appeared to be either within or very close to Diabetes UK guidelines which suggest the macronutrient should not contribute to more than 35 – 40% average daily energy intake. However, SFA consumption was shown to be higher than recommendations of not more than 11% of average energy intake per day (COMA, 1991). In fact findings from the dietary assessments revealed general consumption to be at levels similar to those found in the general public, where SFA contributed towards 12.6% average daily energy intake (NDNS, 2014). That said, this was not the case for females using CSII who consumed 17.1%; considerably more than recommendations; however, given that energy intake was below the EAR it could be argued that perhaps the total amount may be more important that the percentage of energy intake. In the case of females using CSII who completed food diary this equates to 34.8 g/day (± 18.6 g/day) (data not shown in tables) which still exceeds recommendations of 20 g/day for females (British Nutrition Foundation, 2013). It is difficult to source the specific foods which may be responsible for this; however, despite the FFQ illustrating that meat consumption was not particularly high there was no indication of diary intake which could be a contributing factor. This is somewhat concerning, particularly for patients with T1D, as failures to meet guidelines may in turn have health implications. Findings from the EURODIAB study have made it clear how the high saturated fat and high cholesterol diets often favoured by European patients are associated with detrimental changes to serum lipids (Toeller, 1999). Furthermore, the study also highlighted how nutrient intake, in particular high fat and low fibre diets, are also a predictor of waist to hip ratio (Toeller, 2001). This measure of adiposity has been demonstrated to have an association with the development of atherosclerosis and when combined with evidence showing how poor dietary choices may also have a negative impact upon endothelial function and promote inflammation is an alarming cause for concern (Ge, 2014; Soedamah-Muthu, 2013; van Bussel, 2013). This is particularly worrying as CVD is the major cause of death in those with T1D and patients are at an increased risk of vascular disease compared to the general population. Despite presenting alarming findings this evidence is not

without its critics. For example, it may be difficult to truly define a high fat diet and it has been argued that some 'high fat' diets may also be rich in refined CHO that may in turn cause their own issues (Hu, 2010). In addition there is also a current ongoing debate regarding the false demonization of saturated fatty acids, with proponents making the case that their role in heart disease has been exaggerated (Malhotra, 2013). Furthermore, recent evidence has illustrated that the specific type of saturated fatty acid can infer risk, with even chain fatty acids being positively associated with T2D, yet odd and long chain saturated fatty acids instead being negatively associated (Forouhi, 2014).

In addition to these rousing current debates surrounding saturated fatty acids it is also interesting, given the high risk of patients with T1D, that diets which are rich in mono and polyunsaturated fatty acids; the so-called 'Mediterranean diet', have been shown to be associated with an inverse risk of CVD. This has been known for some time, with a meta-analysis by Sofi (2008) describing 9% risk reductions from CVD and cancer and a 13% reduction in incidence of Parkinson's and Alzheimer's disease. These benefits have been further confirmed in a diabetic population with the SEARCH study showing that adherence to the diet may improve not only CVD risk, but also glycaemic control (Zhong, 2015). Furthermore, in the light of this and in the absence of specific RNI guidelines for MUFA and PUFA, it is therefore promising to see that the dietary intakes of these fatty acids by participants, regardless of treatment, were higher than those being consumed by both the general public and recommendations and it is hoped that this may offer some degree of protection (NDNS, 2014).

As well as differences in the intake of macronutrients between treatment groups the study also revealed differences in the consumption of micronutrients. In particular it was noticed that regardless of treatment the intake of sodium was much higher than recommendations of 1600 mg/day and in some cases (particularly with regards to those who completed the food diaries) over double the RNI was consumed per day. This is no surprise, with NDNS data showing that average sodium consumption in the general public is well above the RNI; however, in a population such as those with T1D who are already vulnerable to CVD this is especially concerning. Principally because cardiovascular disease has been associated with raised blood pressure and increases in blood pressure have been

in turn partly attributed to an excess dietary intake of salt (He, 2009). Although some (often dated) sources, such as a meta-analysis by the Cochrane group in 1996, suggest that this statement is somewhat controversial, more recent literature illustrates that salt is likely to be a contributing factor and reductions, such as those suggested by the Diabetes UK nutrition guidelines, should be promoted (Adler, 1996; Graudal, 2014; Dyson, 2011). The benefits of this stance have been demonstrated previously when authors from the FinnDiane study, designed to determine risk factors for kidney disease in a large cohort of patients with T1D, concluded that both high and low dietary salt intakes were associated with increased incidence of cardiovascular and all-cause mortality in those without prior CVD (Thomas, 2011). Although not demonstrating causality these findings further support dietary salt recommendations for those with the disease (*Ibid*). In response to these associations the relationship between salt and CVD has also been investigated experimentally, with diabetic mice consuming either a low or high sodium diet being seen to develop atherosclerotic lesions at a greater rate than those consuming a diet consisting of a moderate amount of sodium, thus producing a 'J-shaped' relationship, similar to that observed in the FinnDiane study and further bolstering recommendations for a diet modest in salt (Tikellis, 2013).

Furthermore, the high observed sodium intake, in addition to the high intakes of saturated fat described previously, may also be indicative of the quality of food items consumed and care should therefore be taken to consider the food matrices in which these nutrients are being held in as well as just focussing on the individual nutrients themselves. Indeed, it is well documented that the nutritional content of foodstuffs can be very much determined by their structure; which can in turn be governed by various factors such as bioavailability, bioaccessiblity and industrial processing, for example heat treatments, homogenisation and supplementation, which can all influence the nutrient quality of foods (Turgeon, 2011). Also, preservation methods such as curing with salt and sodium or potassium nitrate can also influence the nutrient profile and is one example where the sodium content of foods can be increased during the production process. (FAO, 2016). As such, food items should be considered, where possible, in their entirety as an indicator of quality in addition to the focussing only on their constituent nutrients.

In addition to excessive intake of sodium there were also high intakes of other micronutrients. An example of this was vitamin C which was consumed in quantities greater than the RNI of 40 mg/day by the majority of participants, regardless of treatment or gender, with some consuming more than double the recommendations (COMA, 1991). Although this is above the optimum requirement it is unlikely that any ill effects will be experienced as only high doses over 1000 mg/day tend to cause (minor) symptoms and it is generally unfeasible to consume such large doses without the use of supplements (NHS, 2016). These micronutrient excesses were also shown with participants exceeding recommendations for B vitamin intake. Not all will be discussed in detail, apart from the curious case of vitamin B12, which the findings suggested were consumed in large amounts, equating in some cases to over 600% of the RNI. It is difficult to specify which food items contained this vitamin as the participants only consumed slightly more that the recommended intakes of meat and fish products (which are rich sources of vitamin B12). Milk and milk products; however, contributed to a substantial segment of the participants diets and although not being the richest source of vitamin B12, sheer volume of consumption may be an important factor. Despite this it is it is important to note that although intake exceeded the RNI there is little data regarding the toxicity of vitamin B12, with even large oral doses over 2000 µg/day used to treat pernicious anaemia being well tolerated with no side effects (Miller, 2014).

Although excesses pertaining to micronutrient intake have been discussed, there were also incidences of micronutrient consumption failing to meet recommendations. Examples being the intake of potassium and magnesium in which the differences shown by data derived from the food diaries were shown to be statistically significant. In particular these differences appear to be driven by females using CSII who only consumed 58.7% of the RNI of potassium and 63.1% of the RNI of magnesium. These electrolytes are important for biological process such as the growth and maintenance of muscle and neve function, control of the acid/base balance and regulation of blood glucose levels (Medline Plus, 2016). The poor intake of these nutrients is surprising given neither are lacking in the general public and the participants in general were shown to consume a diet rich in fruits and vegetables (NDNS, 2014). Furthermore, it is also important to note

that these findings were not reflected in data derived from the FFQs and therefore may potentially be subject to error. Additionally and perhaps more importantly calcium consumption, although generally being consumed in appropriate quantities, was not the case for female participants using CSII, whose intake equated to 85.2% of the RNI. Furthermore, the average intake of adults in the UK was shown by NDNS data to be above the RNI and therefore the findings show females using CSII are an exception to this. This is concerning as the mean age group of these patients was 42.8 and therefore if a reduced consumption continues beyond the menopause it may contribute towards increased risks of osteoporosis (particularly in older postmenopausal women) (NHS, 2016). This should not be underestimated as evidence suggests that, for reasons not entirely understood, patients with T1D frequently have a lower bone density than healthy counterparts and up to a six-fold increased risk of fracture, therefore further increasing the cause for concern (Hough, 2016). As well as inadequate calcium intakes it is also interesting to note that females using CSII were again shown to fail to meet RNIs for the consumption of iron. This is vitally important due to the amount lost through menstruation; however, was not particularly unexpected as NDNS data shows females typically fail to meet iron recommendations. However, what is surprising is that the NDNS cited the biggest contributor for iron intake in all ages was from cereal products and the intake of these, regardless of treatment group, was high. Furthermore, consumption of iron-rich products such as meat and vegetables was also shown to be generally above recommendations (although it is acknowledged that the breakdown of food items from the FFQ does not give details of the specific foods consumed). Although a number of micronutrients failed to meet the RNIs, perhaps the most spectacular failure involves the intake of vitamin A. Participants regardless of gender or treatment were shown by the food diaries to only consume between 30 – 38% of the RNI. While these particularly low intakes were not reflected by the FFQ results, the findings still generally failed to meet the RNI. Although deficiencies can develop into eye problems leading to blindness this is relatively rare, with no reports in the UK since the 1930s and a lack of these complications presented in the participants (WHO, 2016). Moreover, when considering this together with disputing evidence presented by the FFQs and the small sample size is suggestive that consumption may not be as poor as initially described by the food diary data.

Conclusion

Although this study focused on the eating behaviours of patients with T1D using CSII and MDI therapy and revealed some interesting differences between the diets of the two groups it is important to note that in many ways the eating behaviours were also largely homogenous. Although not controversial this could be regarded as a somewhat positive finding as it indicates that patients can commence the therapy without fear of large, potentially detrimental deviations of diet.

Furthermore, although the majority of dietary intake from both treatment groups remained close to RNI guidelines certain differences were revealed throughout the data. Whilst some may potentially increase the risks of long-term health issues it is important to consider some of the practical aspects of the study which may have influenced the findings before passing judgement. Firstly, the study was cross-sectional in nature which only captured patients' eating behaviours at a single time point and as such may not be truly representative of their actual lives. Although the food diaries attempted to deal with this by capturing data from 5 days it is unknown if these days are typical. Secondly, both the FFQ and food diary are retrospective tools which are only as accurate as the patients who complete them. Also, it should be remembered that the surveys were completed at the participants' leisure in their own homes and that all measurements for food diaries were taken using uncalibrated top pan balances belonging to the participants in uncontrolled conditions and therefore despite all best intensions it is unknown how accurate the findings are. Finally, it should also be remembered that this is only a pilot study using small number of patients from one clinic and so it would be unwise to place too much weight upon the meaningfulness of any statistical outcomes and that care should be taken not to extrapolate the findings to the general population of those with T1D.

Despite these limitations the study offers a unique insight for the first time into the eating behaviours of patients with T1D using a modern form of CSII and who have been educated using contemporary methods.

Chapter 7

Cardiometabolic Risks

7 - Cardiometabolic Risks

7.1 Abstract

Cardiovascular disease (CVD) risk is elevated in those with Type 1 diabetes (T1D) and this is in part mediated by abnormal cardiometabolic risk markers. When focussing specifically on high and low density lipoprotein (HDL and LDL) particles, certain subclasses have been shown to infer increased levels of risk and may exist even if a patient achieves favourable glycaemic control. This risk may also prevail in patients with T1D, even if standard lipid measures suggest otherwise. Given the potential for CSII to improve glycaemia it is therefore prudent that the quality of lipoproteins in those using the therapy is investigated. Furthermore, there is also a dearth of literature in this area. Following ethical approval, the medical records of a group of patients using either CSII (n = 40) and MDI (n = 20) were interrogated for markers of cardiometabolic risk. Plasma from a subsample of patients using either CSII (n= 20) and MDI (n = 9) was analysed for total cholesterol, triglycerides and HDL and LDL subfractions. The findings showed patients using CSII had significantly less HbA_{1c} than their MDI counterparts (7.8% vs. 8.5%; p = 0.072 respectively). This was also the case for systolic blood pressure (123.5 mmHg vs. 135.3 mmHg; p = 0.023). With regard to lipoproteins, those using CSII had comparable levels of LDL-C and HDL-C compared to MDI counterparts. Further similarities were shown with LDL subfractions with CSII and MDI groups displaying identical LDL I and II fractions and near-identical LDL III and IV. Those using CSII also had similar levels of HDL2 compared to patients using MDI and similar amounts of HDL3. Furthermore, the levels of HDL also indicated both groups were largely well protected. Despite this there was a significant difference in the ApoB / ApoA1 ratio between patients using MDI and those using CSII (0.70 vs. 0.60; p = 0.025 respectively), which suggests the former may be at an increased risk of CVD. To conclude, although patients using MDI therapy appeared to be generally well-managed, the same could also be said to a slightly greater degree for their CSII counterparts and future research investigating other measures of lipoprotein quality would be beneficial.

7.2 Introduction

The term ‘cardiometabolic’ (CM) risk is used to describe a cluster of markers which may predispose an individual to an increased risk of diabetes and/or cardiovascular disease (CVD) (Van Der Meer, 2013). The specific factors which contribute towards a preponderance of CM risk are loosely defined, with the general consensus being that typical measures should include body mass index (BMI), waist circumference, smoking habits, blood sugar, insulin resistance, blood pressure, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides (TG) and total cholesterol (TC). Despite this basic framework it should also be noted that the exclusion of these markers and the inclusion of others frequently occur from study to study.

It is well documented that patients with T1D are at an increased risk of CM risks for a variety of reasons. One such reason is that the weight of patients has been increasing over recent decades, with the Pittsburgh Epidemiology of Diabetes Complications Study cohort illustrating how over 18 years the prevalence of overweight patients has almost doubled and obesity has increased seven fold (Conway, 2010). This high prevalence of weight gain has also been shown in the UK with over 62% of patients with T1D now being either overweight or obese (Diabetes UK, 2015). Furthermore, the subsequent insulin resistance associated with this increased weight and/or a family history of T2D may predispose patients with existing T1D to also succumb to T2D. This condition has been recently coined ‘double diabetes’ and although the long-term effects are currently under-studied, patients are likely to be at a greater risk of diabetes-related complications (Cesur, 2008; Cleland, 2012).

Even in the absence of excessive weight and the so-called ‘double diabetes’, patients with T1D remain at an increased risk of macrovascular complications concerning the larger blood vessels such as the aorta, coronary arteries and the wider arteries in the limbs. These frequently result in strokes, coronary artery disease and peripheral arterial disease and are typically referred to using the collective term ‘cardiovascular disease’ (CVD) (Fowler, 2008). Despite great improvements over recent years the risks of these CVD complications remain high and patients residing in the UK are no exception to this. A Diabetes UK funded

cohort study of 23,751 patients by Laing *et al*. (2003) highlighted both high mortality rates and a gender disparity regarding CVD, with standardised mortality ratios of 8.8 for females compared to 4.5 for males (Laing, 2003). Similar findings were also found in a study by Soedamah-Muthu (2006) who interrogated data concerning 7475 individuals with T1D derived from the UK General Practitioners Database. This study also highlighted both the high risk of CVD which those with T1D face as well as the predisposition towards females compared to males, with hazard ratios for major CVD events being 7.7 and 3.6 respectively. It is difficult to find more recent data offering an accurate breakdown of the current state of CVD in UK patients with T1D; however, the last published National Diabetes Audit (2012 – 2013) (which included 71.1% of all patients with diabetes in England and 69.3% of those in Wales) reported that despite cardiovascular complications largely remaining stable over the last 3 audit periods (2009 – 2012), the risk of patients with T1D being admitted to the hospital with heart failure is still 322% greater than those without the disease (HSCIC, 2015).

Despite these concerning figures the pathogenesis of cardiovascular disease in those with T1D has not yet been fully elucidated; however, it is clear that its progression is the result of various insults to the macrovascular system. These have been broadly illustrated in Figure 7.1.

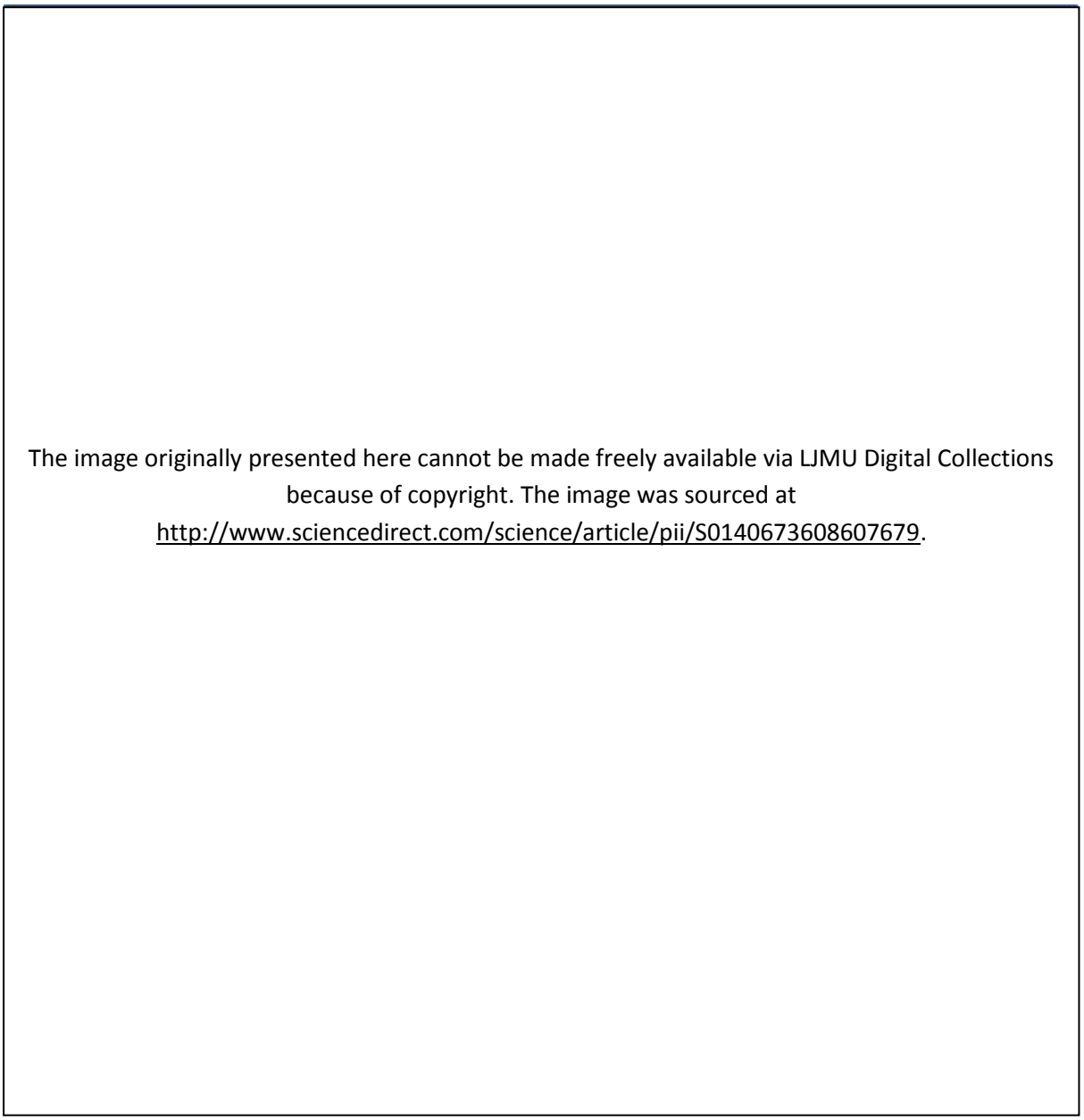


Figure 7.1 – Associated issues which may catalyse macrovascular disease (Adapted from: Retnakaran, 2008)

Atherosclerosis is one of these principle components. It is characterised by the accumulation of ‘fibrofatty’ deposits in elastic and medium to large arteries which over time build up causing the vasculature to become stiffened and blocked as illustrated in Figure 7.2 (Wang, 2012).

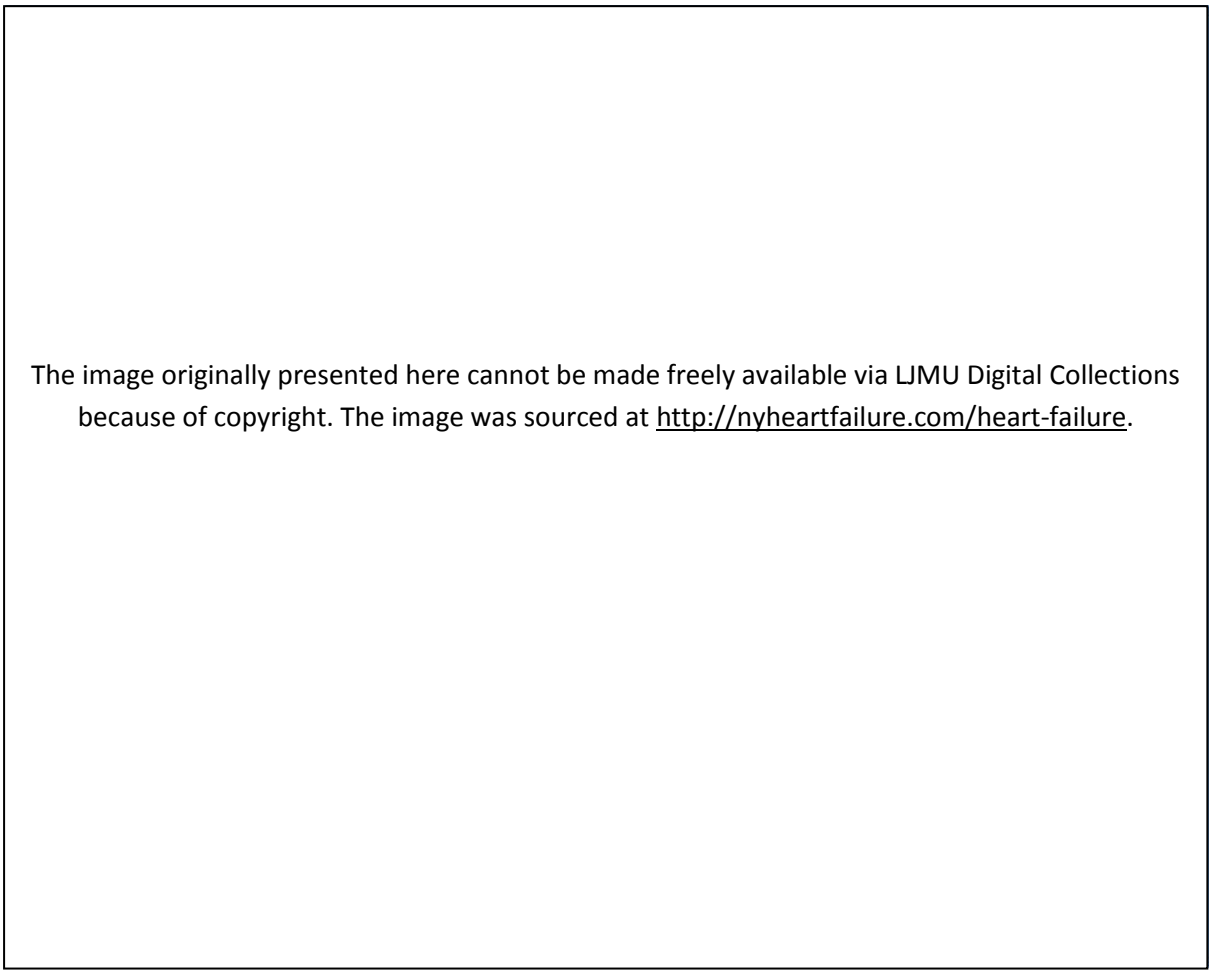


Figure 7.2 –Progression of atherosclerosis (Adapted from: HeartandHealthMedical, 2015)

The progression of atherosclerosis is very much dependent on the presence of lipoproteins. These particles are a biochemical assemblage consisting of both a hydrophilic, polar outer shell comprised of phospholipids, apolipoproteins and free cholesterol and a hydrophobic, non-polar inner core of triglycerides and cholesterol esters (Figure 7.3). This arrangement allows the lipids to be ‘packaged’ and transported through the aqueous blood stream to their destination.

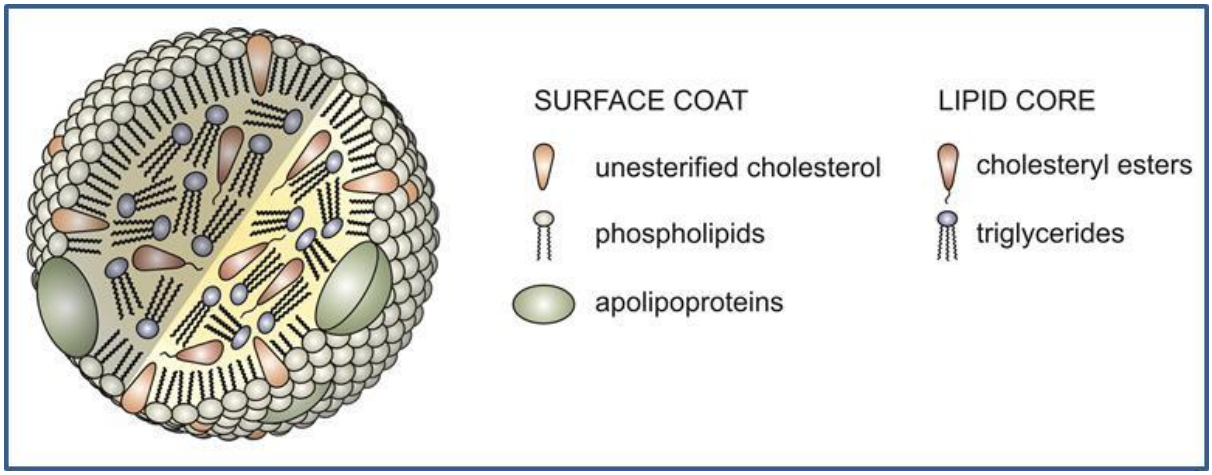


Figure 7.3 – The nomenclature of a lipoprotein particle (Antisense, 2010).

The image originally presented here cannot be made freely available via LJMU Digital Collections because of copyright. The image was sourced at http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4263s1_03_Wood-FDA.pdf.

Figure 7.4 – Lipoprotein classes and subclasses categorised by density and size (Adapted from: Wood, 2006).

Residing under the general term ‘lipoprotein’ there are a number of classes and subclasses which can be categorised according to both their density and size (Figure 7.4). These particles also differ in terms of the proportions of lipids contained in their core and the apolipoproteins which contribute towards their structural integrity (see Table 1).

Lipoprotein	Density (g/ml)	Size (nm)	Lipid Composition (wt%)*	Apolipoprotein Composition
Chylomicrons	<0.930	75 – 1200	Total lipid - 99 Triglycerides - 85 Cholesterol esters - 3 Cholesterol – 2 Phospholipids – 8	Apo B-48, Apo C, Apo E, Apo A-I, Apo A-II, Apo A-IV
VLDL	0.930 – 1.006	30 – 80	Total lipid - 91 Triglycerides - 55 Cholesterol esters - 18 Cholesterol – 7 Phospholipids – 20	Apo B-100, Apo E, Apo C
LDL	1.019 – 1.063	18 – 25	Total lipid - 80 Triglycerides - 10 Cholesterol esters - 50 Cholesterol – 11 Phospholipids – 29	Apo B-100
HDL	1.063 – 1.210	5 – 12	Total lipid - 44 Triglycerides - 6 Cholesterol esters – 40 Cholesterol – 7 Phospholipids – 46	Apo A-I, Apo A-II, Apo C, Apo E

*Most of the remaining material comprises the various lipoproteins

Table 7.1 – The composition of lipoprotein particles categorised by class (adapted from Feingold, 2015 and AOCS, 2015).

These important compositional differences have various functional implications which complement the distinct role each particle plays in the complex metabolism of lipids and the pathogenesis of lipid-based disease. A basic explanation of these processes is shown in Figure 7.5.

This process, although greatly simplified, is complicated by various subclasses which exist within the individual lipoprotein classes as shown in Table 7.2. These are also categorised by density and size and are composed of differing amounts of lipids which also impact upon their function. For example, LDL may be stratified

into four main subfractions:- LDL-I (density = 1.019 – 1.023), LDL-II (density = 1.023 – 1.034),

Figure 7.5 – Human lipid metabolism (Adapted from: Daniels, 2009).

Lipoprotein subclass	Density (g/mL)	Size (nm)
LDL-I	1.019 – 1.023	28.5 - 27.2
LDL-II	1.023 – 1.034	27.2 - 25.6
LDL-III	1.034 – 1.044	25.6 - 24.2
LDL-IV	1.044 – 1.060	24.2 - 23.3
HDL_2 (b)	1.063 - 1.087	12.9 – 9.7
HDL_2 (a)	1.088 - 1.110	9.7 – 8.8
HDL_3 (a)	1.110 – 1.129	8.8 – 8.2
HDL_3 (b)	1.129 – 1.154	8.2 – 7.8
HDL_3 (c)	1.154 – 1.170	7.8 – 7.2

Table 7.2 – The composition of lipoprotein particles categorised by subclass (adapted from Berneis (2002) and Rosenson (2011)).

LDL-III (density = 1.034 – 1.044) and LDL-IV (density = 1.044 – 1.060) (Berneis, 2002). Although the existence of these subfractions has been known for some time their role in lipid metabolism and disease risk is an emerging and frequently debated subject; however, the existing literature suggests that some may be more injurious than others. Specifically, it has been acknowledged that the small, dense LDL subfractions (LDL III and IV) may be more atherogenic than their larger, more buoyant counterparts due to an increased susceptibility to oxidation, decreased rates of degradation and a greater affinity for the arterial wall (Lamarche, 1999). Furthermore, it is also important to note that the prevalence of these particles is rarely seen in isolation, as LDL particle size and buoyancy has been shown to be inversely related to plasma triglycerides and VLDL levels (Krauss, 1980; McNamara, 1987).

Similar categories of subfractions also exist within the individual HDL classes (Table 7.2). These are distinguishable by their density and size and can be categorised as follows:- HDL_2 (density = 1.063 – 1.110) and HDL_3 (density = 1.110 – 1.170) (Rosenson, 2011). The question of which particular fraction is more atheroprotective is a contentious one. Some studies have shown that in patients with dyslipidaemia a reduction in the larger HDL_2 particles and an increase in the

denser, smaller HDL_3 particles occur and that this trend is also present in those with coronary artery disease (Pirillo, 2013). However, a number of other studies suggest that HDL_2 actually may be a better predictor of coronary artery disease than either HDL_3 or total HDL (Drexel, 1992; Lamarche, 1997; Johansson, 1991). These contradictory findings are further confounded by the sparse number of studies available in this area, along with the variety of methods used to separate the particles and therefore it would be premature to suggest which specific subfraction may be more beneficial (Superko, 2012).

In T1D this complex system of lipid metabolism is often disrupted. The large scale DCCT study made clear the positive relationship between glycaemic control and lipids and lipoproteins, as those with poorly controlled diabetes typically have raised total cholesterol, LDL and triglycerides and are in turn associated with an increased risk of CVD (The DCCT Research Group, 1992). This has been replicated elsewhere and is now generally accepted as the conventional wisdom (Feitosa, 2013; Guy, 2009). Conversely, when patients maintain good glycaemic control they often display improved lipid profiles similar to healthy individuals without the disease (Dullaart, 1995). Specifically, triglycerides and LDL-C are often found to be normal or decreased, which are thought to result from hyperinsulinemia originating from the subcutaneous methods of injection generally favoured by patients that in turn may cause a downregulation of VLDL production and an increase in the activity of lipoprotein lipase (Vergès, 2009). Furthermore, HDL levels are often seen to be normal or slightly increased (Mattock, 1982).

Although this overall lipid profile may appear at first glance to confer cardio-protection it is important to remember that even patients with favourable glycaemic control remain at an increased risk of CVD. This may in part be explained by various qualitative abnormalities which are often found to exist, even in patients with good control, which are likely to promote the progression of atherosclerosis. These abnormalities are typified by a predominance of small, dense LDL fractions (LDL III and IV) that are abundant in triglycerides (Vergès, 2009). Whilst a higher number of these particles are directly related to an increased risk of CVD, they are also more prone to oxidation and decreased uptake by the LDL receptor (Wadhera, 2016). Indeed, small dense LDL has also been shown to be more

predisposed to glycation in those with diabetes than their buoyant counterparts, thus further increasing their atherogenic potential (Younis, 2013).

Despite normal or slightly raised HDL in those with well managed T1D it is not conclusive which particular subfraction of HDL is raised; with some studies suggesting HDL_2 and others suggesting HDL_3 (Eckel, 1981; Winocour, 1996). Also, the function of HDL itself is often found to be compromised due to its enrichment with triglycerides, impaired antioxidant properties and increased glycation, which has in turn been shown to decrease the particles' ability to perform reverse cholesterol transport (Dullaart, 1995; Perségol, 2007; Hoang, 2007; Brindisi, 2013; Fievet, 1992). These qualitative abnormalities are no exception in those with T1D, with altered HDL function, even in spite of normal or elevated levels, likely to contribute towards the increased CVD risk experienced by patients (Manjunatha, 2016).

These lipoprotein abnormalities are of interest to the authors of the present study as CSII therapy is well-known to improve glycaemic control and therefore one might expect the standard lipid profile of patients using this treatment to improve; as has been demonstrated previously (Pickup, 2002; Vergès, 2009). Despite this little is known about potential co-existing abnormalities which may occur in relation to lipoprotein quality in those engaging with treatments known to significantly improve glycaemic control, such as CSII (Vergès, 2009). The evidence surrounding this has been discussed in detail previously in the Literature Review chapter (see page 30) and forms the rationale for the focus of the present study on lipoprotein quality in those using CSII, with a particular focus on LDL and HDL subfractions. Additionally, it is also important to remember that typical diagnostic tests used by physicians to observe lipid levels only measure the standard lipid panel (i.e. total cholesterol, HDH-C, LDL-C and triglycerides). Thus, qualitative abnormalities, such as those described previously, are likely to exist 'unseen'. This further emphasises the need for a study of this type to gain a comprehensive overview of this understudied yet important area and how it may be relevant to those using CSII therapy.

7.2 Aims and objectives

Aims

To determine the cardiometabolic risks of adult patients with T1D using CSII compared to those using MDI using a cross-sectional study design.

Objectives

- To inspect participant's medical records with respect to CM risk markers.
- To analyse the quality of lipoproteins.

7.3 Methods

Medical Record Assessment

As previously mentioned in the General Methods section (see page 45) the medical records of participants were interrogated for basic clinical details. All measurements were originally taken by either a Consultant Endocrinologist or Diabetes Specialist Nurse and all laboratory analysis was conducted by a Biomedical Scientist in concordance with standard hospital procedures. The only exception to this was LDL-C concentration, which was calculated using the Friedewald formula (Friedewald, 1972). The most recent measurements were recorded by the author and were all within the previous three months of the study commencement date. The measures which were documented consisted of date of birth, gender, BMI, HbA_{1c}, insulin dose, basal rate, blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (derived from plasma). A record was also taken if patients were using any kind of medication, whether or not they were a smoker and their length of time using either CSII or MDI.

Plasma Preparation

A venous blood sample of 20 ml was taken from each participant by a trained phlebotomist using a lithium heparin BD vacutainer. The blood was immediately centrifuged at room temperature for 15 minutes at 2000 rpm using a Woodley

Clinispin 2000 centrifuge (no brake was used). The resulting plasma was then aliquoted using a Pasteur pipette equally into 1.8 ml cryovial tubes. Plasma was frozen at -80 °C until further analysis (described below) was performed.

Analysis of Whole Plasma

Half of the plasma was thawed and analysed using an Alfa Wassermann spACE Clinical Chemistry System for total cholesterol, plasma triglycerides, Apo-A1 and Apo-B content. All methods were based upon enzymatic or immunoturbidimetric principles, whereby the reaction between the reagent and sample either resulted in a coloured pigment or an insoluble complex. The absorption of these pigments and complexes at a specified wavelength was directly proportional to the concentration of the biochemical compounds of interest. Quality controls of a known concentration were used in all assays to ensure precision and reveal any deviations in sensitivity from acceptable ranges of absorbance. The specific methods for the assays used during the study are described below:-

Total Cholesterol

Total cholesterol was determined following the method of Trinder (1969). The cholesterol was measured after performing enzymatic hydrolysis and oxidation. This resulted in the indicator quinoneimine being formed from hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase. The assay is estimated at having a within-run precision of 3.73% at 1.71 mmol/L and 3.84% at 7.70 mmol/L and a between-run precision of 1.33% at 1.67 mmol/L and 1.39% at 7.52 mmol/L. The chemical equation for the process is shown in Figure 7.6.

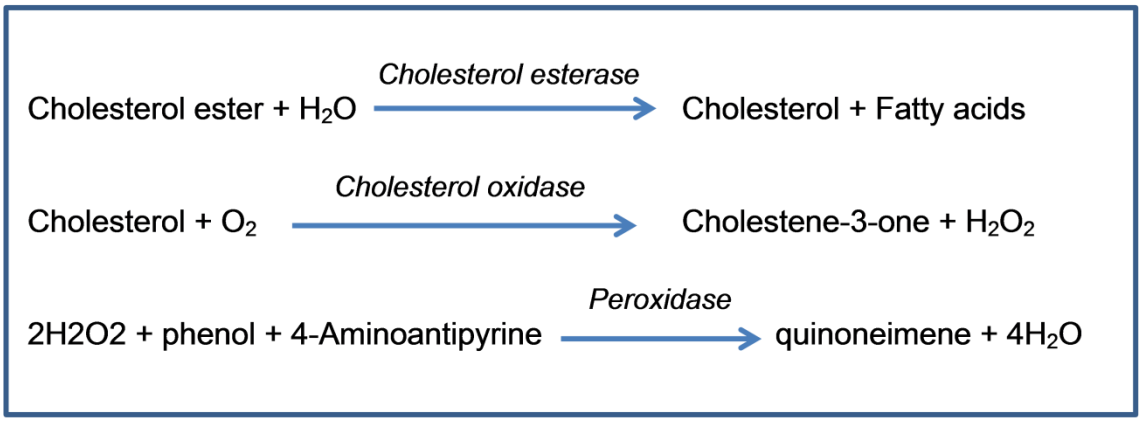


Figure 7.6 – Enzymatic reaction for the determination of total cholesterol

Triglycerides

Triglycerides were measured by using a colorimetric method, based upon their enzymatic hydrolysis with lipases. The indicator quinoneimine was formed from hydrogen-peroxide, 4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase. The assay is estimated to have a within-run precision of 3.29% at 0.308 mmol/L and 1.77% at 5.61 mmol/L and a between-run precison of 3.51% at 0.642 mmol/L and 1.33% at 3.03 mmol/L. The chemical equation for the process is shown in Figure 7.7.

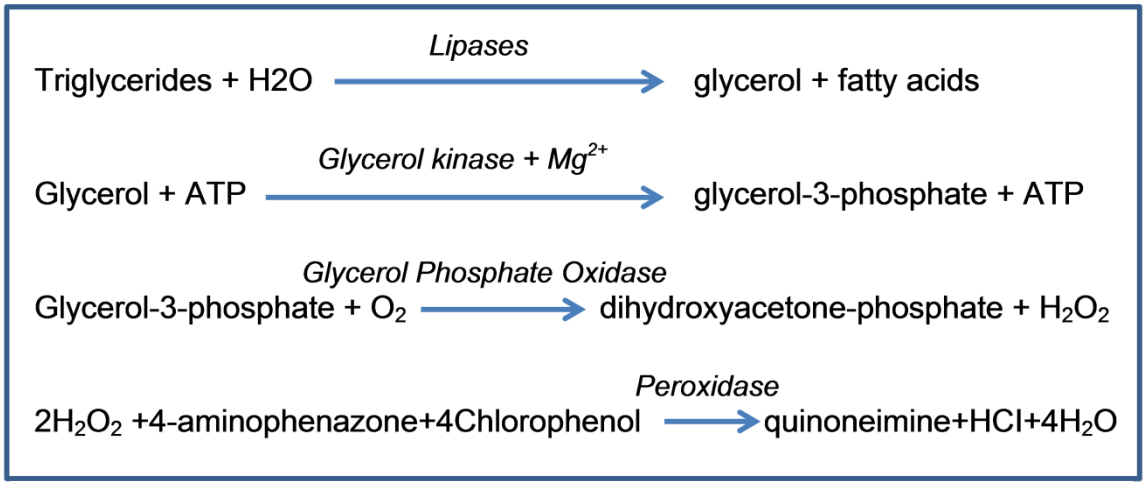


Figure 7.7 – Enzymatic reaction for the determination of triglycerides

Apo-A1 and Apo-B

For the determination of Apo-A1 and Apo-B immunoturbidimetric assays were used. These methods are based upon the reaction of sample containing human Apo-A1 or Apo-B and an antiserum which forms an insoluble complex from which turbidity can then be measured at 340 nm. The results can then be compared to a standard curve to determine the content of either Apo-A1 or Apo-B.

For Apo-A1 the manufacturers estimate that the assay has a within-run precision of 2.67% at 76.0 mg/dl and 4.10% at 221.0 mg/dl and has a between-run precision of 3.1% 70.0 mg/dl and 3.22% at 222.0 mg/dl.

For Apo-B the manufacturers estimate the assay has a within-run precision of 3.86% at 52.7 mg/dl and 4.13% at 154.0 mg/dl and has a between-run precision of 1.79% at 49.4 mg/dl and 2.57% at 127.0 mg/dl.

Separation and Analysis of Lipoprotein Subclasses

The remaining half of frozen plasma was thawed and rapidly separated into LDL and HDL subclasses using ultracentrifugation. The separation of lipoprotein particles in this manner was first performed by John W. Gofman who discovered in the late 1940s that the extremely high speeds which could be achieved using the newly designed analytical ultracentrifuge could also be used to separate lipoproteins into categories (Steinberg, 2007). Over the subsequent years and with the advent of vertical and near-vertical rotors this pioneering work was continued by others and refined to allow the separation of the particles into discreet subclasses in drastically shorter time periods (Havel, 1955; Chung, 1986; Griffin, 1990; Krauss, 1994; Swinkels, 1987). Due to the speed, relative simplicity and ability to easily manipulate gradients ultracentrifugation quickly become an established and frequently used methodology. Work by Graham (1996) revolutionised these techniques by substituting the traditionally used KBr or NaBr salts for iodixanol; a non-toxic, non-ionic and iso-osmotic solution, to create the continuous density gradient required for the successful separation of the principle lipoprotein classes. This method was further developed by Davies (2003) to allow the rapid separation of LDL subclasses and then by Harman (2013) for HDL subclasses. These methods are briefly described below:-

Separation of LDL Subclasses

Materials

Beckman Coulter Optima XPN-90 Ultracentrifuge

Beckman Coulter NVT-65 rotor (capacity for 8 tubes)

Labconco Auto Densi-Flow 115V

Gilson FC203B Fraction Collector

Beckman Coulter rotor accessories (i.e. tube rack, spacers, screw caps, spacer removal tool, torque wrench and adapter).

Beckman Coulter Optiseal™ Tubes (11.2 ml) (and supplied caps)

Axis Shield Optiprep™ solution (60 w/v)

5 ml disposable syringes

Stainless steel cannula

Phosphate buffer solution (PBS)

Methanol

Distilled water

Bijou tubes

Pipettes and tips

Method

A 9% (v/v) solution was prepared using Optiprep™ and PBS as a diluent and 7.9 ml was dispensed into each Optiseal™ tube (1 tube per patient). Iodixanol at 60% (w/v) (0.7 ml) was combined with plasma (2.8 ml) to create a 12% (v/v) iodixanol solution. Next 3.0 ml of this solution was underlayered beneath the 9% solution using a syringe and steel cannula, forming a two-step gradient. The tubes were placed in the rotor and left to stand for 20 minutes. The ultracentrifuge was then programmed to spin for 3 hours at 65,000 rpm at 16°C, with acceleration and deceleration speeds both set to 5.

Each tube was then fractionated using a Labconco auto densi-flow together with a Gilson FC-203B fraction collector. Each 500 µl fraction (consisting of 21 droplets) was collected into 1.5 ml Eppendorf microcentrifuge tubes. The refractive index of

each fraction was then determined using a Bellingham & Stanley Abbe60 refractometer. This was converted into density using the following formula:-

$$\rho = \eta a - b$$

(**ρ** = density, **η** = refractive index, ***a*** = 3.4172 and ***b*** = 3.5637)

All samples were then frozen at -80°C until further subfraction analysis was required.

The further analysis which followed utilised an Alfa Wassermann spACE Clinical Chemistry System to determine the total cholesterol content (method already previously described) of each fraction. These findings, together with the density of each fraction, were used to deduce the presence of different LDL subclasses in each participant and hence determine atherogenic phenotypes. The density ranges pertaining to the different LDL subclasses can be seen in Table 7.3 (Davies, 2003).

Table 7.3 – LDL subclass densities (adapted from Davies, 2003)

Separation of HDL Subclasses

Materials

The materials used were the same previously described for the separation of LDL subclasses.

Method

The method used to separate HDL subclasses was largely the same as that used to separate LDL subclasses; however, a 3-step gradient was employed. To generate the top layer a 15% (v/v) iodixanol solution was produced by adding

PBS. This solution (3.9 ml) was added to an 11.2 ml Optiseal^{TM} tube. Iodixanol was then added to thawed whole plasma to produce a 17.6% (v/v) solution of which 3.4 ml was carefully underlayered beneath the 15% (top layer) solution using a syringe and steel cannula. Finally, a 23% (v/v) iodixanol solution was made by diluting with PBS. This solution was then underlayed beneath the previous solutions again using a syringe and steel cannula, thus producing a three-step gradient.

The same procedure was then followed which was used to separate and analyse the LDL subfractions. The fraction densities used to determine the presence of specific HDL subfractions are denoted in Table 7.4.

HDL Subclass	Density (kg/l)
HDL_2	1.046 – 1.059
HDL_3	1.059 – 1.089

Table 7.4 – HDL subclass densities (adapted from Harman, 2013)

It should be noted that the original protocol by Harman (2013) for the separation of HDL subfractions was intended to be used in conjunction with smaller 4.9ml Optiseal^{TM} tubes and the author had to scale the method up to account for the NVT-65 rotor which only accommodates larger 11.2 ml Optiseal^{TM} tubes. Although no experiments were performed to compare these methods it was hypothesised that the larger tube length would actually facilitate the separation, therefore providing superior resolution.

Quality Control

Before any analysis was carried out a number of quality controls for each assay were run to determine intra-assay variability. Each quality control was run in sets of 15 duplicates. The findings were recorded and a coefficient of variation (CV) was calculated for each quality control. All findings revealed % CV <10, thus indicating low levels of dispersion between each assay and this variability was therefore deemed acceptable. The findings are shown in Table 7.5.

	Quality Control (% CV)		
	Level 1	**Level 2**	**Level 3**
Total Cholesterol	0.907	0.664	N/A
Triglycerides	4.094	5.388	N/A
Apo-A1	3.459	3.545	3.482
Apo-B	2.695	5.256	4.338

Table 7.5 – Coefficient of variation results for each set of quality controls.

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences (SPSS) (v.21). Initially the data was subjected to descriptive statistics after which normality was determined by using the Shapiro-Wilk test. Any data which could be normalised using a log10 transformation was then analysed using Student's *t*-test (the assumption of homogeneity of variance was also tested in this instance). Any data which could not be normalised was subjected to non-parametric Mann-Whitney *U* tests. Spearman correlation coefficients were used to determine relationships between variables of interest. The strength of a relationship between variables was determined according to categories devised by Evans (1996) which are described in Table 7.6. All findings with a *p*-value <0.05 were deemed to be statistically significant.

The image originally presented here cannot be made freely available via LJMU Digital Collections because of copyright or other reason here. The image was sourced at Evans J.D. (1996) 'Straightforward Statistics for the Behavioral Sciences' 1st ed. Brooks/Cole Publishing, California.

Table 7.6 – Correlation *r*-values and their corresponding levels of association (adapted from Evans, 1996).

Lipoprotein Recovery Rates

During the calculations for the lipoprotein subclasses recovery rates were determined for both LDL and HDL separation methods. It was found that when using the LDL separation method the percentage recovery from samples derived from the CSII treatment group was 76.1% (± 2.6) and from the MDI treatment group was 74.1% (± 8.4). When using the HDL separation method the percentage recovery from samples derived from the CSII treatment group was 74.8% (± 4.6)

and from the MDI treatment group was 73.0% (± 7.1). These findings are illustrated in Figures 7.8 and 7.9.

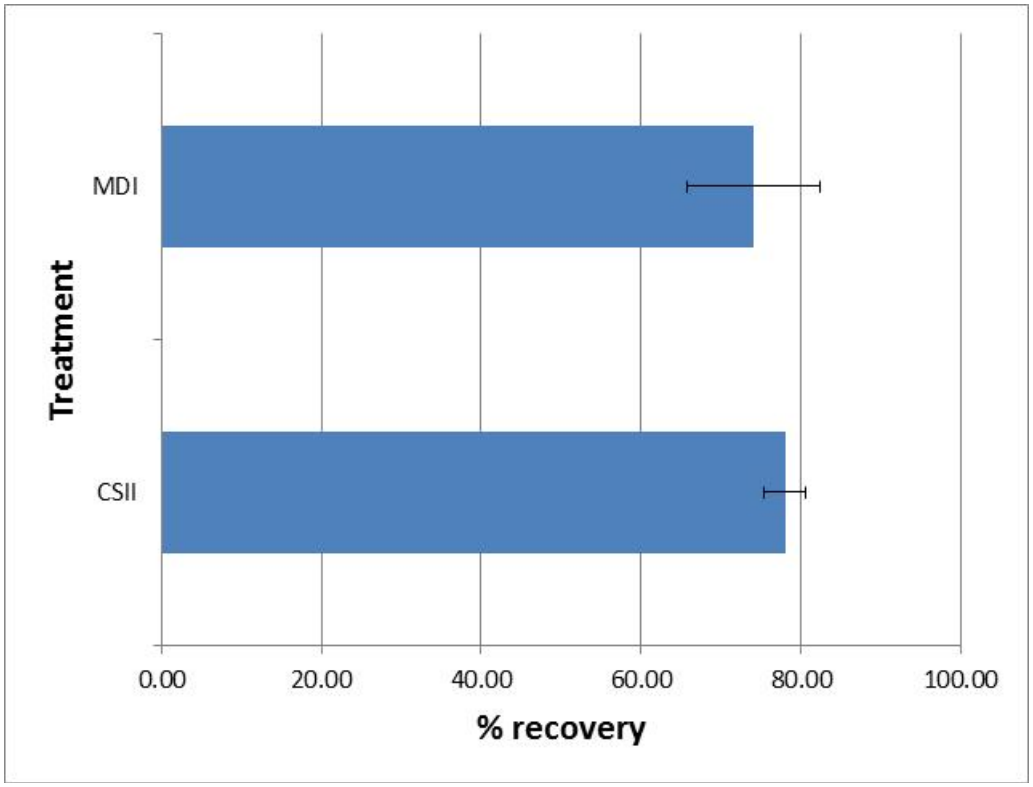


Figure 7.8 – Percentage lipoprotein recovery rates for CSII and MDI treatment groups using LDL separation method.

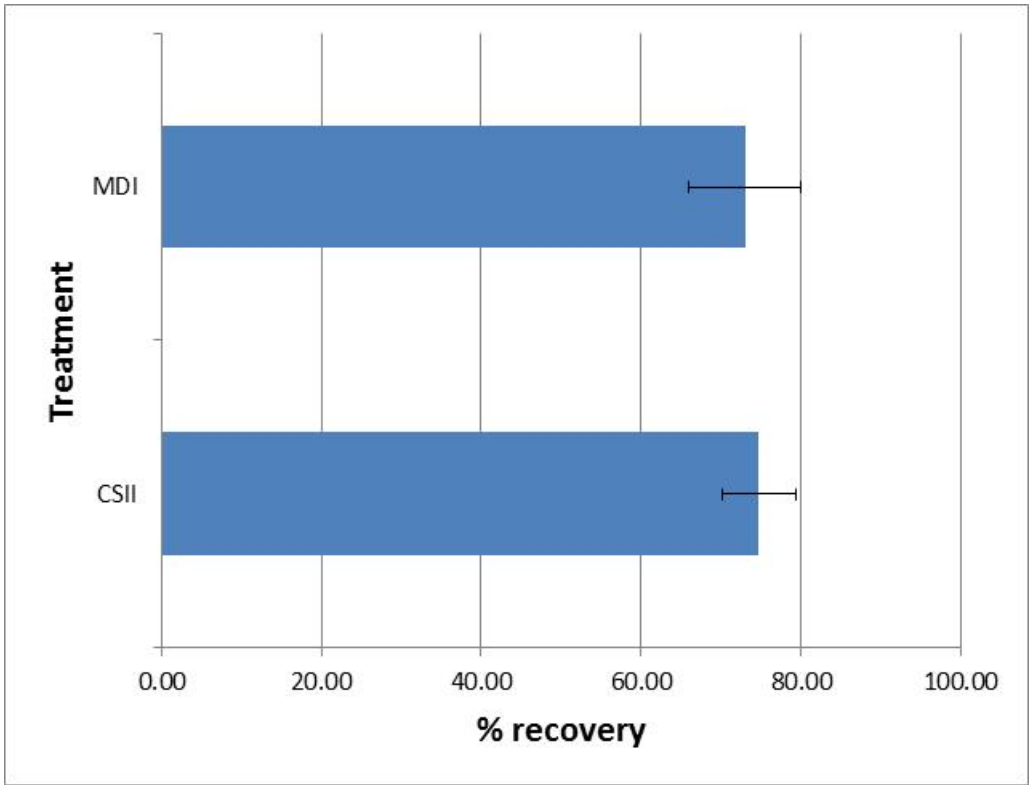


Figure 7.9 – Percentage lipoprotein recovery rates for CSII and MDI treatment groups using HDL separation method.

7.5 Results

Patient Medical Record Data

Basic Characteristics

The medical records of all consenting participants (n = 60) (40 using CSII and 20 using MDI) were assessed. The basic characteristics are summarised in Table 7.7. Please note that although best efforts were taken to retrieve all data some regarding smoking habits was not available in patients' medical records

	CSII (n = 40)	MDI (n = 20)
Age	49.4 (± 14.9)	44.9 (± 17.3)
Sex	13 male / 27 female	7 male / 13 female
Smoker / Non-Smoker	Non-smoker = 34 / Unknown = 6	Non-smoker = 1 / Unknown = 19
Use of lipid lowering medication	40% = Yes / 60% = No	25% = Yes / 75% = No
Use of blood pressure lowing medication	45% = Yes / 55% = No	25% = Yes / 75% = No
Insulin dose (IU/day)	44.1 (± 25.4)	56.9 (± 35.7)
Basal rate (IU/day)	20.3 (± 12.9)	20.4 (± 16.7)

Table 7.7 – Basic sample characteristics of all consenting participants.

Clinical Characteristics

The medical records were assessed for various clinical markers of cardiometabolic risk. These consisted of BMI, HbA_{1c}, total cholesterol, LDL-C, HDL-C, triglycerides and systolic and diastolic blood pressure. The findings illustrated that both treatment groups had a BMI >25 (28.1 kg/m^2 in those using CSII and 25.2 kg/m^2 in those using MDI) and that HbA_{1c} was lower in patients using CSII compared to those using MDI (7.8% vs 8.5% respectively). There was little difference between total cholesterol, LDL and HDL cholesterol levels in either treatment group; however, triglycerides were significantly higher in those using MDI compared to those using CSII (p = 0.021). Furthermore, both systolic and diastolic blood pressure was higher in those using MDI compared to patients using CSII and the difference in systolic pressure reached statistical significance (p = 0.023) (Table 7.8).

Variables	CSII Mean (& 95% C.I.) (n = 40)	MDI Mean (& 95% C.I.) (n = 20)	*p*-value (*=significance)
BMI (kg/m^2)	28.1 (25.6, 30.6)	25.2 (23.3, 27.2)	0.390[2]
HbA_{1c} (%)	7.8 (7.1, 8.5)	8.5 (7.4, 9.6)	0.072[2]
Total cholesterol (mmol/L)	4.3 (3.8, 4.7)	4.4 (3.9, 4.9)	0.503[2]
LDL-C (mmol/L)	1.9 (1.5, 2.3)	2.2 (1.8, 2.6)	0.192[2]
HDL-C (mmol/L)	2.0 (1.8, 2.2)	1.7 (1.2, 2.2)	0.570[1]
Triglycerides (mmol/L)	0.8 (0.6, 1.1)	1.8 (0.7, 1.4)	0.021[2]*
Systolic blood pressure (mmHg)	123.5 (115.8, 131.2)	135.3 (120.8, 149.7)	0.023[2]*
Diastolic blood pressure (mm/Hg)	73.0 (66.0, 80.0)	81.8 (63.8, 100.0)	0.880[2]

Table 7.8 – Clinical characteristics of all consenting patients. All *p*-values derived from Student's *t*-test[1] (or Mann-Whitney *U* test[2] if data was non-normal).

Lipoprotein Quality Analysis

Basic Characteristics

Although 60 patients initially consented to take part in the study, only a subsample (n = 29) consented to donate a sample of blood to allow the further analysis of lipoprotein quality. This subsample of participants consisted of 20 patients using CSII and 9 patients using MDI. A breakdown of clinical characteristics for this subsample extracted from the medical record data are described in Table 7.9.

	CSII (n = 20)	MDI (n = 9)	*p*-value
Age	44.6 (± 15.3)	51.89 (± 15.5)	0.245[1]
Sex	6 males / 14 females	3 males / 6 females	-
Use of lipid lowering medication	35% = Yes / 65% = No	33.3% = Yes / 66.7% = No	-
Use of blood pressure lowering medication	45% = Yes / 55% = No	33.3% = Yes / 66.7% = No	-
BMI (kg/m^2)	27.1 (± 5.4)	26.1 (±3.1)	0.617[1]
HbA_{1c} (%)	8.0 (± 1.6)	7.8 (0.9)	0.910[2]
Insulin dose (IU)	48.9 (±32.3)	59.2 (±48.7)	0.683[1]
Basal rate	23.2 (± 13.2)	18.6 (±19.7)	0.463[1]
Total Cholesterol (mmol/L)	4.3 (± 1.1)	4.1 (± 0.5)	0.605[1]
Triglycerides (mmol/L)	0.9 (± 0.5)	1.1 (± 0.8)	0.942[1]
LDL-C (mmol/L)	2.0 (± 1.0)	1.8 (± 0.4)	0.482[1]
HDL-C (mmol/L)	1.9 (± 0.5)	1.7 (± 0.8)	0.683[1]
Systolic blood pressure (mmHg)	126.5 (± 13.7)	137.1 (± 6.9)	0.060[1]
Diastolic blood pressure (mmHg)	77.3 (± 11.2)	74.1 (± 8.0)	0.499[1]

Table 7.9 – Basic clinical characteristics of the subsample who donated blood to allow the further analysis of lipoprotein quality. All *p*-values derived from Student's *t*-test[1] (or Mann-Whitney *U* test[2] if data was non-normal).

Lipoprotein Subclass and Apolipoprotein Analysis

Table 7.10 describes the findings from analysing the whole plasma for total cholesterol, triglycerides and apolipoproteins, together with the LDL and HDL subclasses which were derived through ultracentrifugation and subsequent analysis. There was little difference in the total cholesterol and triglyceride content of the participants' whole plasma regardless of treatment. This was also true for the LDL I & II which were the same (1.4 mmol/L) in both groups. Furthermore, HDL_3 was also extremely similar between groups, as was Apo-A1 and Apo-B; however, the participants using CSII did possess increased levels of HDL_2 compared to their MDI counterparts (1.7 mmol/L vs 1.0 mmol/L respectively). None of the differences between these variables were shown to be statistically significant. The Apo-B / Apo-A1 ratio was shown to be lower in those with using CSII (0.60) compared to those using MDI (0.72) and this was found to be statistically significant (p = 0.025). These differences are also illustrated in Figure 7.10. When the Apo-B / Apo-A1 ratio was split by gender males using CSII were

found to have a lower ratio than males using MDI and the same was found with females. This breakdown is shown in Table 7.11.

Variables	CSII (Mean and 95% confidence interval)	MDI (Mean and 95% confidence interval)	*p*-value (*=significant)
Total Chol (mmol/L)	4.6 (4.1, 5.0)	4.7 (4.1, 5.3)	0.739[1]
Triglycerides (mmol/L)	0.9 (0.7, 1.1)	1.2 (0.6, 1.8)	0.238[2]
LDL (I & II) (mmol/L)	1.4 (1.1, 1.8)	1.4 (1.1, 1.7)	0.941[1]
LDL (III & IV) (mmol/L)	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	0.779[1]
HDL_2 (mmol/L)	1.7 (0.9, 1.2)	1.0 (0.6, 1.4)	0.713[1]
HDL_3 (mmol/L)	1.1 (0.9, 1.2)	1.0 (0.7, 1.4)	0.214[1]
Apo-A1 (mmol/L)	1.5 (1.4, 1.6)	1.4 (1.2, 1.6)	0.402[1]
Apo-B (mmol/L)	0.9 (0.8, 1.0)	1.0 (0.9, 1.1)	0.103[1]
Apo-B / Apo-A1 Ratio	0.60 (0.54, 0.65)	0.72 (0.60, 0.85)	0.025[1]*

Table 7.10 – Lipid and apolipoprotein characteristics derived from the analysis of whole plasma, together with calculated Apo-A1 / Apo-B ratio and LDL and HDL subclass characteristics resulting from plasma ultracentrifugation. All *p*-values derived from Student's *t*-test[1] (or Mann-Whitney *U* test[2] if data was non-normal).

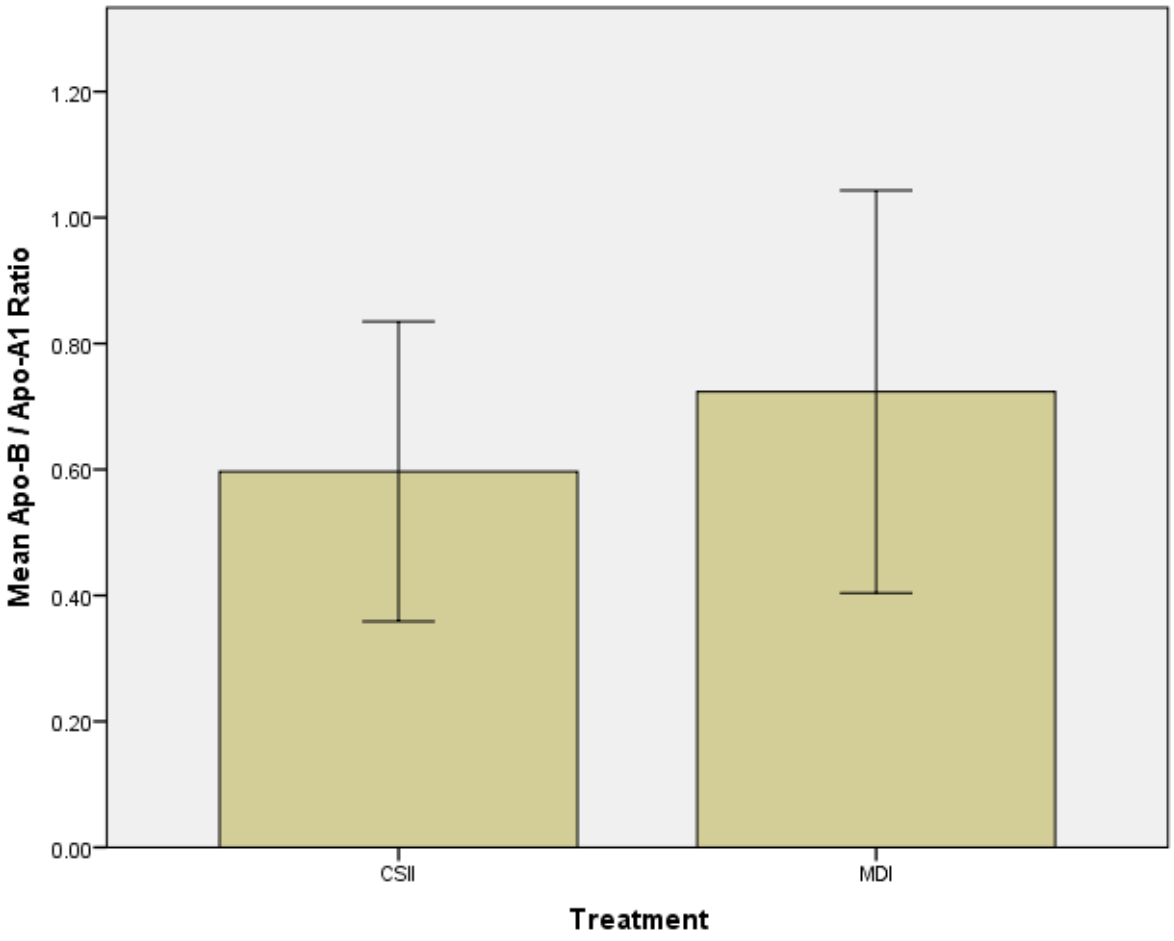


Figure 7.10 – Calculated Apo-A1 / Apo-B ratio difference between subsample using CSII and MDI.

Apo-B / Apo-A1 Ratio split by treatment and gender	Mean Average (95% C.I.)
Males using CSII (n = 6)	0.62 (0.53, 0.71)
Males using MDI (n = 3)	0.73 (0.29, 1.18)
Females using CSII (n = 14)	0.59 (0.51, 0.66)
Females using MDI (n = 6)	0.72 (0.54, 0.90)

Table 7.11 – Apo-B / Apo-A1 ratio split by treatment and gender.

Correlations

The findings from these additional lipid quality investigations were further interrogated by comparing them with the data extracted from the medical records of the subsample (previously described in Table 7.8) to determine any correlations. Spearman's correlation coefficients were used throughout and all significant relationships have been tabulated in Table 7.12.

In participants using CSII a very strong positive correlation was seen between total cholesterol and LDL-C (r = 0.829, p < 0.001) and between HDL-C and Apo-A1 (r = 0.811, p < 0.001).

In those using CSII strong positive correlations were shown to exist between BMI and insulin dose (r = 0.747, p < 0.001), basal rate (r = 0.763, p < 0.001) and triglycerides (r = 0.649; p = 0.003) and also between total cholesterol, Apo-A1 (r = 0.636, p = 0.011), LDL I & II (r = 0.623, p = 0.013) and HDL_3 (r = 0.655, p = 0.008) respectfully. Strong, negative relationships were also revealed in those using CSII between age and total cholesterol (r = -0.601, p = 0.018), as well as between BMI, HDL_2 (r = -0.631, p = 0.003) and HDL_3 (r = -0.639, p = 0.002). Furthermore, additional strong negative relationships were seen between insulin dose and HDL_2 (r = -0.635, p = 0.003) and between triglycerides and HDL_2 (r = -0.687, p = 0.007). In the MDI group strong positive correlations were found between BMI and triglycerides (r = 0.738, p = 0.037) and between total cholesterol, age (r = 0.738, p = 0.037) and systolic blood pressure (r = 0.786, p = 0.036). There was also a similar positive relationship between and LDL and triglycerides (r = 0.786, p = 0.036). Strong negative relationships were seen in those using MDI between total cholesterol and diastolic blood pressure (r = -0.786, p = 0.036), between LDL and HDL (r = -0.795, p = 0.018) and between LDL and HDL_2 (r = -0.771, p = 0.025).

Moderate, positive relationships were found in those using CSII between HbA_{1c} and LDL I & II (r = 0.515, p = 0.024) and between insulin dose and LDL III & IV (r = 0.542, p = 0.017). There were also strong, positive relationships between total cholesterol, HDL (r = 0.562, p = 0.037), Apo-B (r = 0.533, p = 0.041) and HDL_2 (r = 0.550, p = 0.034) respectfully. Further moderate, positive associations were also observed between diastolic blood pressure, systolic blood pressure (r = 0.577, p = 0.008), triglycerides (r = 0.471, p = 0.036), LDL I & II (r = 0.490, p = 0.028) and LDL III & IV (r = 0.461, p = 0.041) respectfully. Moderate negative relationships were seen in those using CSII between age, diastolic blood pressure (r = -0.502, p = 0.024), total cholesterol (r = -0.493, p = 0.027) and LDL I & II (r = -0.487, p = 0.029). Additional moderate negative relationships were shown between insulin dose and HDL_3 (r = -0.473, p = 0.041) and between basal rate, Apo-A1 (r = -0.543, p = 0.013), HDL_2 (r = -0.557, p = 0.011) and HDL_3 (r = -0.581, p = 0.007).

	Positive Correlations			Negative Correlations		
	Variable	***r*-value**	***p*-value**	**Variable**	***r*-value**	***p*-value**
CSII group						
Age				T. Chol. (MR)	-0.601	0.018
				Diastolic BP (MR)	-0.502	0.024
				T Chol. (Auto)	-0.493	0.027
				LDL I & II (Auto)	-0.487	0.029
BMI	Insulin dose (MR)	0.747	<0.001	Apo-A1 (Auto)	-0.563	0.010
	Basal rate (MR)	0.763	<0.001	HDL_2 (Auto)	-0.631	0.003
				HDL_3 (Auto)	-0.639	0.002
HbA_{1c}	LDL I & II (Auto)	0.515	0.024			
Insulin dose	BMI (MR)	0.747	<0.001	HDL_2 (Auto)	-0.635	0.003
	Basal rate (MR)	0.661	0.002	HDL_3 (Auto)	-0.473	0.041
	TAG (Auto)	0.649	0.003			
	LDL III & IV (Auto)	0.542	0.017			
Basal rate	BMI (MR)	0.763	<0.001	Apo-A1 (Auto)	-0.543	0.013
	Insulin dose (MR)	0.661	0.002	HDL_2 (Auto)	-0.557	0.011
				HDL_3 (Auto)	-0.581	0.007
Total Chol.	LDL (MR)	0.829	<0.001	Age (MR)	-0.601	0.018
	HDL (MR)	0.562	0.037			
	T. Chol. (MR)	0.817	<0.001			
	Apo-A1 (Auto)	0.636	0.011			
	Apo-B (Auto)	0.533	0.041			
	LDL I & II (Auto)	0.623	0.013			
	HDL_2 (Auto)	0.550	0.034			
	HDL_3 (Auto)	0.655	0.008			
LDL	T. Chol (MR)	0.829	<0.001			
HDL	T. Chol (MR)	0.562	0.037			
	T. Chol. (Auto)	0.639	0.014			
	Apo-A1 (Auto)	0.811	<0.001			
	HDL_2 (Auto)	0.557	0.038			
	HDL_3 (Auto)	0.790	0.001			
Triglycerides	TAG (Auto)	0.797	0.001	HDL_2 (Auto)	-0.687	0.007
Systolic BP	Diastolic BP (MR)	0.577	0.008			
Diastolic BP	Systolic BP (MR)	0.577	0.008	Age (MR)	-0.502	0.024
	TAG (Auto)	0.471	0.036			
	LDL I & II (Auto)	0.490	0.028			
	LDL III & IV (Auto)	0.461	0.041			
MDI Group						
Age	T. Chol. (MR)	0.738	0.037			
BMI	TAG (Auto)	0.738	0.037			
Total Chol.	Age (MR)	0.738	0.037			
	Systolic BP (MR)	0.786	0.036	Diastolic BP	-0.786	0.036
LDL	TAG (MR)	0.721	0.043	HDL (MR)	-0.795	0.018
				HDL_2 (Auto)	-0.771	0.025
Systolic BP	T. Chol. (MR)	0.786	0.036			
Diastolic BP				T. Chol. (MR)	-0.786	0.036

Table 7.12 – Correlations between clinical characteristics derived from patient medical records and plasma lipid and lipoprotein quality analysis. Data derived from medical records are denoted with 'MR' and data derived from autoanalyser measurements are denoted 'Auto'. Spearman correlations used throughout and only significant (p<0.05) findings

7.6 Discussion

Medical Record Assessment

Upon consenting to take part in the study the participants (n = 60) gave permission for the author to examine their medical records for standard clinical markers pertaining to cardiometabolic risk. It can be seen from the results in Table 7.7 that the majority of patients who participated were using CSII (n = 40) compared to using MDI (n = 20).

On inspection of HbA_{1c} of those using CSII it can be seen that they had substantially lower levels than their MDI counterparts (7.8% vs 8.5% respectively (p = 0.072)). This improvement in blood sugar control is a typical hallmark benefit of CSII and generally occurs immediately after commencing the therapy (Pickup, 2002). Although not statistically significant this may be clinically significant, with previous studies such as the Diabetes Control and Complications Trial suggesting that a 10% reduction in HbA_{1c} is associated with a 43% reduction in the risks of retinopathy (DCCT Research Group, 1995). These favourable reductions are also complimented by those using CSII requiring both smaller daily doses of insulin and a lower basal rate than those using MDI. This is not entirely unexpected as previous studies have demonstrated that the improved glycaemic control typically inferred by CSII is often accompanied by a reduction in insulin requirements (Melidonis, 2016). Despite this being a somewhat predictable finding it remains promising as the large levels of insulin required for subcutaneous methods of administration are generally regarded as physiologically unsound (Wang, 2013). In fact peripheral hyperinsulinaemia, which is common in those with T1D, is associated with inflammation and coronary artery disease and there is additional evidence to suggest that it may impact upon lipid and lipoprotein levels (Wang, 2013; Vergès, 2009).

With respect to the lipid panel, those using CSII generally experienced superior regulation than those using MDI. For example, HDL-C was shown to be slightly higher and total cholesterol and LDL-C was slightly lower (Table 7.8). Triglycerides were the only variable where a significant difference could be seen between those using CSII and MDI (0.8 mmol/L vs 1.8 mmol/L respectively (p = 0.021)). Despite these differences it is important to note that both groups displayed a lipid profile

either bordering upon or lower than recommendations i.e. total cholesterol <4 mmol/L, LDL-C <2.0 mmol/L, HDL-C >1 mmol/L and triglycerides <1.7 mmol/L (NICE, 2015). Furthermore, those using CSII also presented significantly lower systolic blood pressure than those using MDI (123.5 mmHg vs 135.3 mmHg respectively) and diastolic blood pressure was also lower in those using CSII (73.0 mmHg) compared to those using MDI (81.8 mmHg). These findings illustrate that those using MDI are actually hypertensive (when using the NICE hypertension cut-off level of >130/80) compared to those using CSII with blood pressure within the normal range (NICE, 2015).

Despite these somewhat descriptive findings largely 'painting' a promising picture, especially for those patients using CSII, they should be considered in relation to the rest of the results. In particular it is important to note that the mean BMI of participants using both treatments was >25 kg/m^2 and that this predominance of overweight and obese patients is somewhat contradictory to the well maintained blood sugar, lipid and blood pressure parameters illustrated by the findings. That said this is not a particularly controversial finding in itself, with evidence suggesting that after diagnosis BMI typically increases in both children and adults and that the inclusion criteria for the study stipulated all participants must have been diagnosed for a year or longer so weight gain is likely to be expected (de Vries, 2014, Rosenfalck, 2002). The implications of this are far reaching and have been outlined in the introduction, with the incidence of 'double diabetes' becoming more prominent over recent years. Despite these concerns about BMI the other markers of cardiometabolic risk derived from medical records appear at first glance to suggest a population enjoying an absence of wider metabolic abnormalities. However, a closer look at Table 7.7 reveals that this interesting 'alignment of control' may be no coincidence as it is clear there are a relatively high number of patients using both lipid lowering and anti-hypertensive medications, with patients using CSII tending to gravitate more strongly towards these drugs. This may explain the normotensive blood pressure levels, specifically occurring in those using CSII, as well as normalised LDL-C. Furthermore, some evidence suggests that statins may also infer beneficial effects on plasma HDL-C concentrations; with a systematic review of 103 studies by McTaggard (2008) demonstrating that modest increases in both HDL-C and Apo-A1 may occur, likely mediated by

reduced cholesteryl ester transfer protein (CETP) activity. It is unknown why exactly the group using CSII are more highly medicated; however, a reason for this may be that patients using insulin pumps are likely to have more frequent appointments with the same Healthcare Professional, therefore medication requirements may become more 'tailored', as opposed to those using MDI who may only have an annual check-up if their diabetes is well-controlled (as anecdotal evidence suggests is often the case). It should also be remembered that the majority of patients are only offered CSII if difficulties achieving glycaemic control remain despite best efforts; therefore, it is reasonable to suggest that co-existing and related issues may also have been present prior to the commencement of CSII, thus leading to early initiation with these medications. Irrelevant of the reason, medication with these lipid lowering and anti-hypertensive therapies is likely to significantly contribute towards the well-controlled lipid and blood pressure levels described in Tables 7.8 and 7.9 and may explain why they can co-exist concurrently with a raised BMI (which incidentally may be more difficult to control than with medication alone).

Lipoprotein Subclass and Apolipoprotein Analysis

In addition to secondary data derived from patients' medical records, further analysis was also carried out on a sample of blood donated by a subsample. Table 7.9 describes the medical records of the subsample and it is clear to see the findings reflect those illustrated from the larger pool of medical record data pertaining to the general sample. There were only two dissimilarities of note; firstly that the triglycerides in the MDI group appear to be lower than that of the larger sample and display a slight and insignificant difference between those using CSII, with both being below the cut-off value of 1.7 mmol/L (p = 0.942) (NICE, 2015). Secondly, the mean HbA_{1c} of those using CSII was slightly, but non-significantly higher than those using MDI (p = 0.910). This is an unexpected finding and suggests that the patients, who consented to take part in the subsample, whilst possessing an acceptable level of control, may be inferior to that of the general sample as a whole.

After separating the lipoproteins using ultracentrifugation each individual fraction was analysed along with the whole plasma. The results are summarised in Table

7.10 and illustrate that the findings for total cholesterol and triglycerides derived from the analysis of whole plasma are in good agreement with data derived from the assessment of patients' medical records and similarly show little difference between treatments. Furthermore, when looking at the LDL subclasses between treatments it can be seen that both are identical and that there is a predominance of the larger, more buoyant LDL I and II (forming a so-called 'Pattern A') as opposed to the smaller, denser LDL III and IV particles (which contribute toward the more atherogenic Pattern B) (Krauss, 1992). When looking at the literature this is a somewhat unusual finding, with previous research showing how those with T1D, even with good glycaemic control, frequently present a high proportion of small, dense LDL particles (Vergès, 2009).

Although the findings from the present study may be contradictory to this it is important to note that many of the original studies which reported these findings are dated and therefore investigated patients using now antiquated methods of insulin administration (James, 1990; Lahderperä, 1994). Furthermore, many focused on patients with concurrent complications such as kidney disease, which in turn are highly likely to impact upon reported levels of small, dense LDL (*Ibid*). It is therefore hypothesised that the combination of improved glycaemic control inferred by both intensive forms of treatment may have contributed toward this favourable finding. Indeed, this has been shown more recently by Zhang (2016) who used nuclear magnetic resonance (NMR) to measure the lipoprotein subclasses of 1294 patients either randomised to conventional or intensive insulin therapies. The findings demonstrated that although quantitative lipid profiles were similar regardless of therapy, those using intensive treatments presented significantly lower levels of small, dense LDL. When considering that both treatment groups in the present study had not only analogous LDL subclasses but also similar HbA_{1c} levels may indicate that the two groups are similarly controlled and may in turn explain the lack of difference which one might expect considering CSII is typically regarded as a superior method of achieving euglycaemia (Pickup, 2002).

In addition to this another influencing factor may be the proportions of patients using lipid lowering therapies. It can be seen from Table 7.9 that 35% of those using CSII and 33.3% of those using MDI were using statins (with a very small

number using alternative lipid lowering substances). It is well known that the principle mechanisms used by these compounds is to target LDL-C is through both the reduced synthesis of endogenous cholesterol via the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and by increasing the clearance of LDL particles (Stancu, 2001). Furthermore, this group of substances has not only been shown to reduce the risks of CVD by approximately 20% for every 1 mmol/L reduction in LDL-C, but also reduce the concentration of the small, dense fraction of LDL, thus further lowering risks (Ng, 2013). It is therefore reasonable to propose that the engagement by approximately a third of all participants with these drugs is likely to have contributed towards the generally favourable LDL subclass measurements demonstrated in the present study.

Additionally it is equally likely that these substances will also have influenced the HDL subclass profile shown in Table 7.10. It has already been mentioned earlier in this chapter how statins may exert a beneficial effect upon HDL and Apo-A1 and how it is probable that their use may have influenced the lipid profile of the group as a whole. However, when focussing closer on the HDL subclass profiles belonging to the subsample using MDI it can be seen that HDL_2 and HDL_3 were equal and totalled 2 mmol/L. This is again suggestive of a well-protected sample, especially considering that current recommendations advocate obtaining plasma HDL levels above 1 mmol/L (NICE, 2015). Furthermore, it can be seen that those using CSII possessed substantially more of the HDL_2 fractions (1.7 mmol/L) as opposed to HDL_3 (1.1 mmol/L) which totals 2.8 mmol/L and is far greater than recommendations. As mentioned in the introduction it is unknown exactly which particular subfraction infers the most benefit as the number of studies in this area are small with mixed results; however, regardless of this the substantial total HDL-C may initially suggest a high level of cardio-protection. Unfortunately the literature implies that this may not be the case, as despite high quantities of HDL-C very little is known about the functionality of the actual particles. This ‘functionality’ was first considered in the 1990s and it is now accepted that some HDL particles may lose their ability to carry out important functions such as reverse cholesterol transport, as well as the impairment of anti-oxidant and anti-inflammatory properties (Eren, 2012). Interestingly, the findings from recent studies into pharmacological substances designed to increase circulating HDL have proved to

be disappointing. The most recent being a trial on evacetrapib, the latest in a class of failed CETP inhibitors, which reduced LDL and more than doubled HDL, yet the trial was aborted due to no effect on heart disease or stroke (Kolata, 2016). This surprising finding possibly suggests that with regards to HDL perhaps quality may be more important that quantity and in a population at a high risk of CVD, such as those with T1D, further future research investigating this HDL functionality could be useful.

So the question remains; what is an appropriate lipid measure of CVD risk protection in those with T1D? Some evidence suggests that using a ratio of Apo-B / Apo-A1 may be superior. As LDL together with intermediate density lipoproteins (IDL) and very low density lipoproteins (VLDL) all contain an Apo-B molecule in their structure and are regarded as potentially atherogenic particles and Apo-A1 is strongly associated with HDL, a ratio of the two offers a representation of the balance between atherogenic and anti-atherogenic particles (Lima, 2007). There is also evidence that it is a suitable predictor of retinopathy in those with T2D (Hu, 2012). Furthermore, work by Walldius (2004) documented cut-off values to determine risk factors based upon this Apo-B / Apo-A1 ratio. These focussed on cut-off values of 0.69 for low risk to moderate risk and 0.90 from moderate risk to high risk in males. Similar values for females were also defined, with 0.59 being the cut-off from low risk to moderate risk and 0.80 from moderate risk to high risk (Walldius, 2004). When looking at the findings shown in Figure 7.10 and Tables 7.10 and 7.11 it can be seen that regardless of gender patients using MDI were shown to be at a moderate risk of CVD, yet those using CSII appeared to be at a low risk. Although a promising finding, it should be noted that the use of the Apo-B / Apo-A1 ratio has not yet been fully established in the literature as a robust method of determining CVD risk. Also, the small sample size of the present study, which was further reduced when separated by sex, should be observed with speculation and whilst providing interesting findings care should be taken not to over-interpret.

In addition to direct measures various relationships were found between variables derived from patients' medical records and those resulting from the laboratory analysis of plasma which became apparent after performing correlation tests. Among the most striking were the relationships between BMI, insulin dose and

basal rate in those using CSII. Although the associations between this triad of variables were both strong and highly significant they are not entirely unexpected. The literature demonstrates that the higher the BMI the more insulin is required to metabolise circulating glucose as a result of decreased insulin sensitivity (Ferrannini, 1997). Furthermore, in those using CSII specifically it has also been shown that although bolus amounts typically decrease after glycaemic control has been established with the device basal rates actually increase (Chico, 2014). Indeed, this was also shown in the present study, with both basal rates and BMI either being equal to or higher than those presented by participants using MDI, despite lower overall insulin requirements.

In addition to this, a very strong and significant relationship was also seen between total cholesterol and LDL-C in those using CSII. Again, despite being a highly significant finding it is not particularly unexpected, as clear positive correlations have been shown previously between total plasma cholesterol and LDL (Lam, 1990). Furthermore, mechanistic insights reveal that the endogenous synthesis of cholesterol by the liver is a precursor to the production of VLDL particles, which are subsequently stripped of triglycerides, thus forming the LDL used to transport cholesterol to cells (Nguyen, 2007). Interestingly, this endogenous production of cholesterol in those with well controlled T1D is typically undisrupted, unlike those with T2D, hence likely explaining the favourable total cholesterol levels revealed by the results (Gylling, 2004). Despite this, qualitative metabolic disturbances such as increased dietary cholesterol absorption have been reported to exist which may pose risks regardless of favourable quantitative levels, again suggestive of more complex abnormalities which could have had a profound influence, yet were out of the remit of the study (*Ibid*).

Further strong and significant positive relationships were also revealed which have been previously documented by others, such as between age and total cholesterol in those using MDI. It is well known that total cholesterol typically increases from puberty until around age 55 in males and 65 in females, after which time levels diminish. Plasma cholesterol levels originate from three sources; namely the reabsorption of bile salts, the absorption of dietary cholesterol and cellular synthesis and it a reduction in this endogenous synthesis of cholesterol which is predominantly responsible for the decrease in total cholesterol observed in older

individuals (Félix-Redondo, 2013). Additionally, these improvements are often accompanied by a reduction in LDL-C and little change in HDL-C (Ferrara, 1997). Unfortunately, individuals older than 50 years are at an increased risk of CVD and these paradoxical lipid 'improvements' may ultimately offer little atheroprotection (NICE, 2015). Furthermore, in those with obesity, metabolic syndrome or T2D these lipid changes often occur in conjunction with an increase in triglycerides and VLDL and although overall LDL-C may decrease there is typically a predominance of small, dense LDL particles (Strandberg, 2006). Those with T1D are no exception and it is for this reason that NICE recommend patients over 40 years of age with T1D be prescribed statin therapy and is likely to be a principle reason why a high proportion of participants recruited to the present study are using lipid lowering agents (NICE, 2015).

In addition to these relationships, positive associations were also shown in patients using CSII between HDL-C, HDL_2, HDL_3 and Apo-A1, which has again been previously documented (Srivastava, 2000). This, although expected, confirms the symbiotic relationship between HDL-C and it's subclasses and that those with well managed T1D typically experience an increase in Apo-A1 containing HDL particles (Vergès, 2009). This has been shown to be facilitated by an increase in lipoprotein lipase activity resulting from the subcutaneous administration of insulin (Kahri, 1993). Although this may initially appear favourable, those with T1D remain at an increased risk of CVD and these insulin mediated changes may in fact be another mechanism of influence on the Apo-B / Apo-A1 ratio described previously. It may therefore be likely that the reduced insulin dose associated with CSII contributed towards the lower Apo-B / Apo-A1 ratio enjoyed by participants using the therapy, as shown in Tables 7.10 and 7.11 and Figure 7.10 (Pickup, 2002).

Despite these somewhat predictable yet important relationships there were others which were more perplexing. An example is the strong and significant negative association between diastolic blood pressure and total cholesterol in those using MDI therapy. This is unusual because one would not expect levels of cholesterol to decrease with a rise in blood pressure. The evidence also does not support this view, with numerous epidemiological studies highlighting that these CVD risk markers typically develop in tandem rather than inversely (Ferrara, 2002).

Furthermore, there were also negative correlations between age, diastolic blood pressure, total cholesterol and LDL I & II respectfully in those using CSII. As previously mentioned, it is well known that age is often accompanied by detrimental changes in risk markers, even in a healthy population, and in those with T1D these changes are often more pronounced, especially in those with poor glycaemic control; thus further increasing the risks in this already vulnerable population (Vergès, 2009; ADA, 2004). This finding is therefore somewhat difficult to explain.

Limitations

It should be noted that these unexplained relationships were all associated with those using MDI and that the sample size, particularly in this group, was extremely low (n = 9). For correlations to be effective it is useful to use a larger sample as a small number of participants are very susceptible to easily skewed results. Although the data was checked for outliers and none were excluded the standard deviations shown in the results often describe high levels of dispersion from the mean. This is unfortunate; however, the study only had access to one clinic and every possible CSII patient and a matched number of MDI patients were contacted during the recruitment process and so the sample size for this pilot study was saturated within the target area. Needless to say the findings cannot be extrapolated to patients with T1D in general. Additionally, it should also be noted that the quality of data derived from patients' medical records is unknown. Although all measurements were taken / analysed by an appropriate member of hospital staff the conditions under which they were originally derived is unspecified. Furthermore, the method used by the hospital staff to calculate LDL-C (Freidwald equation), despite being cheap and easy to implement also has limitations, with some studies showing the calculation routinely underestimates LDL-C when compared to homogenous assays (Tighe, 2006, Esteban-salán, 2000). These are limitations of this study and although it is acknowledged that some measurements are simple to take (such as blood pressure) and that the author could have made the findings more robust by taking these himself under controlled conditions, the financial cost of others (such as HbA_{1c} and additional lipid analysis) was out of the remit of the study. Despite offering useful insights into the cardiometabolic risks of patients using both CSII and MDI it should also be

remembered that the study was a cross-sectional design. The data therefore only offer a ‘snapshot’ of patients at a single time point with no opportunity to see longitudinal progress. This is unfortunate as the eligibility criteria requested patients to have been using their particular treatment for a year or longer, so all were well-established; however, it would be interesting to see changes immediately after commencement of the therapy where principle improvements in glycaemic control have been shown to take place (Pickup, 2002).

In addition to these study design and medical record assessment issues, there were also various pragmatic problems with the laboratory analysis of plasma which may have influenced the findings. Firstly, as mentioned in the Methods section of this chapter, the HDL method was scaled up from an original protocol devised by Harman (2013). This required the use of 4.9 ml ultracentrifuge tubes whereas the rotor available to the author could only house larger 11.2 ml tubes. Although the method was adapted and it was hypothesised that the larger tube would facilitate a superior separation, without performing a comparative study with the Harman (2013) method it is unknown for sure if this is the case. Hopefully this will be addressed in future work. Secondly, there were also issues with some of the fractionation equipment throughout the process. When fractionating the plasma there were problems with the reliability of the auto-densi flow and it is difficult to assess the damage done. For future studies a more reliable method would be useful, or at the very least an alternative auto-densi flow. It must be stressed that this occurred sporadically and the author immediately intervened where possible to minimise disturbances to the gradient. That said, the recovery rates shown in Figures 7.8 and 7.9 for both LDL and HDL separation methods show disappointing mean percentages, with other published work using iodixanol separation methods recovering up to 100.1% (±4.0) of cholesterol (Kulanuwat, 2015). It is therefore recommended that for future research using these procedures reliability testing is performed.

Conclusion

Despite limitations, the findings from this pilot study show that patients using MDI therapy are generally well-managed and that the same could be said to a slightly greater degree for their CSII counterparts. As expected, glycaemic control overall

was shown to be superior in those using CSII, as was blood pressure; however, very little difference could be seen regarding both quantitative and qualitative lipids and lipoproteins and surprisingly the two groups were remarkably similar. Overall these are promising findings for patients with T1D regardless of which intensive form of insulin therapy is used.

Chapter 8

Quality of Life

8 - Quality of Life

8.1 Abstract

Continuous subcutaneous insulin infusion (CSII) therapy has been shown in the literature to offer improvements in quality of life; however, much of this evidence has been derived through quantitative methods. Qualitative approaches focussing on diabetes-related quality of life and CSII in particular are scarce, yet have the potential to offer unique insights into patients' lived experiences. As such, the author recruited a sample of patients using CSII (n = 40) and MDI (n = 20) to firstly complete a brief quality of life questionnaire. These findings were then used to triangulate responses given by a subsample of patients using CSII (n = 12) and MDI (n = 10) during semi-structured interviews pertaining to quality of life. After the interview data was transcribed verbatim and analysed using thematic analysis the principle findings revealed that diabetes had severely impacted upon patients. The main themes indicated that after diagnosis there was typically an attempt to rationalise the disease and explain why it had developed; together with a fear of the future which sometimes resulted in rebellious behaviour. This was often followed by patients learning to accept and live with the disease; a challenge which for many became an obsession, frequently leading to mental health issues. For those using MDI the concept of CSII seemed pointless; however, for patients with poor control who were recommended the therapy the hope of improved glycaemia was welcome. Despite this many were initially concerned about the physicality of the therapy along with worries about changing their insulin regimen, which had often become an embedded routine. Although many were worried about commencing CSII, after becoming initiated many expressed positive regard for the pump and mentioned that the lifestyle flexibility it inferred greatly improved their quality of life. Aside from emphasising the benefits of CSII and highlighting the improvements in quality of life which can be enjoyed by using an insulin pump this study also revealed important areas of diabetes management which prove difficult for patients and provide areas of focus for future research in this area.

8.2 Introduction

As has been previously discussed, Type 1 diabetes (T1D) is a complex, multifaceted disorder and although daily exogenous insulin administration facilitates the physiological management of the disease, a constellation of additional aspects may lead to detrimental health outcomes, including a decline in quality of life (Rubin, 2000). The term 'quality of life' is itself rather ambiguous and associated with numerous definitions depending on the source consulted; however, one in particular, coined by the Quality of Life Research Unit at the University of Toronto, describes the concept as '*the degree to which a person enjoys the important possibilities of his or her life*' (Quality of Life Research Unit, 2015). The authors then proceed to break this statement down into a number of conceptual categories which in turn are dissected into further subcategories pertaining to their practical 'real-world' components. A more detailed explanation of this is offered in the General Methods section (see page 45). Although this proposed framework refers to the general population, the level of detail is also particularly apt for describing the factors influencing quality of life in those with T1D. This is because the overall well-being experienced by patients is often compromised for a wide variety of reasons which other models often do not account for with more generalised statements.

This plethora of influencing factors has been highlighted in a longitudinal study by Imayama (2011), which revealed that increased health-related quality of life was related to a diverse range of elements, such as being a non-smoker, partaking in physical activity, possessing an ideal body mass index (BMI) and having little co-morbidity. Also, relationships have been shown to exist between quality of life and level of social support, emotional burdens and glycaemic control (Joensen, 2015). Furthermore, due to the issues associated with transitioning from childhood through to adulthood and the increased prevalence of T1D in youngsters, a substantial body of evidence investigating the quality of life of this population exists. This also reveals a variety of factors which impinge on quality of life, ranging from the level of psychological well-being, peer-support and the school environment (Cassarino-Perez, 2014). Additionally, qualitative work by Lowes (2015) shows further relationships between the impact of attending clinics, the communication (or sometimes miscommunication) between patients and

Healthcare Professionals and emotional responses to the disease, which may all impact upon quality of life.

It is important to appreciate that this brief selection of influencing factors is uncomprehensive and serves primarily to demonstrate the complexity of the issue; however, it is also important to recognise that the impact of declining quality of life can be catastrophic for both the individual patient as well as society as a whole. Recent evidence from the Vital Signs report, commissioned by the Richmond Group of charities, described how those with long-term illness are suffering from severely compromised quality of life, with 60% mentioning how their condition impacts upon their daily life (The Richmond Group, 2015). When focussing specifically on diabetes it is estimated that 80% of amputations could be prevented and that the level of access to psychological support is highly lacking, with the UK 'Minding the Gap' survey highlighting how of 85% of patients with diabetes have either no access to psychological support, or at best generic local mental health services (The Richmond Group, 2015; Trigwell, 2008). Furthermore, these disappointing statistics, combined with increased NHS waiting times due to underfunding as demonstrated by a recent report, further compound the issue (NHS, 2016).

Despite this, advances in other areas have improved patient outcomes to an unprecedented level, with the Pittsburgh Epidemiology of Diabetes Complications study showing how the lifespan of those with diabetes has been increasing at rates which far exceed those demonstrated by the general population (Miller, 2012). The UK is no exception to this, with an epidemiological study of 24,000 patients' medical records by Livingstone (2012) illustrating that life expectancy has also increased in those with T1D and whilst patients on average still live 11 years less than the general population, this is a significant improvement on previous research citing a reduced lifespan of between 15 and 27 years.

One factor which is likely to have contributed towards these improvements is the advent of continuous subcutaneous insulin infusion therapy (CSII) in the 1970s. Although initial reports of cannula site infections and incidents of diabetic ketoacidosis briefly tempered enthusiasm for the therapy this was short-lived and as technology and education improved, so too did outcomes and CSII is now

regarded as a safe and effective form of insulin therapy (Pietri, 1981; Pickup, 1982). Consequently, CSII is now associated with improvements in glycaemic control, which in turn may contribute towards reductions in micro and macrovascular disease risk; however, this is not the only benefit of the device, as the very nature of the treatment also infers a level of flexibility above and beyond that offered by its predecessors (Pickup, 2002). For example, the ability of the device to allow the administration of rapid acting insulin in small, regular increments potentially allows patients the opportunity to liberalise their eating behaviours. This has been discussed in detail in the Eating Behaviours chapter (see page 95). Furthermore, the ability to either suspend the insulin basal rate or temporarily detach the device facilitates uncompromised participation in physical activity (Franc, 2015). Additionally, the reduction in hypoglycaemic episodes associated with the therapy is another 'mechanism of encouragement' which may motivate patients with T1D to take part in exercise, which is particularly promising when considering that the main barrier preventing engagement is often cited as being a fear of hypoglycaemia (Brazeau, 2008). Also, the reasonably small inconspicuous size of the device, along with the ability to administer boluses with minimal button presses and with fewer injections is often promoted by manufacturers as providing an extremely quick and unobtrusive method of treatment compared to other therapies (Animas, 2016).

Despite the clear documented advantages and potential benefits of CSII there is very little evidence which examines the therapy in terms of quality of life, not least in terms of patients' thoughts and feelings. This dearth of data has been discussed in detail in the Literature Review chapter (see page 30) where a clear case for further investigation has been proposed. This chapter will therefore describe an investigation, through the utilisation of qualitative and quantitative methods, to determine the influence CSII may have upon the quality of life of adult patients with T1D.

8.3 Aims and objectives

Aim

The aim of this study is to investigate the impact CSII has upon quality of life compared to patients using multiple daily injections (MDI).

Objectives

- To determine patient quality of life using a brief questionnaire.
- To investigate patients lived experiences of T1D with regards to quality of life by using semi-structured interviews.

8.4 Methods

A synopsis of the overall methodology and specific methods used to determine the quality of life of participants are in explained in the General Methods section (see page 45). To summarise, all consenting participants were asked to complete one brief quality of life questionnaire (EQ-5D) as a minimum requirement (Euroqol, 2016). This questionnaire had previously been validated and extensively used in varied populations, including those with T1D (Solli, 2010). A subsample of consenting participants was then asked to take part in one interview. These processes can be visualised through flow diagrams which can be found in the General Methods section on pages 60, 61 & 62.

The interviews were audio recorded and the first interview acted as a pilot. After confirming the data collection method was acceptable (by asking patients if they understood each question during and after the interview) the results were then used as the first data set. The interviews were semi-structured in nature and consisted of open-ended questions grouped around themes designed to investigate participants' 'lived experiences'. The aim of this was to access the thoughts, feelings and subjective understandings of the participants influenced how they experienced quality of life and the manner in which this varied in different contexts (Sparkes, 2014). A detailed explanation of how the structure was determined can be found in the General Methods chapter (see page 45) and examples of the interview structure can be found in appendix 12.6.

Data Analysis

The qualitative data resulting from the semi-structured interviews was analysed using a grounded theory approach. This analytical framework was originally derived from the writings of Glaser and Strauss (1967) which outlines the production of theories and hypotheses generated from systematically collected and analysed data. This process is often recursive, with data collection and analysis often operating in tandem with one another (Bryman, 2004). Since little is known of the quality of life of those using CSII it was agreed by the research team that grounded theory would therefore be an appropriate method to determine the lived experience and thoughts and feelings of participants.

The audio recorded data was transcribed verbatim into separate Microsoft Word documents (1 file per participant). These were then imported into QSR NVivo 10 where the transcripts were coded into themes pertaining to quality of life. This was achieved by following the system outlined by Corbin and Strauss (1990), who suggest three main methods of coding which can be used in grounded theory studies: open coding (where data is broken down and conceptualised and later combined into categories and subcategories), axial coding (where data from open coding is pieced back together in new ways to form relationships based upon their interaction) and selective coding (where coding systematically takes place around a specific framework or central issue). Given that the qualitative aspect of the study is exploratory, combined with a sparse existence of previous evidence and an absence of theories pertaining to the quality of life of those using CSII, the author decided that open coding would be the most appropriate practice to follow due to its propensity to stimulate *'generative and comparative questions to guide the researcher upon return to the field*' (Corbin, 1990, p.12).

The quantitative EQ-5D questionnaire was analysed by inputting the responses into a Microsoft Excel spreadsheet, which was then transferred to Statistical Package for Social Sciences (SPSS) (v.21). The data was then subjected to descriptive statistics. Due to the ordinal nature of the Likert Scale it would be inappropriate to further compare variables using parametric tests. Additionally, as there are only two independent variables to be compared (i.e. the treatment variable which consists of those using CSII and those using MDI) non-parametric

Mann-Whitney *U* Tests were instead deemed more suitable. It should also be mentioned that at the end of the questionnaire participants are asked to complete a visual analogue scale (VAS) to determine present health state. As this is a continuous variable the responses to this were also analysed using descriptive statistics and then examined for normality using the Shapiro-Wilks test. The data was found to be non-normal and attempts were made to correct this by applying a log10 transformation; however, this was not successful and so non-parametric Mann-Whitney *U* tests were again used to compare differences between treatment groups. An example of the questionnaire can be seen in appendix 12.4.

The 'quality' of qualitative data is an important aspect which was considered by the author. In quantitative research this is of key importance, with principle indicators including *objectivity, reliability, generalisability* and *validity* and although it would be inappropriate to apply the same principles directly to qualitative findings, the issue of data quality is no less important (Sparkes, 2014). It is therefore unsurprising that this has been the source of much deliberation which has resulted in the development of various strategies to ensure quality; a thorough review of which is out of the scope of this thesis. Despite the attention this has received most approaches are ultimately founded upon work by Guba and Lincoln (1989), in which key criteria more appropriate to qualitative research was produced, which consisted of *confirmability, credibility, dependability* and *transferability*.

The issue of *confirmability* refers to the level of objectivity presented in the findings. It is important that outcomes are not derived from the researcher's own beliefs or pre-conceived ideas and must be free from bias. One suggestion to tackle this issue is to recruit a '*critical friend*' to encourage reflection and appraise the findings (Sparkes, 2014). In the present study two members of the supervisory team who had no part in the data collection process evaluated the findings in detail. This allowed any findings which were potentially biased to be discussed and evaluated.

Credibility is another important issue which applies specifically to the validity of the data. Traditionally in quantitative data analysis this is typically concerned with the level of confidence concerning the 'trustworthiness' of the data. Although not based around measurements these principles are still relevant in qualitative

analysis to determine that the conclusions made by a researcher reflect reality. Guba and Lincoln (1989) suggest a variety of methods to achieve this, many of which were not suitable for the present study; however, one technique which was incorporated involved the concept of triangulation. This method of observing the research from two or more vantage points required the findings from the interviews and questionnaires to be combined and considered together with a view to validating the outcomes (Denzin, 1989).

Another issue pertaining to the 'quality' of qualitative research is that of *dependability*. In quantitative research this typically describes the reliability of an experiment which the researcher strives to achieve through the manipulation of conditions; however, it would be inappropriate to apply this strategy to qualitative research as the researcher should not try to 'force' something to happen (Wolcott, 1995). Therefore some authors, such as Wolcott (1995), suggest rather than trying to address reliability in qualitative studies, efforts should instead be made to explain to audiences why it is not appropriate. After considering this the author decided that reliability is not an issue which needs not be discussed further.

The final potential issue related to the 'quality' of qualitative data involves the generalisation of findings to the larger population. This is commonly addressed in quantitative research through the use of sample size calculations and other methods founded in probability theory to ensure that study outcomes can be extrapolated to the general population with a degree of confidence (Flick, 2015). This is not a concern of the present study, firstly because it is already acknowledged by the research team that the study was pilot in nature and secondly, because the sample was derived from only one clinic it would be premature to suppose that any findings are representative of a larger population of patients with T1D. Furthermore, some authors such as Chenail (2010) suggest that whereas quantitative research demands that the responsibility must lie with the researcher to ensure generalisability, qualitative research instead requires a large portion of the responsibility to sit with the reader when assessing the value of a piece of research. Therefore, although it is recognised by the author that there may be issues when attempting to relate the findings from the present study to the wider population, the reader may also have to accept this too.

8.5 Results and Discussion

As the study utilised both quantitative and qualitative methodologies this section will firstly describe the findings from the quantitative questionnaire and will then move on to present and discuss the qualitative findings whilst referring back to those obtained from the questionnaire for triangulation purposes. It is hoped that this will not only provide a suitable level of data quality, but that it will also provide a logical 'flow' and allow a story to develop, thus allowing the reader to develop an understanding of the lived experiences and quality of life of patients using both CSII and MDI.

EQ-5D Quantitative Results

The EQ-5D questionnaire was given to every consenting participant of the cross-sectional study to complete (n = 60). A brief summary of the sample characteristics can be seen in Table 8.1.

	CSII (n = 40)	**MDI (n = 20)**
Gender (%)	Male = 32.5% / Female = 65.0% / Missing = 2.5%	Male = 35.0% / Female 65.0% / Missing = 0%
Age (± SD)	46.6 (± 15.1)	46.3 (±17.9)

Table 8.1 – Summary of participant characteristics

It can be seen in Table 8.1 that the majority of participants were using CSII therapy (n = 40) compared to those using MDI (n = 20). Furthermore, in the CSII group there were also fewer males compares to females (32.5% and 67.5% respectively). Similar proportions of males compared to females were also seen the MDI group (35.0% and 65.0% respectively). The ages of the participants were also similar between those using CSII and those using MDI (46.6% and 46.3% respectively).

The outcomes from the main questionnaire are summarised in Table 8.2. When looking at these findings one can see that both treatment groups have nearly identical responses referring to participants' '*mobility*'; however, despite these similarities between groups nearly a quarter of participants using both CSII and MDI reported problems (25.0% and 20.0% respectively). Also, one participant using MDI failed to provide a response for this question.

The levels of '*self-care*' between groups were identical, with 90.0% of those using both CSII and MDI reporting no problems with self-care and only 10.0% of those using either treatment reporting issues.

When looking at the levels of '*activity*' it can be seen that those using CSII reported slightly less issues (70.0%) compared to those using MDI (75.0%); however, there were still approximately a quarter of participants using both CSII and MDI who reported some problems engaging in activity (25.0% and 20.0% respectively). A small proportion of participants using both treatments (5.0%) reported extreme problems engaging in activity.

Participants using both treatments (55.0%) reported no problems regarding '*pain*'; however, a large amount using both CSII and MDI reported some problems (35.0% and 40.0% respectively) and a smaller amount in those using both CSII and MDI reported extreme problems (10.0% and 5.0% respectively).

When looking at the responses given to the '*anxiety*' question it can be seen that the majority of participants using CSII (72.5%). The majority of those using MDI (65.0%) also reported no issues. Despite this, over a quarter of those using both CSII and MDI reported some problems (27.5% and 30.0% respectively) and a small amount of those using MDI reported extreme problems (5.0%).

After performing Mann-Whitney *U* tests on each variable it can be seen in Table 8.2 that none of the differences were statistically significant.

Category		CSII	MDI	*p*-value
Mobility	**No problems**	30 (75.0%)	15 (75.0%)	0.917
	Some problems	10 (25.0%)	4 (20.0%)	
	Extreme problems	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	1 (5.0%)	
Self-care	**No problems**	36 (90.0%)	18 (90.0%)	1.000
	Some problems	4 (10.0%)	2 (10.0%)	
	Extreme problems	0 (0.0%)	0 (0.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
Activity	**No problems**	28 (70.0%)	15 (75.0%)	0.705
	Some problems	10 (25.0%)	4 (20.0%)	
	Extreme problems	2 (5.0%)	1 (5.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
Pain	**No problems**	22 (55.0%)	11 (55.0%)	0.873
	Some problems	14 (35%)	8 (40.0%)	
	Extreme problems	4 (10.0%)	1 (5.0%)	
	Missing	0 (0.0%)	0 (0.0%)	
Anxiety	**No problems**	29 (72.5%)	13 (65.0%)	0.485
	Some problems	11 (27.5%)	6 (30.0%)	
	Extreme problems	0 (0.0%)	1 (5.0%)	
	Missing	0 (0.0%)	0 (0.0%)	

Table 8.2 – Findings from the EQ-5D questionnaire quality of life categories and *p*-values derived from Mann-Whitney U tests investigating the difference between treatment groups

The findings for the EQ-5D VAS question showed that those using CSII on average reported a mean health score of 69.9 ± 20.6 (with 0 denoting worst possible health and 100 denoting best possible health). Those using MDI reported a higher score of 77.3 ± 13.9; however, after performing a Mann-Whitney *U* test it can be seen that the difference between these findings was not statistically significant ($p = 0.307$).

Semi-Structured Interview Results and Discussion

Interview Summary

In total 22 semi-structured interviews were carried out (12 with participants using CSII and 10 with participants using MDI). The overall group consisted of 31.8% males and 68.2% females. As mentioned in the General Methods (see page 45) and earlier in this chapter a number of definitions pertaining to quality of life exist and the author thought it appropriate to utilise one definition in particular to underpin the structure of the interviews. This definition was derived from the University of Toronto and although it has been previously discussed in more detail it is important to point out that despite many of the points bring covered during the interviews the aim was not to use it as a rigid 'checklist', but rather a general guide to inform the direction of the research (Quality of Life Research Unit, 2016). Copies of the interview guides which were used can be found in appendices 12.6. Also, the real names of participants have been anonymised to protect their identities and each was instead assigned a code, which are referred to herein. Each interview lasted between 1 – 1½ hours.

During the analysis of the interviews various themes emerged. It became apparent that these could be grouped into three broad categories concerning '*the impact of T1D on the sense of 'self'*', '*the principles and realities of CSII and MDI*' and '*the future of living with T1D*'. These then contained various principle subthemes. This structure is summarised in Table 8.3 and discussed in detail thereafter.

Broad Theme	Specific Principle Subthemes
Impact of T1D on the sense of 'self'	Desire to 'rationalise' diagnosis
	Difficulties during diagnosis
	Adaptation to life with T1D
	Barriers associated with T1D and divorce from a 'normal life'
	Stigma and T1D
	Resentment of T1D
	Fear and T1D
	Decline in mental health after diagnosis
The principles and reality of CSII and MDI	Potential of CSII to allow lifestyle flexibility
	Practical challenges of CSII
	Perceptions of CSII
The future living with T1D	Health aspirations

Table 8.3 – Specific principle themes which emerged from semi-structured interviews

The impact of T1D on the sense of 'self'

Desire to 'rationalise' diagnosis

It is well known that T1D is a progressive autoimmune disorder which may develop asymptomatically for a number of years; however, by the time noticeable onset occurs the patient is likely approaching a 'critical mass', typically leading to an onslaught of rapid and serious metabolic disturbances, which if left untreated can quickly become fatal (Atkinson, 2000). During the interviews participants were asked to describe themselves before T1D and most emphasised how their lives previously were '*typical*' or '*normal*'; however, a common theme which surfaced was desire to unpick and rationalise the onset of the disease. For instance, many believed that the diabetes was triggered by a traumatic experience. An example of this was given by patient C006 (a female, CSII user, aged 30) who suggested it was …

> *'really strange because there was no family history or nothing, but when I was seven I fell asleep on top of a twelve foot fence. I fell off … the shock of that caused my pancreas then to stop working'*

Patient C055 (a male, MDI user, aged 55) also explained how after being unexpectedly punched after intervening in a street fight …

'I actually felt this shudder inside me and I don't know what it was but I went back home to my wife and my wife said I was really reacting funny saying "oh I feel really strange", you know and then 10 days later I was diagnosed as a Type 1 diabetic … so I'm convinced that the shock of it kicked it off'.

These imagined links are often seen in those with chronic illness, with work by Williams (1984) revealing how patients with arthritis also revealed a strong desire to determine an exact reason for their condition, which is likely the result of the medical profession unable to explain the cause. When bringing the focus back to diabetes this appears to be no exception, with current knowledge unable to determine the exact aetiology of the disease and interview findings suggestive of a strong desire to determine the cause. Unfortunately, the scientific evidence placing trauma as a cause of T1D is not quite as enthusiastic, with controversies surrounding the topic being decades old. Dr Elliott Joslin discussed this phenomenon in a review over 70 years ago and concluded that the concept had lost favour in the medical profession, yet more recent evidence has shown correlations between traumatic experiences in early life and the onset T1D (Joslin, 1943; Nygren, 2014). Despite this, existing studies are few in number and it would be premature to infer causation as it highly likely that those who experience a traumatic situation may consequently acquire the disease by chance alone and many reports fail to account for the time where the disease develops 'covertly' prior to symptoms (Atkinson, 2014). Healthcare Professionals may do well to note this desire of patients to rationalise their disease and whilst supporting them through diagnosis also ensure that an evidence-based approach is utilised to ensure any conclusions based upon reflections aren't unfounded.

Difficulties during diagnosis

Aside from the traumatic pre-diabetes experiences which many patients reported, it was also common for the actual onset and diagnosis of T1D to be described in detail. This was almost universally regarded, for a multitude of reasons, as a powerful and life-changing experience. Initially participants generally offered descriptive, longitudinal accounts of the symptoms which typically consisted of increased weight loss, tiredness and urination as well as an unquenchable thirst (Diabetes UK, 2015). Many patients remarked about how they initially mistook or

downplayed their symptoms with Patient C008 (a female, CSII user, aged 38) remarking that …

> *'I put it down to completely different things … I was up in the middle of the night [to go to the toilet] … but then I'm not a medic so I didn't put it together, but thinking about it now I think it all fitted in'.*

Despite attempting to ignore the warning signs they often became unbearable and providing the patient hadn't already collapsed they would usually make an appointment to see their family doctor. It was at this point an assortment of themes emerged. A principle theme which became quickly obvious was that this misdiagnosis all too often extended from the patient to the medical profession. Patient C020 (a female, MDI user, aged 69) illustrated this when she mentioned how …

> '*I went to my G.P. and she took a specimen of my urine and she tested it and it was blue and she berated me for wasting her time and she said that I shouldn't try and self-diagnose by reading books and a lot of other stuff and the thirst she said must have been due to eating too many spicy foods that I didn't eat*'.

She later explained how she was rushed to hospital after collapsing and falling into a coma and that the G.P. should have in fact performed a blood test to check blood sugar levels. These stories in addition to being common also highlighted a frequent mistrust of the medical profession, even in the early stages of T1D.

In a society where consumers typically rule and medical information is easy to obtain patients often feel like they no longer have to obediently follow Healthcare Professionals and erosion of trust can have profound implications (Rowe, 2006). The healthcare system has recognised this and responded by adopting so-called 'patient-centred' care which was revealed by the interviews to frequently play a key role during and immediately after diagnosis where many patients explained how their knowledge of the disease was generally poor and many were initially shocked and worried about their health and future. Patient C049 (a female, using MDI, aged 23) illustrated her high regard for this by stating that …

'I started coming to the Diabetes Centre at the hospital and the nurses would talk you through things here and they would have presentations and they would talk you through all the treatments and any complications and I felt that having these things explained and why you have to do this certain type of treatment in this way really helped me to understand it and I think that that really helped to make it a lot easier'.

In contrast, participants diagnosed with the disease some time ago described a distinct lack of information and communication from doctors and nurses, with Patient C026 (a female, using MDI, aged 68) explaining how …

'you weren't told anything in them days and you didn't have the internet to read things up so it was just what a nurse or a doctor told you really and I mean you never knew about your own condition and the complications that came with it'.

Admittedly, diabetes knowledge in the healthcare profession is now greater, which may in part have contributed towards the level of disseminated information; however, it has been known for some time that these positive patient-Healthcare Professional relationships may in themselves improve metabolic control (Viinamäki, 1993). Therefore, this trend towards patient-centred healthcare can potentially result in swiftly broken relationships if poorly managed, can also be built upon to empower patients and ultimately improve outcomes.

Adaptation to life with T1D

After the initial shock of diagnosis and the subsequent discovery of information about T1D, the participants then typically reported a number of lifestyle adaptations which took place to accommodate T1D into their lives, aside from the daily administration of insulin alone. One such lifestyle change was that patients had to give extra consideration to physical activity, with Patient C009 (a male, using CSII, aged 39) explaining how …

'post-diabetes you have to know what your blood sugar levels are, how much insulin you're taking and you have to plan everything, everything has to be planned. You know you can't just get up and think right I'm going to go

out and play football. You've got to get up, you've got to test, you've got to eat, so it makes you a lot more structured'.

In addition to this alterations to diet were required to 'feed' excess insulin and were also referred to as being challenging. Patient C059 (a male, using MDI, aged 33) emphasised this by mentioning how …

'I would have to make sure I have breakfast, make sure I have lunch and make sure I have an evening meal throughout the day and it was something I struggled with for a number of years really, just making sure I had arranged all those meals and just making sure they were all balanced and everything and it caused me problems with my blood sugars and stuff'.

Lifestyle changes regarding diet and physical activity in general are notoriously difficult to achieve in both the normal population and in other populations where changes are essential to improve outcomes, such as the obese. The literature is awash with records of poor attainment, such as the NDNS showing frequent failures by the public to meet dietary recommendations and the Active People Survey highlighting how 57% of adults in the UK do not take part in any form of sport (NDNS, 2014; Sport England, 2014). When focussing on diabetes, the Eating Behaviour chapter revealed failures by the participants' to meet some dietary recommendations and Diabetes UK data illustrated how only 39% males and 29% females with the disease fail to meet recommended physical activity levels (Diabetes UK, 2014). Furthermore, it is also important to reiterate salient findings shown by the EQ-5D questionnaire which revealed how despite the majority of participants reporting no problems with their levels of activity or mobility, there remained approximately a quarter who mentioned either some problems or extreme problems regardless of treatment type. It is therefore easy to understand why these required changes may pose such a challenge to patients and these findings should emphasise that consideration and support is required by Healthcare Professionals (Young, 2014).

Barriers associated with T1D and divorce from a 'normal life'

These practical aspects, whilst providing their own individual challenges, contributed to the wider theme of 'barriers' which were associated with the

disease. For example, career opportunities were viewed as restricted, with Patient C010 (a male, using CSII, aged 58) remarking how his aspirations were dented when …

> *'the doctor said to me "the army's out for you", which was a bit of a shock really as I sort of thought I had my life laid out'*.

There were also various authoritative restrictions imposed, with Patient C059 describing how …

> *'you still want to live a normal life and you can't….it's stuff like the DVLA saying that you need to take your blood sugar before you go out driving and stuff'*.

Interestingly, some of the barriers, aside from those imposed by the disease itself or societal requirements were also imposed by those who cared about the participants the most, with Patient C013 (a female, using MDI, aged 60) remembering how …

> *'my Mum was very protective and I remember … it was a big impact. You couldn't do anything. You couldn't go out with your friends. You know it just impacted such a lot'*.

The specific descriptions of barriers to the *'normal life'* mentioned by Patient C059 were reoccurring themes throughout the interviews and have been previously recognised by others and it is for this reason that charities such as Diabetes UK offer support through the organisation of holidays and information weekends for newly diagnosed patients and their carers (Diabetes UK, 2016). Unfortunately, despite support, this idyllic notion of a '*normal life*' remains impossible to define and equally as unfeasible to achieve, yet it remained an aspiration which was often expressed as the participants took the author through the journey of their lives.

Stigma and T1D

Unfortunately, this mirage of a hallowed *'normal life'* was frequently juxtaposed against a backdrop of stigma, with participants opening up about unjustified vindications resulting from the disease, thus further compounding the perception

that their lives were in some way distinctly different to those without. An example was when Patient C001 (a male, using CSII, aged 45) mentioned that on a night out …

> *'I've had a bouncer come up to me and ask me what I was doing cause he thought I was doing drugs but I just said "no I'm just checking my bloods to see if I could have another drink … I could always do it in the toilet and make it look even more dodgy" and he said "well fair enough, but if anyone complains we are going to have to ask you to leave"'*.

This public shaming even occurred in places where individuals should be better protected, such as in the workplace, with Patient C048 (a female, using MDI, aged 62) mentioning how when sat in the staff canteen at her supermarket job …

> *'I used to say to the girls sitting round the table "if you don't like needles look away now" and I just used to stick it [insulin pen] in and one of the managers, a section manager, said "it's enough to put yourself off your food isn't it", so I said to her "it doesn't look like anything puts you off your food love!" because she was so overweight and everyone on the table started to laugh ... I was surprised, I was shocked, but I thought "you're not getting the better of me love!".*

These remarks, although shocking and discriminatory, are not unusual, with the literature also confirming how the scope of this stigma is widespread and how derogatory comments made through either a lack of knowledge, misconceptions or prejudice serve only to isolate and are likely to further catalyse the feelings of *'abnormality'* referred to above (Browne, 2014).

Resentment of T1D

Maintaining control of T1D on a daily basis is a large obligation to shoulder, requiring high levels of patient motivation and responsibility. Unfortunately, these were shown to often suffer under the pressures of directly managing the disease combined with additional factors such as those previously described and stories of participants deviating from the required disciplined approach were common. Patient C026 aptly described this by mentioning how …

'I used to feel really sorry for myself…."why me?, Why do I have to do this? Why can't I eat this? Why can't I have what I want?", you know I really really resented it as a teenager and I really went off the rails and I freely admit that … in terms of my food. I just ate everything, I couldn't have cared. I really rebelled against it. I can remember drinking bottles of Vimto. I liked it and I thought "well I'm gonna drink it". I used to forge my blood urine test results. Oh I can remember doing it yes. Really really resented it. Hated every minute of it'.

This strongly voiced denial of the disease and the neglect of responsibility is not restricted to Patient C026 alone, but is a common trait in newly diagnosed patients and particularly in those passing through adolescence and this rebellious behaviour is often regarded as a coping strategy (Graue, 2004). The implications of this behaviour are profound, as non-adherence to insulin regimens has been associated with declines in glycaemic control, which are in turn associated with increased risks of complications (Hood, 2009; The DCCT Research Group, 1998). Fortunately, with support from Healthcare Professionals many patients may refrain from this behaviour as they emerge from adolescence or the shock of diagnosis fades; with Patient C026 herself embodying this by describing how when she got married she started to think … '*hang on, I'm only doing harm to myself here'* (Taddeo, 2008). Despite this it is unknown quite how much damage is caused during these periods of deviation; however, it is known that metabolic disturbances begin at an early age, with adolescents with T1D frequently presenting disrupted lipid profiles and reduced insulin sensitivity in those with poor control, indicating a potential area of risk in which Healthcare Professionals should pay close attention to (Bjornstad, 2015).

Fear and T1D

Despite the grave implications of these disturbances it is not to say that patients are oblivious. In fact the opposite may be true, with 'fear' being a common theme interwoven throughout the interviews and with regards to long-term health implications patients understandably expressed unease. Patient C049 explained this by mentioning how …

'I was quite concerned when I first got it [diabetes] and it was quite a lot to take on board that all of these horrible things might happen to you'.

However, despite the long-term complications it appeared to be the more immediate, short-term issues which seemed to cause the most distress. In particular a fear of hypoglycaemia was often referred to as being an important aspect of the disease which when uncontrolled had a crippling effect on patients' lives. Due to the unpredictability of the events and the severity of their nature many recovered and were left feeling embarrassed, ashamed and lacking confidence, which in turn often manifested in patients withdrawing from activities. Furthermore, in some cases the participants also explained how their warning signs had disappeared making the experiences even more alarming. Although the examples are too numerous to describe individually a particularly vivid insight was expressed by Patient C030 (a female, using CSII, aged 59), who mentioned how when working alone at work …

'I was passed out under the table and it wasn't until somebody else came up and they walked around the table and they found me … yes, it's embarrassing being carted through the office on a chair!'.

Also Patient C059 proceeded to describe how when in Spain …

'I had a really scary hypo when I was on the train back to Barcelona and everyone was asleep on the train and I woke everybody up screaming and banging my head against the window and stuff'.

He then explained how this subsequently developed into …

'a fear about blood sugars because you aren't aware [of the onset due to diminished awareness] and you are worried that you are going to have a hypo so you will … change your food and lifestyle and the first thing that is easiest to change is to not do much exercise'.

These characteristics are common in those with T1D and the evidence suggests the intensity of the fear grows with the severity and frequency of the episodes and that in some cases the apprehension of patients may even exceed anxieties

regarding long-term issues such as vascular diseases (Anderbro, 2010; Pramming, 1991).

Decline in mental health after diagnosis

The complex interactions previously described unfortunately often culminate in a decline in mental health. This has been extensively investigated in the literature, with estimations suggesting that up to a third of patients with diabetes experience depression or anxiety or both (Anderson, 2001; Grigsby, 2002). The participants in the present study appeared to be no exception to this, with some describing how the permanency of the disease caused a perceived loss of control and a perpetual feeling that diabetes is 'always on the mind'. This it turn frequently resulted in certain obsessive behaviours, with Patient C006 illustrating this by explaining how …

> *'I'd get an A4 sheet of paper and I'd highlight my highs, this is how crazy I am, highlight my highs in red, highlight my lows in yellow and do the green for the normal bloods and I'd say like "I've had say four highs in one day", so that's like fifty percent … I became obsessed and diabetes was my life and it didn't work!'*.

These disorders were typically accompanied by other numerous issues such feelings of guilt and hopelessness which in turn often manifested themselves as depression and anxiety. Interestingly the findings from the EQ-5D questionnaire shown in Table 8.2 also describe that over a quarter of those using both CSII and MDI reported suffering from anxiety, corroborating comments made both in the interviews and the literature about these common mental health disorders in this population.

The principles and reality of CSII and MDI

When patients were asked about living with T1D the comments were invariably negative; however, in contrast the commencement of CSII was held with generally positive regard considering the steep learning curve of the therapy and the requirement to adopt a completely new way of managing the disease. Perhaps the most obvious benefit which was initially expressed was the ability of the device to improve glycaemic control and hypoglycaemia. Furthermore, the EQ-5D

questionnaire also showed how patients reported no problems in their self-care, further indicating that participants were generally pleased with the therapy overall. Although these are positive attributes they were not unexpected as improvements in glycaemic control upon the commencement of CSII have been reported extensively in the literature (Pickup, 2002). Interestingly, although it is likely that these positive findings may have had an impact upon quality of life when considering the anxiety and fear poor glycaemic control can instigate, it was surprising that the participants were somewhat reluctant to spend time discussing this and were more eager to explain how the benefits from other areas of the therapy had more of an impact upon their quality of life.

Potential of CSII to allow lifestyle flexibility

A principle reoccurring theme was the opportunity provided by CSII for patients to escape the rigid structure imposed when using other regimes such as MDI. A specific example of this was the ability to relax the diet. Participants mentioned specifically how the relatively structured diet associated with MDI was partly responsible for the obsessional behaviours mentioned earlier and how this in turn frequently resulted in food and drink items becoming 'medicalised'. An example of this was highlighted by Patient C009 who stated that …

> *'I did start to see biscuits as a sort of medicine on the basal bolus regime, it was sort of "you've got to take your snack before bed" and emotionally there is a loss of control and feelings'*.

This relaxation of dietary habits is a currently under-researched area, with a thorough review of the topic in the Literature Review and Eating Behaviour chapters (see page 30 & 95); however, it was clear from the interview data that the participants regarded CSII as a vehicle to break free from this imposed structure. Interestingly, patients using MDI who had recently completed a carbohydrate (CHO) counting course also reported this opportunity for dietary liberalisation and couldn't see how CSII could offer any benefit in this regard. The literature surrounding the physiological benefits of this are somewhat controversial, with a meta-analysis by Bell (2014) showing that weak, non-significant improvements in HbA_{1c} are typically seen after completing a CHO counting course. Furthermore, there was only one study included in the analysis which lasted over 12 months and

so the long-term impact is disputable (*Ibid*). Despite this, research by the DAFNE Study Group (2002) does indeed suggest the courses are associated with quality of life benefits, with significant self-reported improvements when compared to controls which substantiate the participants' comments. Unfortunately, it is unknown if these changes are the result of the course *per se* or from spending 5 days focussing on T1D with enthusiastic facilitators (The DAFNE Study Group, 2002). Furthermore, it should be noted that all CSII patients have to complete a CHO counting course before commencing the therapy; however, no such requirement exists for those using MDI (who typically perform the course voluntarily). Also, when considering that only 1.1% of patients in 2012 - 2013 attended a structured education programme illustrates that the participants using MDI may therefore be indicative of a particularly well disciplined group of patients (Diabetes UK, 2015).

This increased flexibility was not limited to dietary practices alone, with some patients also describing how other practical aspects of CSII helped to improve their quality of life. In particular the convenience of the therapy and its relative inconspicuousness was held in high regard. Patient C019 (a male, using CSII, aged 54) described how his experience in social situations had changed for the better upon commencing the therapy by saying how …

> *'when I was first diagnosed I would go to things like formal dinners with round tables and things like that and you would have to get up and you would have to go out to the toilets or … and you were carrying boxes round with you and you walk into an evening do and there you are walking in with a little box of stuff with you and it wasn't socially acceptable … socially it became a lot easier on the pump and now when we go out with friends with 4 or 6 of us all I do is sit at the table and do my bloods under the table and check what it is and we are sitting chatting and then my pump goes away and I'm dealt with'*.

Furthermore, aspiring triathlete Patient C010 also explained how …

> *'when you are on the bike you can actually do it [inject insulin]. It doesn't happen very often but you can actually do it so again one of the advantages*

of the pump is that. You can give yourself a jab very quickly … it's very very convenient'.

This allowed patients unprecedented opportunities to keep the disease private and for their lives to continue uninterrupted by the necessity of insulin administration which would have been impossible when using MDI.

Practical challenges of CSII

Despite these favourable comments it would be wrong to think that CSII is a panacea for T1D. The participants also mentioned various negative aspects to the therapy. Some of the most prominent were somewhat in contrast with previous comments regarding the convenience of the device, with various participants describing issues with the physical dimensions of the pump, such as Patient C030 who mentioned how …

'the hardest part is….men they just put it on their belt or trousers so it is probably not as noticeable, but you know if you are wearing a dress you haven't a belt to put it on and even if I did have a belt it would probably be on the outside and it would be a bit obvious ... but now I've found out what my bra is for so I can shove it down that [Laughs]'.

These issues are well known, with Barnard (2007) also finding that patients often had problems with the physical size of the pump; however, there is unfortunately nothing that can be done about this at present, although manufacturers are making efforts to minimise the profile of the devices and developing more friendly alternatives, such as patch pumps.

Furthermore, participants frequently reported finding the process of commencing the therapy initially overwhelming due to the substantial information to take in as operating the pump and the regimen in general is considerably different to MDI. This was summarised by Patient C009 (a female, using CSII, aged 42) who mentioned how …

'it took a while to 'get'….I remember sitting and going through the manual thinking "how on earth am I going to remember all this", so it obviously took time'.

Patient C004 (a female, using CSII, aged 63) also explained how she was initially concerned about the level of technology involved and the thought of handing over control of their diabetes to the hospital staff. She described how …

> *'it's very nerve racking really, going from when you've sort of got control. To have that taken off you and then to go on something entirely different. I was thinking "would at my age would I be able to control and programme myself in to do this and do that"*.

Despite these concerns the rigorous week-long education course provided by the hospital, although challenging, was regarded as an excellent induction process which prepared patients well for independently managing their diabetes using CSII. Patient C008 explained how …

> *'it was over 2 weeks virtually and intensive. So yeah every other day for 2 weeks seeing (DSN) and with the presentations and stuff and having a practice and learning how to draw up a vial and stuff and talking about it and you know the consequences and stuff like that and why it's important to monitor and check and kind of getting it drummed into you'.*

Patient C007 (a female, using CSII, aged 42) emphasised how the nurse who facilitated the session was …

> *'absolutely brilliant'*.

The importance of appropriate, structured education cannot be understated, with Morrison (2013) describing how it is a critical factor for success with the therapy. It should be noted that not all of the participants were inducted to CSII at the Royal Liverpool Hospital and that a recent audit revealed education sessions vary considerably over the UK, with some Trusts allowing pump manufacturers to commandeer the sessions (White, 2014). In sharp contrast to the positive comments regarding the educations sessions attended in Liverpool some participants complained about being referred to the hospital from other Trusts, often arriving with poor glycaemic control and stories of disappointing education sessions. Patient C030 emphasised this by mentioning how …

'it was basic, "you do this and you do that", a bit like when I first got diabetes and they said "you take your insulin at 5 o'clock and you eat at half past 5 and never the two shall meet" … even my own doctors had never seen one [insulin pump] before so they weren't supportive and they couldn't tell you how to use it or anything and it was all a bit "do it yourself" if you like. Do you know what I'm saying? It all relied on me reading the book and being really interested in it'.

It is important at this point to note that the Royal Liverpool Hospital Diabetes Centre is an NHS Centre of Excellence and that these tales from other Trusts are likely not due to negligence, but rather the result of funding and staffing constraints, as was illustrated in the insulin pump audit (White, 2014). Nonetheless, this evidence reveals the impact both good and bad education may have upon patients' quality of life with CSII, as well as the influence positive relationships with Healthcare Professionals may infer; the importance of which has previously been discussed.

Although issues exist, CSII was generally held in high regard with participants welcoming the opportunity to regain control of the disease. Patient C004 summarised this by saying how …

'it's always hard work. A lot of self-discipline … but the pump has definitely made life easier because I feel more in control than I did before' and that *'the diabetes was controlling me….it still controls me, but I can control it now'*.

This in turn often resulted in patients developing a more relaxed attitude towards T1D and enabled their focus to shift towards looking ahead instead of having to continually deal with the present, which Patient C006 highlighting by saying how …

'I can look ahead now on the pump, I never could with the injections which is one big difference as well'.

Perceptions of CSII

This is not to say that the patients who used MDI felt like their treatment was inferior. In fact many participants were quick to point out how happy they were with MDI, with many patients having graduated from conventional insulin therapy as their control deteriorated and found that MDI offered a method of superior management compared to once or twice daily injections. As such, this increased flexibility was perhaps the main positive theme which patients attributed to the therapy. Patient C055 described this by explaining how he …

> *'was on 2 injections a day, one in the morning and one in the evening so you had to make sure you ate at certain times through the morning or you would go low or whatever, whereas now if I inject in the morning I have a piece of toast, and if I'm busy all morning I don't go low it doesn't matter if I don't have something to eat, so I can be in meetings all morning and everything else and I don't have to have a bottle of Lucozade or a chocolate bar with me'*.

Despite this praise it was interesting to note that these patients generally could see no obvious benefit which CSII could give with regards to flexibility, with Patient C009 mentioning how …

> *'unless I'm missing something I can't really see how that [CSII] would help because it would still be up to me to eat at the right times and eat the right amount and make sure I had enough or used the right amount of insulin'*.

Furthermore, those using MDI also had an extremely negative perception of being permanently connected to the device (although it can be removed for up to an hour maximum). Patient C020 highlighted this by saying …

> *'I just don't particularly want anything on me the whole time and it probably is psychological because when you have your injection you put your pen away and here you are without any physical signs of diabetes and you can carry on living and it is possibly this idea that I have that I want to cling onto for as long as possible. That if I have something on me or attached to me it is a constant reminder of the diabetes'*.

This desire by patients to 'escape' their T1D is not unique and work by Saarinen also highlighted how patients commencing the therapy found wearing the device made their diabetes 'visible', both to themselves and others. This contrasts with the absence of comments from established users of CSII which may potentially be a result of becoming accustomed to the device over time.

This therefore poses an interesting divergence between those using CSII, the majority of whom previously used MDI and who deplored the treatment's rigid structure and those currently using MDI who praise it and are sceptical of CSII. It is likely that the participants using CSII may have the benefit of hindsight and have only realised the true benefits after commencing the therapy. It should also be remembered that to be offered CSII strict criteria must be met and therefore it is likely that glycaemic control could not be reached in these patients using MDI and their time using the injections may have been torrid. Furthermore, as mentioned previously, given that many of those using MDI had attended carbohydrate counting workshops and had kindly volunteered to take part in the study it could also be speculated that may be a particularly disciplined group. That said, those using CSII made it clear that they were very happy with the device with Patient C001 mentioning how …

> *'I'd recommend the pump to any diabetic I know. I say "try and get on the pump, not injections, get on the pump and you'll notice the difference" … the worst thing that can happen is it doesn't work for you and that's that. The best thing is that it does work for you and gets everything in your life sorted. It gets your sugar levels down. It gets you feeling better'*.

The future living with T1D

Health aspirations

Although the participants were engaging with very different insulin therapies, it became apparent that when looking to the future both sets of participants had similar aspirations, which were typically focussed around health outcomes. Nearly all patients reported fears about their future health, with Patient C004 highlighting these concerns by stating how …

'I worry because I haven't got perfect control … you do worry, but there's no point. You know, if you see something on the television and someone loses their sight, but I think it just makes you more determined that you've got to keep on the ball with it'.

Some also had optimism for future developments which may assist with the management of T1D. Patient C060 (a female, using MDI, aged 57) explained this by mentioning how …

'there have been big changes and changes are coming all the time and more and more, I wouldn't say cures have been found for things, but they have developed things for high blood pressure and high cholesterol and things and they can be controlled now whereas they couldn't be controlled .... 40 odd years ago they wouldn't be able to be as well controlled … It makes me feel reasonably optimistic you know. I mean, not that I want to live to be 120 because I certainly don't, but I want to live a normal lifespan and be able to do things'.

These universal health concerns appeared to be at the fore of the majority of the participants' minds, regardless of treatment and that living a life free from complications with an acceptable quality of life was their priority. This is understandable considering the increase risks posed by T1D and despite often unfavourable circumstances the patients should be commended for their commitment and overall attitude to their self-care.

Limitations and recommendations

Despite this research producing some novel findings there are various limitations which should be acknowledged. Firstly, the participants all belonged to one hospital and although some may have been referred from other areas it would not be appropriate to extrapolate the findings to the wider population with T1D. Furthermore, it has been stated various times throughout this discussion that the participants using both CSII and MDI may have been particularly well disciplined. As such they may even not be truly representative of patients belonging to the clinic itself, which should be considered by the reader when judging the generalisability of the data. Also, despite best efforts to build rapport and the

utilisation of active listening techniques it is difficult to gauge how honest the participants were when talking about their experiences with T1D. Although no particularly sensitive questions were asked the topic in itself was still very personal and it is hoped that all participants felt comfortable enough to be open; however, this cannot be confirmed for sure. The cross-sectional design of the study also hindered this as it meant that the author only met each participant once, which made building rapport in a relatively short space of time a challenge.

For future similar studies, although it is difficult to gather a truly representative sample due to the relative rareness of CSII, perhaps considering a multi-site design may ensure more generalisable results. Furthermore, it may also be useful in future to ensure adequate rapport is built before the interviews and perhaps pre-study briefing sessions may help to ensure this.

8.6 Conclusions

To summarise, although this study revealed interesting findings regarding the quality of life of those with T1D using both CSII and MDI it is important to recognise that both sets of participants generally held their therapies in high regard and that both treatments appeared to assist with their principle function of attaining glycaemic control, which in turn was a catalyst for improved quality of life. Furthermore, it also became apparent that many participants conveyed great optimism in the face of harsh realities. It is an unfortunate truth that those with T1D experience shorter lifespans and greater risks of complications than the general population; however, once control of the disease had been regained using either method of treatment the participants often began to focus on the future rather than the present and to look further afield than the sometimes all-consuming management of diabetes. It also became clear through the interviews that a ‘if its’ working don’t fix it’ mentality often prevailed. An example of this was that many patients on MDI couldn’t see any direct benefit of using CSII when their current regimen is already working and that if anything it would be more of a hindrance. This was an unexpected discovery and whilst the author would not want to suggest that well-controlled, happy patients would be better off using CSII, it would

surely be better to at least ensure they are aware of the benefits of other therapies to allow more informed choices to be made. That said, it could also be hypothesised that those using MDI, if well-controlled, may realise that they may not be eligible for CSII funding and become resigned to MDI, hence the praise for the therapy.

Overall, although more robust research would be welcomed in this area, this study has produced novel findings which the author hopes may be of use to those working in this currently under-researched area of diabetes. In particular, it is hoped that these findings illustrate the positive regard for effective education and services and given the currently poor provision for patients serve to highlight their importance. On the other hand they have also clearly shown the detrimental effect poor services may have and upon the lives of patients and it is hoped that evidence such as this will allow Healthcare Professionals to gain a deeper insight into the patient experience which can then be used to forge stronger relationships between the two parties.

Chapter 9

Case Studies

9 - Case Studies

9.1 Abstract

There is a dearth of data which focuses on the longitudinal transition of patients from multiple daily injections (MDI) onto continuous subcutaneous insulin infusion (CSII) therapy, with a specific focus on eating behaviours, quality of life and cardiometabolic risks. It is important that this is elucidated as it is currently unknown if these aspects change over time after commencing the therapy. In the light of this the author carried out a number of case-studies (n = 5). Patients were asked to complete a number of food diaries to investigate their eating behaviours, take part in semi-structured interviews pertaining to quality of life and donate samples of blood, as well as allowing the author to access to their medical records for the determination of cardiometabolic state. These aspects were each carried out every three months over a one year period. The findings, although not statistically meaningful, offered a deep insight into patients' transition onto the therapy. Initial concerns about the physicality of the device were revealed, but also excitement about the ability of CSII to potentially improve glycaemic control. Funding inequalities were also demonstrated with some patients having advantages over others. When commencing the therapy the consistency of care and improved level of support received was highlighted as being a highly favourable attribute of the therapy. Overall, the case studies revealed the complexity of patients which diabetologists regularly encounter; an issue which can complicate matters. These challenges mean that effective management of the disease can only be achieved through an individualised approach when adequate support networks are in place. Further research using a larger sample investigating the implications of CSII over time would be beneficial.

9.2 Introduction

Despite offering improvements in glycaemic control and the potential for additional lifestyle benefits, CSII is not a panacea for those with T1D and commencing the therapy can be extremely challenging for a number of reasons (Pickup, 2002; NICE, 2008). For example, the device itself is based upon sophisticated

technology and although the complex workings are hidden beneath a relatively simple user interface the thought of managing such a complicated piece of equipment may intimidate some patients (Jones, 2008). Others have also previously reported that the idea of being connected to a pump can be a constant reminder of the disease (Saariner, 2014). Furthermore, for initiation of the therapy to be a success, a high degree of education and support is required, which the patient must be open and receptive to (Morrison, 2013). These examples and others have been highlighted in the present study during the cross-sectional interviews described in the Quality of Life chapter (see page 173). Data derived from food surveys and blood samples also illustrated subtle behavioural and metabolic differences between patients using CSII and their counterparts engaging with MDI. Unfortunately, despite offering an insight into under-researched areas of CSII therapy the cross-sectional design of the study did not lend itself well to illustrating how these differences may change over time. The study inclusion criteria also required that all participants must have been using their specific treatment for a year or longer. Therefore all participants using CSII were well acquainted with the therapy and any opinions of the challenges they faced during its commencement were described retrospectively and as such the findings may not truly represent their experiences at the time.

This therefore provides an opportunity for further research investigating CSII over time, both during and after its inauguration. A longitudinal study was initially proposed to examine this, but as described in the 'Recruitment Feasibility' chapter (see page 65), issues beyond the control of the research team prevented this from occurring to the extent originally planned. Despite this a small number of patients did consent to take part and the research team agreed that the resulting data would instead be better presented as a series of brief case studies.

Case-studies were deemed to be an appropriate method for presenting the findings primarily for pragmatic reasons as any quantitative measures would be statistically redundant with such a small sample size. Despite this limitation the descriptive analysis of data derived from an individual can still offer valuable insights, upon which questions can be posed to inform subsequent, more robust studies (Budgell, 2008). Furthermore, it was also clear that any qualitative data derived from interviews, if described 'per participant', may also allow a deeper

understanding into the complexity of a particular individual's specific lived experience, as opposed to discussing data in the context of a group of participants, as is typical of other qualitative methods. The intension of these case studies is therefore to utilise these advantages to offer a 'flavour' of the transition from MDI to CSII through a combination of quantitative and qualitative data pertaining to the lived experiences, physiological changes and lifestyle habits of a small number of individuals. This will allow the reader to understand the transitionary process from MDI to CSII at an individual level and appreciate the challenges and complexities involved.

9.3 Aims and Objectives

Aim

The aim of these case studies is to investigate the eating behaviours, quality of life and cardiometabolic risks of adult patients with T1D commencing CSII therapy.

Objectives

- To determine the eating behaviours of patients commencing CSII therapy using food diaries.
- To assess the quality of life of patients commencing CSII using a brief questionnaire and semi-structured interviews.
- To evaluate the cardiometabolic risks of patients commencing CSII therapy through the assessment of medical records and the laboratory analysis of plasma.

9.4 Methods

As the originally designed longitudinal study did not occur due to recruitment issues and a series of case studies were instead proposed this inferred an important methodological shift. Rather than adhering to the planned 'concurrent embedded' strategy (meaning data is collected together and that the qualitative element would be smaller and hypothesis forming), the methodology changed to a 'concurrent integrated' strategy (where all data would be equally combined to tell a

story) (Creswell, 2009). As such, the quantitative and qualitative data were treated with equal weight and used together throughout the case studies.

The actual data collection methods used for each case study remained the same as described for the original longitudinal study and are outlined in the General Methods chapter (see page 45). To summarise, each participant was asked to attend an appointment to collect baseline measurements shortly before they received their insulin pump and prior to the commencement of CSII education. The participants were then asked to attend a further four appointments every three months for one year. During each appointment every participant was asked to complete a 5 day weighed food diary, an EQ-5D quality of life questionnaire, donate a small sample of blood (20 ml) and to take part in a semi-structured interview to determine quality of life. Standard markers of risk were retrieved from patients' medical records after consent from the participants. These consisted of age, BMI, HbA_{1c}, insulin dose, total cholesterol, triglycerides, LDL-C, HDL-C and systolic and diastolic blood pressure. A note was also taken if the patient was taking any lipid lowering medication.

All quantitative data was analysed using Microsoft Excel 2010 to determine basic mean averages and standard deviations where appropriate. As each case study only consisted of one participant, often with single measurements for each variable, no further statistical analysis was performed.

All semi-structures interviews were audio recorded and transcribed verbatim. The resulting transcripts were then exported to NVivo (version 10) where coding took place. All qualitative data was analysed using a grounded theory approach. The interview and analysis process has been previously explained in detail in the General Methods and Quality of Life chapters (see pages 45 and 173).

It should be noted that the quantitative and qualitative findings were combined using triangulation. This is a concept outlined by Guba and Lincoln (1989) and involves using two or more other forms of data to support and offer different viewpoints and in the present study involved the data collected from patients' medical records, food diaries, quality of life questionnaires and the laboratory analysis of plasma samples to be combined with qualitative semi-structured

interviews concerning quality of life. It is hoped that this will offer the reader an intimate insight and allow the validation of the outcomes (Denzin, 1989).

All findings have been presented following the method of Budgell (2008). This method requires the author to firstly describe the patients' perspective using an efficient narrative style and draw from all relevant sources of information with a clear emphasis. In the case of the present study this involved focussing specifically on the transition onto CSII and patients' subsequent engagement with the therapy for one year. Each case study then finishes by briefly discussing the outcome of CSII and the overall salient points regarding the process of transition (Budgell, 2008). A final section then concludes the case studies by briefly summarising all findings and outlining any limitations and recommendations.

9.5 Results and Discussion

These case studies describe specifically the process of transition from MDI to CSII for five individual patients from the Royal Liverpool Hospital Diabetes Centre. The patients all consented and began the study just before they were due to be issued CSII and before the education sessions were scheduled to begin. The results are presented as brief individual, anonymised case studies and alphanumeric codes have been assigned to each participant to retain this anonymity. These codes and the basic characteristics for each participant are shown in Table 9.1 Each case focuses specifically on the immediate transitionary process from MDI to CSII and where possible reports their engagement with the therapy for the following year. All patients were previously using MDI and none had any prior experience with CSII. It should also be noted that not all participants completed all parts of the study. The reasons for these discrepancies are varied and will be described within each individual case study.

Patient Code	Sex	Age	Nationality	Profession
L001	Male	41	British	Factory worker
L002	Female	24	British	Unemployed
L003	Male	23	British	Healthcare professional
L004	Female	28	Northern Irish	Teacher
L005	Female	18	British	Student

Table 9.1 – Anonymised patient codes and basic characteristics

Patient L001

As mentioned in Table 9.1, Patient L001 was a white, British 41 year old male factory worker from Liverpool with long-standing T1D. The patient commenced CSII in December 2013. When consenting to the study he stipulated that he did not want to take part in semi-structured interviews. This was agreed by the author; however, after attending the second scheduled study appointment the patient's personal life had become difficult with abnormal shift work and family commitments. He decided that whilst he would still be prepared to donate a sample of blood (as the short phlebotomy appointment could be easily fitted around work and combined with other clinic appointments to minimise the burden), he would no longer have the time or inclination to complete any more surveys or food diaries. The author accepted this and mentioned that the blood sample would still be very much appreciated. This therefore explains the missing data, particularly for visits 3, 4 and 5 and the lack of qualitative data.

Although CSII is often noted for its inherent ability to improve glycaemic control and offer reductions in insulin requirements (Pickup, 2002), it can be seen in Table 9.2 that neither of these occurred in the case of Patient L001. In fact his HbA_{1c} actually increased from 8.6% to 8.9% and insulin dose remained circa 32 IU per day. This was an unexpected finding; however, the patient made it clear that after commencing CSII his personal life had become more stressful and it is well known that stress can mediate HbA_{1c} through activation of the corticoid and epinephrine systems (Pickup, 2004). For example, work by Kawakami (2000) revealed that occupational stress, even in healthy individuals, may have an adverse impact. Furthermore, the impact of stress upon blood sugars in those with diabetes has been well documented, with chronic and acute stressors, both directly and indirectly related to diabetes being associated with higher HbA_{1c} (Hillard, 2011). Therefore, perhaps it could be said that the patient's challenging lifestyle issues may be partly responsible for these glycaemic anomalies; although with the absence of definitive evidence it is difficult to say with certainty. That said, the findings shown in Table 9.3 contradict this by indicating that at baseline the patient felt he was in good health with no perceived problems, thus further confusing matters.

L001	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
BMI (kg/m^2)	26.1	25.9	-	25.9	-
HbA_{1c} (%)	8.6	8.9	-	8.9	-
Insulin dose (IU)	32	32.8	-	32.8	-
Lipid lowering medication? (Yes/No)	Yes	Yes	Yes	Yes	-
Total cholesterol (mmol/L)	4.17	4.56	4.73	4.40	4.36
Triglycerides (mmol/L)	0.63	0.64	0.54	0.57	0.70
LDL-C (mmol/L)	1.20	-	1.3	-	-
LDL I & II (mmol/L)	0.61	0.80	0.93	0.80	0.82
LDL III & IV (mmol/L)	0.37	0.44	0.48	0.40	0.48
Apo-B (mmol/L)	0.75	0.87	0.89	0.73	0.78
HDL-C (mmol/L)	2.70	-	2.9	-	-
HDL_2 (mmol/L)	1.45	1.58	0.51	1.36	1.54
HDL_3 (mmol/L)	1.43	1.56	1.39	1.46	1.44
Apo-A1 (mmol/L)	1.78	1.77	1.88	1.71	1.61
Apo-B / Apo-A1 ratio	0.42	0.49	0.47	0.43	0.48
Systolic BP (mmHg)	129.0	134	-	134	-
Diastolic BP (mmHg)	71.0	84	-	84	-

Table 9.2 – Basic clinical measurements and lipoprotein subfraction findings. All data derived from patient medical records apart from total cholesterol, triglycerides, apolipoprotein and lipoprotein subfraction data (which were derived from auto-analyser measurements).

The increases in HbA_{1c} were also accompanied by increases in blood pressure to borderline hypertension (NICE, 2008). Although little literature exists to suggest that CSII can influence blood pressure it is well known that stress is associated with hypertension, thus further bolstering the hypothesis that the lifestyle of Patient L001 may be mediating some of these metabolic changes. Although Table 9.3 illustrates no perceived problems in terms of quality of life and overall health, this is perhaps an indication that whilst Patient L001 may consider himself to be

dealing well with stress, aspects of his physiology suggest otherwise. It is unfortunate that there is a lack of qualitative data to further elaborate upon this hypothesis.

Despite a lack of glycaemic improvements and increases in blood pressure Patient L001 appeared to have a relatively stable lipid profile, which although not changing greatly throughout the course of the therapy remained protective. His LDL-C levels were below recommendations of 2 mmol/L and his HDL-C was consistently above 1 mmol/L (NICE, 2015). Furthermore, subfraction analysis demonstrated a predominance of the less atherogenic LDL-I and LDL-II subclasses and the patient was found to possess a favourable Apo-B / Apo-A1 ratio (consistently around 0.40 – 0.50), suggestive of low cardiovascular disease risk according to the criteria of Walldius (2004). Although these are promising findings it is important to note that Patient L001 was also using statins which may account for this well-managed lipoprotein profile and in the light of his challenging lifestyle and poor glycaemic control may also be an indicator of the benefit of regular appointments with Healthcare Professionals ensuring his medication is well 'tailored' to his needs.

L001	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Mobility	No problems	-	-	-	-
Self-Care	No problems	-	-	-	-
Activity	No problems	-	-	-	-
Pain	No problems	-	-	-	-
Anxiety	No problems	-	-	-	-
EQ-5D Health Scale	80	80	-	-	-

Table 9.3 – Findings from the EQ-5D questionnaire. (A finding of 0 on the EQ-5D Health Scale denotes worst possible health, whereas 100 denotes best possible health).

When focussing attention on Tables 9.4 and 9.5 it can be seen that Patient L001 consumed considerably less than the EAR of energy per day (although this increased after commencing CSII), which contrasts against his BMI measurements indicating he was slightly overweight.

L001	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Energy (kcal)	1021.2	1481.6	-	-	-
% of EAR	40.8	59.3	-	-	-
Total CHO (g/day)	117.1	214.6	-	-	-
% energy intake	43.0	54.3	-	-	-
Total sugar (g/day)	23.6	60.9	-	-	-
% energy intake	8.7	15.4	-	-	-
NSP (g/day)	7.3	8.0	-	-	-
% of RNI	24.3	26.7	-	-	-
Protein (g/day)	57.4	54.1	-	-	-
% energy intake	22.5	14.6	-	-	-
Total fat (g/day)	38.9	47.6	-	-	-
% energy intake	34.3	28.9	-	-	-
Saturated fat (g/day)	11.1	18.1	-	-	-
% energy intake	9.8	11.0	-	-	-
MUFA (g/day)	9.7	17.3	-	-	-
% energy intake	8.5	10.5	-	-	-
PUFA (g/day)	5.8	6.5	-	-	-
% energy intake	5.1	3.9	-	-	-

Table 9.4 – Average daily macronutrient findings from 5 day weighed food diary.

This paradox could be the product of under-reporting, which is particularly common in those who are overweight or obese (Black, 2000). Furthermore, the patient's consumption of CHO, although being close to recommendations, consisted of an increased intake of total sugars. Despite being below recommendations of 90 g/day it is unlikely that this increase in total sugars is the result of an increased consumption of fruits and vegetables as vitamin C and NSP levels remained static after the commencement of the therapy and may be perhaps suggestive of an increased consumption of sugary foods and drinks (European Food Safety Authority, 2009). Furthermore, this patient also appeared

to be consuming substantially more sodium than recommendations of 1600 mg/day which is again concerning given his increased blood pressure. It has been proposed in the literature that CSII may allow patients the opportunity to liberalise their diet and these findings reiterate that Healthcare Professionals should encourage any relaxation to take place with healthful food choices.

L001	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Sodium (mg)	2419.2	2515.4	-	-	-
% of RNI	151.2	157.2	-	-	-
Calcium (mg)	398.6	656.6	-	-	-
% of RNI	56.9	93.8	-	-	-
Iron (mg)	7.9	12.1	-	-	-
% of RNI	90.8	139.1	-	-	-
Vitamin A (µg)	635.4	363.0	-	-	-
% of RNI	90.8	51.9	-	-	-
Vitamin C (mg)	32.6	33.4	-	-	-
% of RNI	81.5	83.5	-	-	-
Vitamin B12 (µg)	2.8	2.3	-	-	-
% of RNI	186.7	153.3	-	-	-

Table 9.5 – Average daily micronutrient findings from 5 day weighed food diary.

Despite these concerns it is striking that the amount of calcium consumed by Patient L001 doubled after the commencement of CSII and he was virtually meeting recommendations. When considering this with the increased consumption of saturated fats and MUFA may perhaps be suggestive of a higher intake of dairy products. Therefore it could be argued that as some of these foods, in particular cheese, has been shown to infer neutral effects and in some cases improve the lipid profile, offer a potential mechanism which may be working in tandem with pharmacological lipid lowering treatments resulting in the patient's positive lipid profile (Nilsen, 2015). Despite these favourable findings they reveal very little about other qualitative lipid abnormalities which may be present, such as glycation

and oxidation which have been shown to exist even in those with well controlled T1D and which may infer an increased level of CVD risk (Vergès, 2009).

These findings, whilst offering interesting perspectives on an individual patient's progress from commencing CSII are not without limitations. A lack of qualitative data makes it difficult to further investigate questions regarding some of the quantitative changes demonstrated. Also, as Patient L001 completed the food diaries at home it is impossible to say with certainty the accuracy of the data. In a similar respect, some of the data was derived from his medical records and it is impossible to know the conditions they were measured under, although that said the LDL-C and HDL-C results are largely similar to the combined sum of their respective subclass measures determined by the author, which is suggestive of a degree of accuracy. Despite these issues the data still offers a useful, if incomplete, view of a patient's 3 month journey through the commencement of CSII.

Patient L002

Patient L002 was a white, British, 24 year old unemployed female from Liverpool with long-standing T1D who commenced CSII therapy in December 2013. Prior to being a patient at the Royal Liverpool Hospital this patient mentioned how she had experienced poor service at another hospital which interfered with her regular appointment schedule. She described how…

> *'I got lost in the records … and I was supposed to be going to [names hospital], but then I ended up coming into A & E [at the Royal Liverpool Hospital] with ketoacidosis and I saw a diabetic nurse and she took us to be referred. I hadn't seen anybody for two years.'*

Unfortunately, this temporary hiatus allowed the development of a host of diabetes related issues including insulin insensitivity, retinopathy and liver problems. This medley of complex issues was further complicated by uncontrolled diabetes and it was the onset of severe gastroparesis which finally persuaded her Consultant Diabetologist to suggest that she may achieve better management through the use of CSII; a strategy which has been shown to offer significant improvements in glycaemic control in patients with the condition (Sharma, 2011).

The patient expressed concerns about commencing the therapy, mainly related to…

> *'the change, cause it's like starting all over again. Having to do everything different … It's just remembering everything isn't it. The way you've got to do things is a lot different.'*

However, despite these anxieties Patient L002 explained in detail her complications, the impact they have had upon her quality of life and how she was very much looking forward to commencing CSII to improve not only her blood sugars, but also reduce her retinopathy risks and improve her gastroparesis symptoms. It was this condition in particular which appeared to cause much distress and is typified by the delayed gastric emptying due to damaged autonomic nerves, leading to nausea, vomiting and bloating which has additional nutritional implications as the patient may be unable to eat (Abrahammson, 2007).

When considering these issues the data presented in Tables 9.6, 9.8 and 9.9 begin to form meanings. Firstly, when looking at BMI it can be seen that the patient was approaching obesity. It is well-known that having a raised BMI perpetuates insulin insensitivity and it is therefore likely to be a contributory factor for this patient's own insulin sensitivity problems; a suspicion further substantiated with the high subcutaneous doses of insulin shown in Table 9.6 (Pickup, 2004). Furthermore, despite her raised BMI the patient's energy intake was markedly below recommendations. Although an element of under-reporting may be occurring (as is typical in those who are overweight or obese) Patient L002 was also suffering from severe gastroparesis (Black, 2000). In fact during the brief interviews which the author conducted to ensure the quality of the food diary data the patient made it clear that she was eating very little. Furthermore, this did not appear to improve even after the commencement of CSII and after 3 months she stated that…

> *'It's the same at the moment. I've had a bit of a flare up of my gastroparesis over the last couple of weeks and not feeling very well.'*

This will also likely explain the very poor consumption of a number of micronutrients such as calcium, iron and vitamins A and C which actually

decreased after using CSII and as the symptoms of her gastroparesis increased. These vitamins and minerals are individually extremely important for a number of key biological processes and if prolonged these sub-optimal intakes may place the patient at risk of additional issues such as poor immune function (Wardlaw, 2002).

L002	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
BMI (kg/m^2)	29.7	-	-	-	-
HbA_{1c} (%)	9.6	-	-	-	-
Insulin dose (IU)	75	-	-	-	-
Lipid lowering medication? (Yes/No)	Yes	-	-	-	-
Total cholesterol (mmol/L)	5.91	5.42	-	-	-
Triglycerides (mmol/L)	1.44	0.94	-	-	-
LDL-C (mmol/L)	2.4	-	-	-	-
LDL I & II (mmol/L)	1.92	1.75	-	-	-
LDL III & IV (mmol/L)	0.79	0.83	-	-	-
Apo-B (mmol/L)	1.40	1.14	-	-	-
HDL-C (mmol/L)	1.7	-	-	-	-
HDL_2 (mmol/L)	1.34	1.34	-	-	-
HDL_3 (mmol/L)	1.27	1.10	-	-	-
Apo-A1 (mmol/L)	1.68	1.31	-	-	-
Apo-B / Apo-A1 ratio	0.83	0.87	-	-	-
Systolic BP (mmHg)	120.0	-	-	-	-
Diastolic BP (mmHg)	79.0	-	-	-	-

Table 9.6 – Basic clinical measurements and lipoprotein subfraction findings. All data derived from patient medical records apart from total cholesterol, triglycerides, apolipoprotein and lipoprotein subfraction data (which were derived from auto-analyser measurements).

L002	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Mobility	Some problems	Some problems	-	-	-
Self-Care	Some problems	Some problems	-	-	-
Activity	No problems	No problems	-	-	-
Pain	Some problems	Some problems	-	-	-
Anxiety	No problems	No problems	-	-	-
EQ-5D Health Scale	50	50	-	-	-

Table 9.7 – Findings from the EQ-5D questionnaire. (A finding of 0 on the EQ-5D Health Scale denotes worst possible health, whereas 100 denotes best possible health).

The difficult time that Patient L002 was experiencing was also reflected in her responses to the EQ-5D questionnaire presented in Table 9.7. She described no problems with her activity levels; however, for every other category there were 'some problems' and none of these improved after commencing the therapy. This was further compounded by the patient rating her overall health at a score of 50 both before and after the commencement of the therapy, thus showing no improvement at all.

Despite Patient L002 initially appearing at risk, some positive aspects were revealed after the commencement of CSII. Although there was a slight decrease in both HDL-C and LDL-C, there were also reductions of 0.49 mmol/L of total cholesterol and 0.50 mmol/L of triglycerides. These are promising findings given her initial poor glycaemic control and complications, although it is likely that they may also be the result of a decreased consumption of food as a result of gastroparesis. Furthermore, despite her initial reluctance, the patient also highly praised the transition onto CSII, by mentioning that…

> *'it has been brilliant really cause [says DSN's name] is on hand if you need to speak to her and she always phones you back and stuff like that so there is no worry there … and I do think that [says DSN's name] and [says doctors name] are a lot better than the doctor and nurses I had before. They [previous doctors] just left me to get on with things.'*

Additionally, it was also mentioned how despite issues out of her control the patient still managed well to control her blood sugars…

> *'At first I found it a bit difficult to control my blood sugars, but now it's stable. it's still a bit up and down now because I've had a constant water infection for 3 months so my blood sugars have been a bit up and down but they've levelled out now.'*

Despite this there were two main issues specifically with the pump itself which were emphasised. Firstly, the patient mentioned how the cannulas often fell out, leaving her at high risk of diabetic ketoacidosis (DKA), but was impressed with the service she received. She described this by remembering how…

> *'I panicked a bit a few weeks ago when my cannulas were messing up because I had ketones and my blood sugars were through the roof so I came into hospital and they were all sorted out within a few hours. So it's just better.'*

Secondly, the alarm system on the pump device which sounds after insulin administration has taken place to remind the patient to check their blood proved to be disruptive, particularly for the patient's partner…

> *'It's like a song. It's the only song on the pump. It's just a bit of a nightmare. You can switch it off, but I don't in case I don't remember to check my blood sugars … half the time I sleep through it and my partner has to switch it off … it keeps him awake!'*

This is not an isolated issue and has been previously reported with insulin pump devices and is a major disruption to sleep, not only for the patient, but also their significant others (Barnard, 2016). This is out of the remit of the patient or physician to solve; however, the device manufactures may do well to take comments such as these on board and amend their products to better deal with this issue.

Although presenting some interesting findings the reader has no doubt been drawn to the fact that there is a significant amount of missing data, particularly pertaining to visits 3, 4 and 5. After visit 2 Patient L002 informed the author that

she was pregnant and whilst she wanted to remain part of the study this development combined with her concurrent complications would prevent her from doing so.

L002	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Energy (kcal)	881.2	918.0	-	-	-
% of EAR	44.1	45.9	-	-	-
Total CHO (g/day)	86.5	79.7	-	-	-
% energy intake	36.8	32.6	-	-	-
Total sugar (g/day)	20.2	14.9	-	-	-
% energy intake	8.6	6.1	-	-	-
NSP (g/day)	5.5	4.4	-	-	-
% of RNI	18.3	14.7	-	-	-
Protein (g/day)	47.7	48.5	-	-	-
% energy intake	21.7	21.1	-	-	-
Total fat (g/day)	40.5	47.5	-	-	-
% energy intake	41.4	46.6	-	-	-
Saturated fat (g/day)	12.0	17.9	-	-	-
% energy intake	12.3	17.5	-	-	-
MUFA (g/day)	11.2	13.7	-	-	-
% energy intake	11.4	13.4	-	-	-
PUFA (g/day)	7.8	7.3	-	-	-
% energy intake	8.0	7.2	-	-	-

Table 9.8 – Average daily macronutrient findings from 5 day weighed food diary.

The author accepted this and the patient therefore unfortunately withdrew from the study. Despite this the findings gathered from the short time she did participate gave an interesting insight into a highly complex case. It is this complexity which illustrates exactly why data should perhaps be considered more holistically instead of compartmentalising findings. For example, the dietary data pertaining to Patient L002 reveals very little alone, but when considered in the context of her

complications helps to partly explain some of the abnormal findings. It is this benefit of case-studies which the author would like to exploit to hopefully give a deeper insight into the world of individuals; a trait which often gets missed in studies where participants are grouped into categories and assessed 'on-mass' using probability theory.

L002	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Sodium (mg)	1853.6	1544.0	-	-	-
% of RNI	92.7	77.2	-	-	-
Calcium (mg)	301.8	200.4	-	-	-
% of RNI	43.1	28.6	-	-	-
Iron (mg)	4.17	2.8	-	-	-
% of RNI	28.2	18.9	-	-	-
Vitamin A (µg)	111.2	191.0	-	-	-
% of RNI	18.5	31.8	-	-	-
Vitamin C (mg)	13.4	11.6	-	-	-
% of RNI	33.5	29.0	-	-	-
Vitamin B12 (µg)	3.02	3.38	-	-	-
% of RNI	201.3	225.3	-	-	-

Table 9.9 – Average daily micronutrient findings from 5 day weighed food diary.

Patient L003

Patient L003 was a white, British, 23 year old male, living in Liverpool who, upon commencing the study had just completing his third year of a degree and was due to begin a placement as a Healthcare Professional. The patient had only been diagnosed with T1D four years ago and had found coming to terms with the disease initially challenging with regards to the habitual routine of an insulin regimen; however, he quickly adapted to using MDI and found the therapy adequate for his needs. He commenced CSII therapy in April 2014.

Patient L003's route to being offered CSII was somewhat different than most other patients and was in part attributable to his profession. He described this by explaining how when working …

> *'I got talking to one of the specialist nurses who specialises in sport and managing diabetes and she asked me if I was on injections or a pump. I said I was on injections and she asked me if I had ever thought about a pump and I was under the impression that you could only get a pump if your diabetes was badly controlled and that there was a certain threshold for your HbA_{1c} and mine was below that. She said "no, email [says doctors name] and see what he says", so I emailed him and he emailed me back in November or December 2013 and that just got it all going really.'*

L003	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
BMI (kg/m^2)	23.2	-	-	-	-
HbA_{1c} (%)	-	-	6.8	-	-
Insulin dose (IU)	58	-	-	-	-
Lipid lowering medication? (Yes/No)	No	-	No	-	-
Total cholesterol (mmol/L)	4.18	-	4.85	4.19	4.60
Triglycerides (mmol/L)	0.76	-	1.12	0.64	0.74
LDL-C (mmol/L)	2.70	-	2.00	-	-
LDL I & II (mmol/L)	1.16	-	1.25	1.29	1.18
LDL III & IV (mmol/L)	0.52	-	0.47	0.49	0.55
Apo-B (mmol/L)	0.81	-	1.08	0.70	0.86
HDL-C (mmol/L)	1.90	-	1.60	-	-
HDL_2 (mmol/L)	1.06	-	1.01	1.16	1.44
HDL_3 (mmol/L)	0.99	-	1.03	1.12	1.27
Apo-A1 (mmol/L)	1.29	-	1.43	1.38	1.42
Apo-B / Apo-A1 ratio	0.63	-	0.76	0.51	0.61
Systolic BP (mmHg)	-	-	-	-	-
Diastolic BP (mmHg)	-	-	-	-	-

Table 9.10 - Basic clinical measurements and lipoprotein subfraction findings. All data derived from patient medical records apart from total cholesterol, triglycerides, apolipoprotein and lipoprotein subfraction data (which were derived from auto-analyser measurements).

This exposure to the medical 'establishment' afforded to this through this patient's profession is atypical and it could be said that the expert advice he received regarding who to contact and the steps required to obtain CSII approval are tools which are out of reach for the majority of patients and certainly not documented in NICE guidelines. Furthermore, after then researching the benefits of CSII the patient became convinced that the therapy could improve his lifestyle. He explained how…

‘*when I looked into it and realised that you can improve your control and have much more freedom in what you eat and she [colleague] did say to me that you get more freedom with regards to sport because I obviously like sport quite a lot so I thought I’d give it a go.’*

This newfound conviction combined with a clear understanding of the process involved in obtaining an insulin pump were then used by Patient L003 to build a case of why CSII would be the best solution for him, even in the absence of any glycaemic control issues which NICE states as being essential criteria. The patient did this by using flexibility as a principle reason and explained that he was currently going through a stressful time with university examinations and how he would be eventually going to start working chaotic shift patterns, which would in turn make managing his diabetes difficult. He also mentioned how since developing the disease his participation in sports and eating patterns had suffered due to the structure of MDI; both of which he would like to regain.

Despite these clearly thought out benefits he also had various hesitations regarding the device…

‘I’d always disliked the idea of them because I’ve always disliked the idea of having something attached to me, constantly reminding me that I’m a diabetic sitting in my pocket.’

Comments such as these are not exclusive to Patient L003, with other authors demonstrating that these concerns of ‘diabetes made visible’ are typical of patients’ initial worries; however, it is common that these issues disappear after the commencement of the therapy (Saarinen, 2014; Todres, 2010).

L003	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Mobility	No problems	-	No problems	No problems	No problems
Self-Care	No problems	-	No problems	No problems	No problems
Activity	No problems	-	No problems	No problems	No problems
Pain	No problems	-	No problems	No problems	No problems
Anxiety	No problems	-	No problems	No problems	No problems
EQ-5D Health Scale	90	-	90	90	90

Table 9.11 – Findings from the EQ-5D questionnaire. (A finding of 0 on the EQ-5D Health Scale denotes worst possible health, whereas 100 denotes best possible health).

After the first visit and upon completing his university examinations the patient decided to go travelling for three months. This explains the absence of data when visit 2 should have taken place. Upon his return Patient L003 mentioned how this trip truly tested the device and overall had been a positive experience; however, his diet in particular had become somewhat chaotic…

> *'I couldn't carb count at all really because the nature of what I was eating … I just kind of accepted the fact that I would not have great BMs [blood sugar].'*

and that his diet typically consisted of…

> *'a lot of bread and a lot of cakes and things. Not the best kind of food for me to be eating but yeah, it wasn't really representative of what my diet is normally like because I never usually eat things like that.'*

Interestingly, when looking at Table 9.10 it can be seen that during visit 3 although LDL-C had decreased, unfortunately so had his HDL-C and there was an increase in total cholesterol and triglycerides. Furthermore, the patient's Apo-B / Apo-A1 ratio also increased to 0.74, thus changing his risk status from low risk to moderate risk, according to the criteria of Walldius (2004). Despite these detrimental changes when looking at the patient's diet in Tables 9.12 and 9.13 it can be seen that his energy intake on visit 3 was actually lower than visit 1 and all

macronutrients as well as total sugar, saturated fat and sodium were lower than his baseline measurements.

L003	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Energy (kcal)	**2910.6**	**-**	**2421.2**	**2833.8**	**2077.0**
% of EAR	116.4	-	96.8	113.3	83.1
Total CHO (g/day)	**309.3**	**-**	**242.3**	**318.9**	**271.5**
% energy intake	39.9	-	37.5	42.2	49.0
Total sugar (g/day)	**114.9**	**-**	**79.9**	**114.9**	**76.0**
% energy intake	14.8	-	12.4	15.2	13.7
NSP (g/day)	**17.6**	**-**	**13.4**	**18.2**	**17.4**
% of RNI	58.7	-	44.7	60.7	58.0
Protein (g/day)	**123.3**	**-**	**117.9**	**143.2**	**98.0**
% energy intake	16.9	-	19.5	20.2	18.9
Total fat (g/day)	**112.6**	**-**	**106.0**	**112.4**	**75.7**
% energy intake	34.8	-	39.4	35.7	32.8
Saturated fat (g/day)	**42.3**	**-**	**41.8**	**50.3**	**31.1**
% energy intake	13.1	-	15.5	16.0	13.5
MUFA (g/day)	**25.9**	**-**	**26.5**	**18.1**	**16.8**
% energy intake	8.0	-	9.9	5.7	7.3
PUFA (g/day)	**10.4**	**-**	**9.9**	**4.4**	**6.2**
% energy intake	3.2	-	3.7	1.4	2.7

Table 9.12 – Average daily macronutrient findings from 5 day weighed food diary.

After speaking with the patient it quickly became apparent that these paradoxical metabolic changes were likely to be remnants from his trip and he emphasised how the relatively uncontroversial food diary findings shown in visit 3 illustrate his attempts to improve his diet upon his return …

'now I am back I am a lot more strict [with diet] because I need to be but out there I didn't care really.'

L003	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Sodium (mg)	4063.6	-	2399.6	2603.2	2619.4
% of RNI	254.0	-	150.0	162.7	163.7
Calcium (mg)	1097.0	-	883.2	1139.2	2619.4
% of RNI	156.7	-	126.2	162.7	374.2
Iron (mg)	10.7	-	6.4	5.7	11.9
% of RNI	123.0	-	73.6	65.5	136.8
Vitamin A (µg)	327.4	-	496.6	485.2	353.6
% of RNI	46.8	-	70.9	69.3	50.5
Vitamin C (mg)	92.8	-	53.4	58.0	87.2
% of RNI	232.0	-	133.5	145.0	218.0
Vitamin B12 (µg)	4.8	-	5.7	9.2	3.4
% of RNI	320.0	-	380.0	613.3	226.7

Table 9.13 – Average daily micronutrient findings from 5 day weighed food diary.

Despite this uncharacteristic deviation in diet, Patient L003's eating behaviours appeared to generally stabilise over the following two visits; however, what became particularly apparent was his praise for the flexibility inferred by the device and the ability to better manage blood sugars on occasions when unusual dietary behaviours may occur. A typical example of this was his experience with tackling a large Christmas dinner which in previous years had been an issue. He mentioned how…

'having the extended boluses on the pump has made it easier. If you are eating a big meal you need a large extension on the boluses and you can't do that on the injections.'

This flexibility was the principle reason for the patient wanting to use CSII in the first place and as time went on he mentioned really enjoying the convenience and how this flexibility also allowed him to take part in physical activity again…

'I wouldn't say that it has helped with my performance, but it usually means that my blood glucose is normal for exercise and that it stays normal. If I was running high I would never perform quite as well because I would be dehydrated and it makes you feel a bit crap, but it just means it is more predictable what my blood glucose is going to be.'

Furthermore, CSII also has a large impact during Patient L003's final exam period; a time which he noted as being notoriously stressful and which he summarised by saying how…

'it is really good for if you are getting stressed. During the exams it always sent my blood sugars absolutely sky high, but you can just 'up' the basal rate and have normal BMs so it make it a hell of a lot easier.'

The patient also made clear as the interviews progressed that his life was not particularly bad before engaging with CSII; however, the therapy has simply improved it and made tasks easier which he would have attempted to engage with anyway. It is also interesting to remember the patient's unique position as both a patient and Healthcare Professional and how his view of both sides of the healthcare industry shaped his views and how he has still benefitted greatly, even in the absence of any glycaemic control issues. This case study therefore poses questions of whether other patients who may be 'metabolically healthy' may too benefit from other aspects of the therapy, in addition to its principle ability to improve glycaemic control.

Patient L004

Patient L004 was a white, 28 year old female from Northern Ireland residing in Liverpool. She worked as teacher at the time of the study and commenced CSII therapy in April 2014. It should be mentioned before proceeding that the patient initially agreed to participate in all parts of the study; however, after the second visit it became impossible to contact her. Furthermore, during her second appointment she also mentioned that she had forgotten her second food diary and quality of life survey and would forward them on later. After numerous failed attempts to retrieve these documents and arrange another appointment the author had no choice but to presume the patient no longer wished to be part of the study

and she was regretfully withdrawn, thus explaining the dearth of data for some sections of this case (particularly visits 3, 4 and 5). Despite this the interviews were extremely enlightening and provided a comprehensive insight into the transition onto CSII from MDI.

Patient L004 had long-standing T1D which developed during her childhood and after diagnosis she devised and habitually adhered to a strict routine for the successful management of her blood sugars. Unfortunately, when the patient attended university in Liverpool for three years this routine was lost. This was in part due to not wanting to bring attention to her disease. She explained this by saying how…

> *'I think that when I went to Halls [of residence] I didn't do myself any favours in the sense that I hated bringing attention to it [T1D]. Not the way that I am embarrassed by it, but that I would hate anyone to think I was being an attention seeker from it, you know? I would never say I need to go and have something to eat now, like I would wait until everybody was ready to eat and then eat.'*

This fear of what others think, need for approval and lack of self-confidence were to be important reoccurring themes in the interviews which ultimately led to the patient's referral for CSII as the management of her blood sugars began to spiral out of control. Interestingly, when looking at Table 9.14 it can be seen that although her metabolic control may seem reasonable on average, it was the day to day challenges of managing chaotic blood glucose levels which proved to be the biggest challenge. She also described how upon leaving university and commencing her job as a newly qualified teacher was when the situation got worse, particularly as…

> *'I find myself running slightly high [blood sugars] at work because I don't want to go low and leave the classroom to go and have to sort it out. You know I can't leave the job if that makes sense … I just don't want someone to think that I can't do it [the job] properly.'*

L004	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
BMI (kg/m^2)	22.2	-	-	-	-
HbA_{1c} (%)	8.9	-	-	-	-
Insulin dose (IU)	35.0	-	-	-	-
Lipid lowering medication? (Yes/No)	No	-	-	-	-
Total cholesterol (mmol/L)	3.83	4.10	-	-	-
Triglycerides (mmol/L)	0.84	0.90	-	-	-
LDL-C (mmol/L)	1.60	-	-	-	-
LDL I & II (mmol/L)	0.94	1.07	-	-	-
LDL III & IV (mmol/L)	0.41	0.45	-	-	-
Apo-B (mmol/L)	0.70	0.72	-	-	-
HDL-C (mmol/L)	2.00	-	-	-	-
HDL_2 (mmol/L)	1.01	1.07	-	-	-
HDL_3 (mmol/L)	1.02	1.07	-	-	-
Apo-A1 (mmol/L)	1.34	1.60	-	-	-
Apo-B / Apo-A1 ratio	0.52	0.45	-	-	-
Systolic BP (mmHg)	124.0	-	-	-	-
Diastolic BP (mmHg)	74.0	-	-	-	-

Table 9.14 - Basic clinical measurements and lipoprotein subfraction findings. All data derived from patient medical records apart from total cholesterol, triglycerides, apolipoprotein and lipoprotein subfraction data (which were derived from auto-analyser measurements).

This constant, self-imposed high blood glucose not only made the patient feel physically ill, but it also began to affect her mental health and the constant balancing act and consequent failure to achieve suitable glycaemic control began to manifest in anxiety, obsessive behaviours and depression. This can be seen from the results of the EQ-5D survey in Table 9.15, in which the patient describes how her anxiety causes her ‘some problems’ and that her overall self-perceived health is only 60 out of a possible 100. After a number of unsuccessful attempts to

explain her predicament to dismissive Healthcare Professionals and her glycaemic control becoming progressively worse her struggle culminated with a breakdown during a routine appointment.

She described the situation…

> *'I just kind of broke down and begged for help basically and then they got the head guy [Consultant Diabetologist] in and he said straight away "you are the ideal candidate for a pump", just like that. So it was kind of something that I've been asking for the last couple of years and then all of a sudden one breakdown and "oh you can have it"'.*

L004	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Mobility	No problems	-	-	-	-
Self-Care	No problems	-	-	-	-
Activity	No problems	-	-	-	-
Pain	No problems	-	-	-	-
Anxiety	Some problems	-	-	-	-
EQ-5D Health Scale	60	-	-	-	-

Table 9.15 – Findings from the EQ-5D questionnaire. (A finding of 0 on the EQ-5D Health Scale denotes worst possible health, whereas 100 denotes best possible health).

Upon hearing this news Patient L004 mentioned how she was excited about the prospect of not only improving her glycaemic control, but also allowing her to enjoy a more relaxed diet and participate in sports; both of which had become difficult. In fact the findings shown in Tables 9.16 and 9.17 illustrate this and show how her self-imposed restrictive diet resulted in her consuming less than the EAR of energy, as well as being deficient in key nutrients such as NSP, calcium and vitamin A. Also, the potential to reduce the risks of retinopathy were appealing as the patient had recently been diagnosed with small haemorrhages which were the source of great anxiety (Zabeen, 2016). Furthermore, the patient also mentioned how she was looking forward to hopefully being part of a consistent medical team which she had previously lacked and which she hoped may offer her a 'guiding

hand'. Despite these aspirations she also had apprehensions, with concerns ranging from the complexities of the device itself to the physical dimensions of the pump and where to put it. The patient also mentioned how she was initially worried about the idea of being actually connected to a device and how…

> *'one of the reasons I didn't want to go on the pump is because I didn't want something permanently attached to me. I always thought that would bring attention to me and that it would make me feel like have a disability if that makes sense?'*

L004	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Energy (kcal)	**1324.0**	-	-	-	-
% of EAR	66.2	-	-	-	-
Total CHO (g/day)	**156.4**	-	-	-	-
% energy intake	44.3	-	-	-	-
Total sugar (g/day)	**56.9**	-	-	-	-
% energy intake	16.1	-	-	-	-
NSP (g/day)	**13.5**	-	-	-	-
% of RNI	45.0	-	-	-	-
Protein (g/day)	**66.4**	-	-	-	-
% energy intake	20.1	-	-	-	-
Total fat (g/day)	**51.1**	-	-	-	-
% energy intake	34.7	-	-	-	-
Saturated fat (g/day)	**18.7**	-	-	-	-
% energy intake	12.7	-	-	-	-
MUFA (g/day)	**15.8**	-	-	-	-
% energy intake	10.7	-	-	-	-
PUFA (g/day)	**6.4**	-	-	-	-
% energy intake	4.4	-	-	-	-

Table 9.16 – Average daily macronutrient findings from 5 day weighed food diary.

L004	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Sodium (mg)	2369.6	-	-	-	-
% of RNI	148.1	-	-	-	-
Calcium (mg)	447.0	-	-	-	-
% of RNI	63.9	-	-	-	-
Iron (mg)	10.8	-	-	-	-
% of RNI	73.0	-	-	-	-
Vitamin A (µg)	233.0	-	-	-	-
% of RNI	38.8	-	-	-	-
Vitamin C (mg)	84.2	-	-	-	-
% of RNI	210.5	-	-	-	-
Vitamin B12 (µg)	4.5	-	-	-	-
% of RNI	300.0	-	-	-	-

Table 9.17 – Average daily micronutrient findings from 5 day weighed food diary.

After meeting with Patient L004 for a second time after she had commenced CSII it was apparent that these concerns had dissipated and that she was extremely pleased with the therapy. Her initial reluctance to be connected to a machine was now seen as a small price to pay for the flexibility it offered. This is not unusual and has been previously documented in the literature, with work by Saarinen (2014) showing how despite initial hesitations, the device often becomes seen as a natural 'part of the body'.

Furthermore, the flexibility offered by the pump also allowed the patient to participate in sporting activities with minimal disruption; an activity she very much enjoyed. This is known in the literature and was to be expected, but nonetheless the implications this freedom and control had were profound (Yardley, 2013). She mentioned how…

> *'I can't really explain it because I don't know how it has made such a big difference … with a [netball] match if my blood sugars were wrong I just couldn't play in the match and I was being stubborn [previously] by playing*

on when I shouldn't have, but now I feel in control of that and I can play and I know roughly what it's [blood sugars] going to do and roughly with it will be and if it's at a certain level I know how to rectify and manage.'

The patient also offered some interesting and unexpected comments regarding dietary freedom. In particular she explained how although the pump offers the potential for dietary liberalisation this never transpired due to a continued mentality that snacking and administering bolus insulin before meals will lead to an excess of 'insulin on board' and therefore she chose to shun the opportunity of dietary flexibility. Furthermore, these concerns were also extended to sugar-containing alcoholic beverages and soft drinks; despite comments prior to commencing the therapy that she was very much looking forward to having the option to indulge. Unfortunately, no food diaries were collected from Patient L004's second visit and so it is impossible to quantitatively confirm these comments in relation to data collected at baseline (shown in Tables 9.16 and 9.17) and is a concept little discussed in the literature. Also, this habitual, 'better the devil you know' mentality may offer a potential explanation why previous studies have found little evidence of metabolic disturbance, even after patients had the opportunity to consume a liberalised diet upon the commencement of CSII (Chantelau, 1983).

In addition to this flexibility Patient L004 also mentioned the commencement of the therapy almost immediately improved her mood, whether that was through physiological or psychological methods is unknown; however, she reported that her partner had also commented that she appeared '*brighter*'. It is highly likely that improvements in quality of life may be mediating this and indeed this has been shown in the literature, with a systematic review by Barnard (2007) showing improvements in not only general health, but mental health in particular after the commencement of the therapy. The patient expands on this by describing how…

'I feel as though I've got control over it [T1D] again so it's a brilliant feeling because that was what was leading me feel the anxiety and I think I put in the first [EQ-5D] questionnaire that I was feeling extremely anxious and moderately depressed and I think that it was because it [T1D] was taking over everything.'

Despite these benefits there were some negative sides to the commencement of CSII which the patient explained. These included the physical aspect of the pump and how on occasion it is difficult to 'wear'. She also mentioned how she sometimes finds it difficult to distinguish when she is actually tired or experiencing the symptoms of hyperglycaemia and although this is not an issue with the pump *per se*, poor judgement can cause her to force through situations which she would perhaps be better off abandoning, such as strenuous sporting activities. Although these issues had a small impact on the patient's life it must be stressed that she emphasised they were minor compared to the benefits that the pump infers and in her own words she described the joy of…

> *'having something that's going to work for me because it got to the point where I thought "I can't do it any more" and not to sound dramatic, I got to the point where I just didn't want to do it anymore and nothing seemed to be working so I think that having that positivity back and knowing that this isn't something that is going to control me and I'm able to control it again … and in hindsight you look back and you don't realise how bad things had got until you are so much happier with it … I can't believe the difference both mentally and emotionally'*

Although many of these aspects are attributable directly to the device itself; Patient L004 also mentioned how the support from the Healthcare Professionals was a key element in the process. She emphasised how the consistent nature of the service and seeing the same doctors and nurses made her feel she was getting the 'guiding hand' she previously desired…

> *'[says DSN's name] and [says doctors name] are experts in their field and it's lovely knowing they are there and that's the thing with the pump, you almost are getting that bit of special treatment and their numbers are available and if you ever need a question answering they are there to call, whereas before if I had any questions I didn't know who to speak to or even how to go about getting in contact with someone … now [says DSN's name] knows me, or knows my name if not anything else, whereas before I would have thought "oh I can't ring you", so it's almost like a comfort knowing that there is a lot more support being on the pump.'*

This support is discussed in the literature and is an important part for the successful transition onto CSII and this patient's experience is a testament when the fine line between patient autonomy and appropriate support is met (Morrison, 2013).

These findings in their totality show how for Patient L004, despite initial hesitations, the commencement of CSII principally improved her glycaemic control, which in turn allowed her to regain control of her life. For example she was once again able to take part in sporting activities and this level of freedom consequently improved the patient's mental state, thus highlighting how the benefits of CSII can often transcend the physiological. Despite these benefits it would be unfair to say they are solely the result of the device, as the support service offered by the hospital was also held in high regard and gave the patient the ability to successfully manage her T1D independently, yet was always there when she most needed it.

Patient L005

Patient L005 was a white, British 18 year old female residing in Liverpool and about to embark on a college course with aspirations of becoming a Heathcare Professional. The patient was diagnosed with diabetes when she was 16 and had only been living with the disease for two years and commenced CSII in April 2014. She completed all parts of the study.

L005	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
BMI (kg/m^2)	18.0	19.0	-	-	-
HbA_{1c} (%)	8.3	7.3	-	-	-
Insulin dose (IU)	32	32.4	-	-	-
Lipid lowering medication? (Yes/No)	No	No	-	-	-
Total cholesterol (mmol/L)	3.83	3.60	3.49	3.78	4.00
Triglycerides (mmol/L)	0.65	0.68	0.52	0.64	0.44
LDL-C (mmol/L)	1.00	1.00	-	-	1.20
LDL I & II (mmol/L)	0.83	0.93	0.85	0.94	0.79
LDL III & IV (mmol/L)	0.37	0.60	0.36	0.37	0.40
Apo-B (mmol/L)	0.47	0.50	0.49	0.58	0.62
HDL-C (mmol/L)	2.40	1.90	-	-	2.20
HDL_2 (mmol/L)	1.28	1.07	1.10	1.20	1.27
HDL_3 (mmol/L)	1.23	0.90	0.95	0.96	1.25
Apo-A1 (mmol/L)	1.51	1.37	1.43	1.49	1.54
Apo-B / Apo-A1 ratio	0.31	0.36	0.34	0.39	0.40
Systolic BP (mmHg)	132.0	123.0	-	-	-
Diastolic BP (mmHg)	77.0	79.0	-	-	-

Table 9.18 - Basic clinical measurements and lipoprotein subfraction findings. All data derived from patient medical records apart from total cholesterol, triglycerides, apolipoprotein and lipoprotein subfraction data (which were derived from auto-analyser measurements).

As Patient L005 had only been living with T1D for two years she had little experience of growing up with the disease; however, after diagnosis she found her life drastically change and in addition to the task of learning to manage daily insulin injections she also found that upon returning to school to complete her A-level studies she was faced with another challenge from a very unexpected source…

'my friends weren't very supportive of it and were just quite harsh really … they didn't want their friend to inject because it was a kind of like freak thing to do so that was kind of like weird, so I left school and got an apprenticeship thinking that it will be fine, you know the people I was working with were in their sixties and that it would be cool.'

Unfortunately, the patient was not to know that these more mature individuals working at a well-respected charitable organisation would also hold prejudiced views towards those with diabetes. In her own words the patient describes how…

'because I was going to the hospital quite a bit because I was doing the carbohydrate counting course … I was getting told that I wasn't committed enough because I was going to the hospital and then I wasn't allowed to check my blood sugars and I wasn't allowed to inject at my desk and then I got told that I wasn't allowed to leave my desk, even in the lunch hour.'

The stigma which Patient L005 encountered was not only an illegal breach of the Equality Act (2010), but was also clearly upsetting and she described making the decision to leave rather than pursue a legal battle against a charity which she held in high regard for the good work it did. Unfortunately, despite leaving the organisation the scars remained and she mentioned how…

'I didn't expect people to be like that, especially when it's your first job and you've only just been diagnosed … so every time I meet someone new this is what they are going to do?'

In addition to having to manage the psychological aspects stemming from other peoples' stigma of T1D the patient also had to deal with blood sugar levels which were rapidly becoming uncontrollable. The hospital she was under at the time in Liverpool was, from her point of view, not particularly supportive. She explained how because her HbA_{1c} was generally fair and her other metabolic markers were acceptable (as can be seen in Table 9.18) she was told that she would not be eligible for CSII. This frustrated the patient because despite possessing a reasonable HbA_{1c}, her daily blood sugars were extremely chaotic and interspersed with uncontrollable hypoglycaemic episodes. After speaking with various friends she decided to transfer her care to the Royal Liverpool Hospital where she had

been told she may be better listened to. Immediately after being referred she was informed she would be an excellent candidate for CSII and the process began to commence the therapy.

The patient was excited about this for a number of reasons. In addition to the obvious benefit of offering superior control of blood sugars, the prospect of being able to keep the disease hidden also appealed after seeing another female of a similar age using the device to great success. The patient described how…

> *'she was a volunteer at the hospice that I worked at and I seen the way she was getting treated compared to me and they [other staff] didn't know she was diabetic because she was on the pump and it was like amazing. I was like "so your life's completely changed?" She was like "oh, yeah yeah I don't even have to tell people anymore that I'm diabetic because I don't get this needle out and everything".*

This inspired the patient, especially seeing the contrasting treatment this other person received. In addition to this she was also excited about the prospect of being able to better manage her blood sugar during sports; an area of her life which she was passionate about and which had been made difficult as a result of her chaotic blood sugar levels.

After meeting up with Patient L005 during the subsequent appointments after she had commenced CSII it could be seen that definitive changes had occurred. Firstly, she remarked that her glycaemic control had been drastically improved and hypoglycaemic episodes were now rare. These albeit predictable findings were highly favourable, particularly as improving glycaemic control was the principle reason the patient had initially desired CSII (Pickup, 2002). These improvements can be seen in Table 9.18, where reductions from 8.3% to 7.3% occurred, which are particularly favourable when considering that a 10% decrease in HbA_{1c} is associated with a 43% reduction in retinopathy risk (DCCT Research Group, 1995).

Despite this obvious benefit the patient was keener to discuss other aspects of her life which had been improved as a result of the therapy. For example, she expressed that participating in physical activity was now far easier and although no

change was observed in the responses given to the EQ-5D questionnaire (see Table 9.19), the interviews highlighted how important this ability to take part in physical activity was.

L005	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Mobility	No problems	No problems	No problems	No problems	No problems
Self-Care	No problems	No problems	No problems	No problems	No problems
Activity	No problems	No problems	No problems	No problems	No problems
Pain	No problems	No problems	No problems	No problems	No problems
Anxiety	No problems	No problems	No problems	No problems	No problems
EQ-5D Health Scale	100	100	100	100	100

Table 9.19 – Findings from the EQ-5D questionnaire. (A finding of 0 on the EQ-5D Health Scale denotes worst possible health, whereas 100 denotes best possible health).

She mentioned how…

> *'my blood sugars have been really really good. They have been a lot better than on injections because I have learned how to manipulate it a little bit because I know that if I turn the pump down to 30% then I can eat something as well before and I can have stable blood sugars whereas before the adrenaline would make them go really high.'*

This benefit of CSII with regards to taking part in physical activity is well documented and the ability to precisely adjust basal and bolus rates and the option to easily remove the device for a limited time are features which were utilised extensively by Patient L005 (Hammond, 2008).

In addition offering newfound flexibility in terms of physical activity the patient also mentioned flexibility with regards to dietary behaviours. During the second interview she described how after losing a significant amount of weight since diagnosis she now wanted to regain this mass along with muscle.

L005	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Energy (kcal)	1051.8	1443.2	1232.0	1246.8	1656.2
% of EAR	52.6	72.2	61.7	62.3	82.8
Total CHO (g/day)	125.5	169.4	160.8	162.5	201.6
% energy intake	44.7	44.0	48.9	48.9	45.6
Total sugar (g/day)	52.3	49.6	40.3	45.0	57.1
% energy intake	18.6	12.9	12.3	13.5	12.9
NSP (g/day)	9.0	8.9	8.3	10.0	14.3
% of RNI	30.0	29.7	27.7	33.3	47.7
Protein (g/day)	49.2	70.9	69.9	51.8	72.4
% energy intake	18.7	19.7	22.7	16.6	17.5
Total fat (g/day)	42.3	57.7	36.3	47.8	65.3
% energy intake	36.2	36.0	26.5	34.5	35.5
Saturated fat (g/day)	16.6	24.7	17.7	22.4	30.1
% energy intake	14.2	15.4	12.9	16.2	16.4
MUFA (g/day)	11.3	15.5	10.1	12.9	10.5
% energy intake	9.7	9.7	7.4	9.3	5.7
PUFA (g/day)	4.0	5.5	3.4	4.0	3.1
% energy intake	3.4	3.4	2.5	2.9	1.7

Table 9.20 – Average daily macronutrient findings from 5 day weighed food diary.

She explained her reasons for this by describing how…

> *'Yes, I've put weight on. Because I've got a little goal I set myself and before the pump I was struggling to get up to 8 stone and so I had a little goal that on the pump I wanted to reach 8 stone and I've managed 8 stone so it's quite good … I definitely want to be a little bit heavier, just for college as well. Just after seeing all the people at college. They are all massive, with muscle and it's quite scary and they've all got these protein shakes and stuff. They're arms are just massive.'*

These aspirations, although seemingly harmless given that at the time of study the patient was underweight (18 – 19 kg/m^2), should also perhaps be treated with a small degree of caution. When looking at Tables 9.20 and 9.21 it can be seen that after visit 1 the patient's energy intake does indeed go up, along with her protein intake; however, her micronutrient intake is often still far below recommendations, particularly regarding iron and vitamin A. This is concerning as it may potentially signal issues pertaining to the quality of food being consumed. Furthermore, it is important to remember that during the study Patient L005 was passing through an important adolescent transition period known for the development of disordered eating habits and in this search for weight gain and a muscular physique care should be taken to ensure this behaviour does not become obsessive (Young-Hyman, 2016). This has been described in previous work as 'muscle dysmorphia' and although more prevalent in males is not unheard of in females, especially in those with an interest in bodybuilding exercise (Hale, 2013). Healthcare Professionals should perhaps heed stories such as these and be receptive to ensure patients are adequately supported to make healthful dietary choices and pursue their goals in a non-destructive manner.

L005	Visit Number				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Sodium (mg)	1777.0	2577.8	2229.4	2590.4	2199.8
% of RNI	111.1	161.1	139.3	161.9	137.4
Calcium (mg)	615.8	1014.8	762.6	578.2	556.2
% of RNI	88.0	145.0	108.9	82.6	79.5
Iron (mg)	6.4	8.2	6.3	6.3	6.7
% of RNI	43.2	55.4	42.6	42.6	45.3
Vitamin A (µg)	137.2	310.4	158.0	258.2	189.8
% of RNI	22.9	51.7	26.3	43.0	31.6
Vitamin C (mg)	110.4	34.8	47.6	31.6	76.6
% of RNI	276.0	87.0	119.0	79.0	191.5
Vitamin B12 (µg)	2.2	4.0	3.1	2.2	1.7
% of RNI	146.7	266.7	206.7	146.7	113.3

Table 9.21 – Average daily macronutrient findings from 5 day weighed food diary.

A final benefit associated with CSII which Patient L005 was keen to exploit was its discreetness. After being previously inspired by the female pump user at her previous job the patient hoped that the therapy may offer her a degree of 'privacy' and reduce the future occurrences of stigma associated with T1D. Interestingly, as the interviews progressed she explained that whilst the device did indeed allow the discreet administration of insulin, she found that rather than others rebuffing the device they were actually interested in it. The patient explained how…

> *'I've been asked why I wear my Walkman on my trousers so I've explained and they kind of wanted to know about it a bit more and then somebody else asked me and I told them and she started asking loads of questions … I quite like it because the 'Types' of diabetes get mixed up and sometimes I do get asked questions like "you've done well to lose the weight then", and I'm like "no it's not like that", so I quite like getting the awareness out because we didn't expect for me to get diabetes because my lifestyle is quite healthy.'*

This was a sharp contrast prior to the commencement of the therapy where she wanted to avoid confrontation about her diabetes at all costs and was looking forward to CSII making the disease less conspicuous, whereas now her confidence has grown to a point where she would actively seek to engage with interested parties to inform them about the disease. This is a remarkable transformation and one which has been previously documented in work by Saarinen (2014) who described how patients often receive positive interest regarding the device from the public and that many then felt compelled to talk more about their diabetes than when they were using MDI.

9.6 Conclusions

Although these case studies are brief they highlight the transition from MDI to CSII in a longitudinal manner and by describing a selection of the principle issues that the participants faced, the changes they made and the benefits they received serve to provide an intimate insight into this particular period of patients' lives. Although far more attention could be given to the data collected to offer a deep understanding of the lives of each case, the aim was more to provide a succinct flavour of the transitionary process which is lacking in previous literature.

Furthermore, the equal weighting which was given to qualitative and quantitative data during the triangulation process allowed each participant's story to be described and supported with data from the other methods where appropriate. This technique has also been used in previous studies, for example, a multiple methods longitudinal study by Huxley (2015) that investigated potential improved outcomes following diabetes education found that the combination of equally weighted qualitative and quantitative elements offered unique insights into how baseline variables are associated with specific outcomes. The present case studies were no exception to this and also offered unique understandings which would not have been possible using either quantitative or qualitative methods alone. For example, the dietary habits of Patient L003 upon his return from travelling could not have been explained using only food diaries. Similarly, Patient L005's aspirations to become more muscular, which she described in her interviews, were further substantiated using quantitative findings derived from food diaries. This mutual relationship resulting from the combination of methods in

these circumstances has therefore been successful in allowing a brief, yet highly informing overview of each of the cases to be formed.

In addition to focussing on how the differing methods complement each other, when considering the findings as a whole specific insights regarding the transition from MDI to CSII can be found. In particular the results showed how patients often experienced some initial negative aspects associated with CSII, typically regarding the physical size of the pump and hesitations about being connected to a machine; however, these issues were quickly dispelled as patients became more familiar with the device. In fact the majority of comments made after commencement of CSII were highly positive and the therapy was praised for a variety of elements, typically pertaining to its overall flexibility and ability to improve glycaemic control. These aspects frequently resulted in patients' regaining control of the disease and consequently their lives, which in turn often had profound implications on both their confidence and mental state. Furthermore, in addition to the device itself the case studies brought to the fore important external issues regarding CSII as a service. For example, the cases revealed funding inequalities and demonstrated how not only are hospitals different in their willingness to apply for funding, but also that successful applications can also depend on a patient's knowledge of the system and how to maximise their chances accordingly. These inequalities are not unique to Liverpool, with a recent audit of CSII practices revealing nationwide disparities of CSII use, resulting principally from staffing issues (White, 2014). Also, the level of care was revealed as being an important aspect which became more consistent upon the commencement of the therapy as the same member of staff was typically seen and informal contact could easily be made through email or phone call without having to make an appointment. Although little has been discussed in the literature regarding this aspect its impact appeared profound and the additional support was highly regarded.

The findings from these case studies, although illuminating, are also highly likely to be of interest to Healthcare Professionals from a practical viewpoint. As mentioned in the Quality of Life chapter (see page 173), there is a dearth of data regarding the lived experience of patients with T1D who are using CSII and it is important that specialists working in this field understand the therapy from a patient perspective. Furthermore, these findings will also be useful for non-specialist

Healthcare Professionals with an interest in CSII to realise how transition onto the therapy can be complicated in those with complex concurrent conditions, yet how fulfilling the treatment can be when implemented correctly.

Despite enlightening insights and potential practical uses for those in the field these case studies are certainly not perfect. There are a number of fundamental limitations which may unfortunately dilute the quality of the findings. In particular there is a substantial amount of missing data as patients dropped out of the study for various reasons. There were also issues when assessing patients' medical records as measurements were supposed to be taken by the medical team at the hospital but this sometimes did not occur and therefore various data points are missing. These issues could be resolved in future studies by ensuring that all measurements are taken directly by the research team. It may also be useful to consider that some of the patients may have varied and complex conditions and as such may be unfit to participate. Therefore care should be taken at the study design and recruitment stages to ensure that only the most appropriate patients are targeted and that the participant burden is minimised as much as possible. Once recruited perhaps the use of incentives may also be a further strategy which could be considered to improve attrition. Furthermore, the reader should also appreciate that the case studies only investigate individual patients who were all recruited from a single clinic and as such the findings cannot be extrapolated to a larger population.

This, of course, is not the point of case studies though, and it is hoped that rather than offering outcomes which may be statistically meaningful or representative of a larger group, they will instead offer the reader some 'food for thought' regarding the patient experience at a more intimate level and provoke further questions. This is of principle importance, because, as has been demonstrated in these five short cases, when focussing on the individual it becomes apparent that there are invariably underlying factors driving a patient's results, which in turn reveal lives that are generally more complex than quantitative and qualitative data combined to represent a group can ever suggest.

Chapter 10

Synthesis

10 – Synthesis

10.1 Introduction

The diagnosis of Type 1 diabetes (T1D) is a life-changing event induced by the autoimmune destruction of pancreatic ß cells and the current best practice for the management of the condition is the daily exogenous administration of insulin (Pickup, 2004). Unfortunately, it is naïve to consider this a remedy which is either simple to adopt, or a panacea yielding results comparable to the endogenous production of insulin. Both physiologically and psychologically this treatment places a considerable burden upon patients; the impact of which can result in a constellation of additional issues directly and indirectly related to the management of the disease.

This study has referred in detail to some of the issues faced by patients upon diagnosis and the subsequent impact the disease has had upon their lives. Unfortunately, these issues often culminate in patients becoming unable to manage their diabetes using multiple daily injection (MDI) therapy (which is now the 'first line' of treatment for those with T1D) (NICE, 2015). According to National Institute for Health and Care Excellence (NICE) guidelines, if a patient possesses HbA_{1c} levels of 8.5% or above, or is experiencing disabling hypoglycaemic episodes whilst making every effort to co-operate with their physician, they may be offered continuous subcutaneous insulin infusion (CSII) therapy (NICE, 2015). This treatment has been shown to improve glycaemic control in those with poor management of T1D and may potentially offer a greater degree of dietary and lifestyle flexibility (Pickup, 2002).

The study presented within this thesis embodies a comprehensive effort to, for the first time, address gaps in the evidence specifically related to the eating behaviours, cardiometabolic risks and quality of life of patients using CSII both over time and compared to MDI counterparts. These aspects were investigated using multiple methods, comprising of food diaries and food surveys to determine participants' eating behaviours. Quality of life was explored using a brief questionnaire and semi-structured interviews. Finally, a sample of blood was

drawn and medical records were examined to elucidate the cardiometabolic risks and overall metabolic health state of participants.

The data revealed a number of outcomes which confirmed existing evidence, for example, improvements in HbA_{1c} and reductions in insulin dose in those using CSII. There were also improvements in various aspects of quality of life; some of which have been previously alluded to by others. Aside from findings which were in agreement with the existing literature, there were a number of novel and unexpected outcomes which cast new light on CSII therapy, such as subtle changes in eating behaviours, improvements in blood pressure and previously unknown quality of life benefits. Although each experimental chapter puts forward a detailed, compartmentalised discussion of these outcomes, this final synthesis will summarise the principle findings as a whole in relation to the literature; offering the reader a 'birds-eye' view, from which an overall formation of judgement can then be constructed.

It should be noted that this study is not without limitations. These will also be discussed in this chapter with the benefit of hindsight and recommendations will be made regarding future research in this area. Despite issues, the findings from this study nonetheless make an original contribution to the literature in an under-researched and important area of diabetes care. This is important to increase the knowledge of those belonging to the scientific community, for Healthcare Professionals working in the field and perhaps most importantly, for patients with T1D. Furthermore, it is also important to remember the economic burden T1D places upon the NHS, with direct costs totalling £1 billion and with predicted 2035/36 costs projected at £1.8 billion (Hex, 2012). Therefore any studies which enhance understanding and improve patient care may not only improve quality of life for the patient, but may also reduce NHS costs. It is therefore hoped that whilst being limited in scope and highly focused, these findings may ultimately have an impact, however small, upon the lives of patients with the disease who are either already using or considering CSII therapy and the wider society as a whole.

10.2 Discussion of findings

Cardiometabolic risks

The findings from this study revealed that a number of physiological changes occurred in those using CSII related to cardiometabolic risk. Perhaps the most prominent alteration was to HbA_{1c}, which was found by the audit (n = 260) to significantly decrease during the first 12 months of commencing the therapy from 8.3 to 7.6% (mean difference: -0.7%; 95%CI: 0.5-1.0; $p < 0.001$); a finding shown throughout the literature and which although positive was not unexpected (Pickup, 2002). These reductions were maintained for the subsequent 3 years, with HbA_{1c} stabilising between 7.6 and 7.9%. Long-term reductions such as these have also been shown in previous literature, with Melidonis (2016) highlighting a highly significant decrease in HbA_{1c} after 3 years of pump use. This is favourable as the benefits in terms of reduced risks from complications are considerable; indeed, a 10% decrease of HbA_{1c} may potentially lead to a 43% reduction in retinopathy risk (DCCT Research Group, 1995). The reduction shown in the present study may therefore offer promise for patients, especially given both the fear regarding complications expressed during the study and the life-changing impact these issues can infer.

Although the audit revealed that reductions in HbA_{1c} occurred, on average, across the total population of patients using CSII at the Royal Liverpool Hospital, it is important to note that the case studies illustrated that these benefits were not experienced by everyone. For example, when focussing on Patient L001 it can be seen that his HbA_{1c} after commencing the therapy actually increased from 8.6 to 8.9% during the first 3 months, where it remained for the duration of the study. It should be remembered that after agreeing to take part in the study this patient's personal circumstances changed as he became encumbered with additional commitments both at work and at home that he mentioned were very stressful. Although there is little evidence to determine a causal link between these lifestyle changes and the patient's increase in HbA_{1c}, it is probable that it was a contributing factor and it could possibly be argued that if he had remained on MDI the increases may have been even greater. Although an exact cause cannot be pinpointed and given that these comments are speculative they do serve to

illustrate that the beneficial aspects traditionally associated with the therapy may not work for everyone and that individuals often lead complex lives which observational research frequently gives little credit for.

In addition to improvements in blood sugar there was also an unexpected reduction in blood pressure which was illustrated by the audit. This has never been found previously and showed a slow yet statistically significant decline in systolic blood pressure, from borderline hypertension to within the normal range over a 4 year period (128.2 to 122.1 mmHg; $p = 0.003$). Similar significant reductions were also shown with diastolic blood pressure (72.5 to 72.0 mmHg; $p = 0.027$). Furthermore, when compared to patients using MDI, those using CSII were shown to have significantly lower systolic blood pressure (123.5 mmHg vs. 135.3 mmHg; $p = 0.023$). This is contrary to the literature which suggests that CSII has little impact upon blood pressure and it is unknown exactly why the findings in the present study occurred. A hypothesis may be enhanced, personalised medication resulting from a higher frequency of appointments with regular physicians; although one might then expect an aggressive initial reduction rather than the slow, steady decrease described in the findings. Furthermore, reductions in hypoglycaemia have been previously associated with corresponding reductions in blood pressure and this may also have been a potential mediating factor (Sommerfield, 2007). Unfortunately, neither of these theories can be substantiated as no data concerning the medication or frequency of hypoglycaemic episodes of patients were collected.

Despite changes in some variables there were also others which remained static upon the commencement of CSII; with one such example being BMI. Despite participants remarking that CSII restored their ability to participate in physical activity, the majority of patients remained either overweight or obese, as shown in the audit where BMI persisted between 25 and 26 kg/m^2 (see page 85 and Table 5.2). The cross-sectional study again showed that those using CSII were largely overweight; as were their MDI counterparts (28.1 kg/m^2 vs. 25.2 kg/m^2 respectively) (see page 155 and Table 7.8). Despite these issues it is useful to consider that 61.7% adults in the UK are also either overweight or obese and this finding may be a reflection of that (HSCIC, 2014). Nonetheless, this it still concerning when remembering that those with T1D are already at an increased

risk from a host of complications and being overweight serves to further exacerbate these risks (Redondo, 2015).

In addition to this, other metabolic markers, such as the standard lipid profile, appeared at first glance to remain similar over the long-term, with the audit showing few changes over a 4 years period and the cross-sectional study showing little difference between those using CSII and those using MDI (see page 87 and page 156). However, a closer inspection reveals that subtle variances did exist, for example, there was a statistically significant difference in the Apo-A1 / Apo-B ratio between patients using CSII compared to those using MDI (0.60 vs. 0.72 respectively; p = 0.025), which predisposes those using MDI to be a greater risk. Despite this there were attributes pertaining to both groups of patients which initially appeared to infer a degree of atheroprotection. In those using CSII high density lipoprotein cholesterol (HDL-C) remained between 1.7 and 1.9 mmol/L throughout the audit and an average of 2.0 mmol/L was measured in those who took part in the cross-sectional study. Similarly, those using MDI who took part in the cross-sectional study possessed levels of HDL-C measuring 1.7 mmol/L. These levels are far greater than the 1 mmol/L recommended for the general population (Heart UK, 2016). Unfortunately it is a reality that the risk of cardiovascular disease (CVD) is a raised in those with T1D and that the HDL-C may potentially be dysfunctional, despite being present in favourable quantities (Vergès, 2009; Manjunatha, 2016). These subtle differences in lipid parameters and ubiquitous levels of HDL-C combined with the high rate of CVD in those with T1D and a lack of understanding regarding the underpinning mechanisms pose questions for future research to further investigate the quality of lipids and lipoproteins in greater detail.

Eating behaviours

Another area of focus during this study which initially revealed few changes were the eating behaviours of those using CSII compared to those using MDI. Many of the levels of nutrients consumed were similar with few significantly different variables. This in itself was an interesting finding as it indicated that despite having the opportunity adopt a liberalised diet patients failed to take advantage of this and chose not to consume lower quality foods high in sugar, salt and fat, which may

potentially be detrimental to health. This has never been previously shown in patients using modern insulin pump therapy and is a novel finding. Furthermore, as detailed in the case study of Patient L004, a relaxed diet was one of the benefits this individual was most looking forward to exploiting; however, this failed to occur and the patient's diet actually changed very little. In fact she retained the habitual eating behaviours she had become familiar with due to a fear of metabolic disturbances caused by previous deviations from her structured diet, resulting in a 'better the devil you know' mentality. This 'retained fear' could potentially explain the lack of dietary change shown upon the commencement of CSII; however, further research focussing on this would be required to confirm this hypothesis.

Despite few dietary changes occurring upon the commencement of CSII, some elements of the diets appeared to be less than optimal regardless of treatment group, with some findings also suggestive of misreporting. An example of this can be seen when looking at the energy intakes of both treatment groups as shown in the cross-sectional study (see pages 112 & 119). These were shown to be below the EAR, regardless of treatment. A finding which clashes with the mean BMI findings described previously, which highlighted how the majority of patients, regardless of treatment, were either overweight or obese. This paradoxical finding points towards potential under-reporting, which the Goldberg equations suggest is likely to have occurred and which the literature reveals is often the case in those with a BMI >25 kg/m^2. Furthermore, when looking closer at both the cross-sectional study and the individual case studies it can be seen that the certain key nutrients such as fibre were often severely lacking and some micronutrients, such as iron in females, were typically consumed in amounts less than the RNI. Furthermore, there was an excess consumption of other nutrients such as sodium and total sugars, which have been associated with blood pressure and obesity respectively (Bray, 2014; He, 2007). Interestingly, it could also be hypothesised that these nutrient measures may be conservative at best, as it has been known for some time that individuals who underreport energy intake are also more likely to underreport poor quality foods high in sugar and fat and over report those regarded as 'healthy', such as fruits and vegetables (Bingham, 1995). Findings such as these point questions towards the overall quality of the diet regardless of treatment and should be an area monitored closely in this at-risk population.

The route to CSII and its impact upon quality of life

Although the practical commencement of CSII consists of a week-long education session, the route to this point and the time thereafter can involve many changes in diabetes-related quality of life. These were outlined by patients who participated in the present study and the prominent themes provide a chronological insight into the lived experiences of those with T1D from pre-approval of CSII through to the transition onto the therapy.

Although there were many themes which were revealed during the course of the interviews, perhaps one of the most striking was that after diagnosis, aside from the practical difficulties of coming to terms with the disease, many participants felt that their life with diabetes was in some way 'abnormal'. Furthermore, rather than addressing the problem participants mentioned that it was often easier to ignore it. This was evidenced as many revealed they had found the condition difficult to accept and rebelled at points in their lives; typically during adolescence. Although often short-lived, episodes of poor compliance have been shown to incur a cost, with the early development of complications being seen even in youngsters with poor control (Hood, 2009; The DCCT Research Group, 1998). Furthermore, many also encountered stigma from not only strangers, but also people closer to them, such as friends and work colleagues, which only served to further polarise patients.

Fortunately, the majority of participants who mentioned these issues at some stage described taking responsibility for their condition and then making 'sacrifices' for an overall improvement in glycaemic control when using MDI in the hope of minimising the risks of future complications. These forfeits typically came in the forms of restricted physical activity (which patients often feared would result in short-term issues such as hyper or hypoglycaemia (Pickup, 2004)) and the amendment of diet. The present study focused on dietary aspects and revealed how the non-continuous nature of MDI was typically accommodated by patients though the adoption of a relatively structured diet which was frequently arbitrated by obsessive behaviours and the subsequent 'medicalisation' of certain food items which came to be associated with disease. These issues serve to highlight the need for more access to psychological support. Diabetes UK has recognised this

and outlined in their '15 Essentials' programme that all patients should have access to these services, yet in reality only 25% of patients have reported psychological care to be in place when they needed it (Diabetes UK, 2015). Furthermore, ensuring timely access to alternative therapies such as CSII may also improve these issues due to its ability to allow patients to live a more flexible life, as described throughout this thesis. Interestingly, despite the discipline and hardship required to surrender to the structure of MDI many patients actually praised the flexibility of the therapy and the ability of the regimen to allow, with the caveat of personal investment, a relatively unhindered life.

In the light of this it was therefore surprising to hear patients not only express concerns about the physical nature of CSII, but also the ability of the device to offer an unprecedented level of flexibility. Many using MDI perceived the pump to be of little benefit over injections and it was frequently suggested that learning a new method simply wasn't 'worth it'. This scepticism was usually based upon little knowledge of the therapy, with many admitting to having only briefly read about CSII in the literature or hearing about it though short discussions with friends, family or Healthcare Professionals. Furthermore, if they were deemed ineligible the therapy then typically became consigned to a realm of diabetes care thought of as being both unattainable and unbeneficial.

At this point it is important to point out that those eligible for CSII were often characteristically bonded by the common denominators of poor glycaemic control and evidence of co-operating with Healthcare Professionals to manage the issue (NICE, 2015). Indeed this can be seen when looking at the audit (see page 87) and case studies (see page 206), which show that that prior to engaging with the treatment HbA_{1c} is typically raised. It could therefore be argued that patients due to commence the therapy largely consist of unique selection of disciplined individuals suffering, in many cases and despite best efforts, from challenging symptoms. The impact of these can be profound, with many patients describing the effect they have had upon their lives; from stories of collapsing at work, through to losing the awareness of hypoglycaemia, thus further exacerbating anxieties. It is little wonder that those due to commence CSII often had a contrasting outlook and attitude to their MDI counterparts previously described. These patients spoke generally of excitement and optimism for the therapy, with the case studies (see page 206) in

particular revealing how despite minor apprehensions the broad feeling was one of positivity, with participants typically looking forward to the prospect of regaining control of their lives. For these patients the device took on a different meaning and was almost seen as a ‘beacon of hope’. Although these accounts are favourable it is difficult to imagine what the likely outcome of these patients would have been had they not been offered CSII at this point. Some presented highly complex physiological and psychological issues and although there is an absence of literature investigating the outcomes of poorly controlled patients who were specifically refused CSII, it is clear that those with uncontrolled T1D are at an increased risk of a number of complications (Pickup, 2004). Therefore it is encouraging to see not only the improvements in risk factors, but also the patients’ lives in general.

Although the majority of participants due to commence CSII followed the path outlined above there was an important exception; notable in its singularity yet pronounced in its significance. This was a case study concerning Patient L003 (see page 223) which revealed his unconventional route to instigating approval for CSII. The literature is flecked with reports demonstrating CSII being used to successfully treat those with Type 2 diabetes, Addison’s disease (by replacing insulin with cortisol) and pregnant women with T1D and although rare these examples illustrate how the therapy can be used beyond the confines of poor glycaemic control alone (Reznik, 2014; Gagliardi, 2014; Kallas-Koeman, 2014). Therefore, as a Health Professional this patient took advantage of the ability of CSII to offer more than just glycaemic control. After being informed by a senior colleague of the benefits CSII could offer and subsequently self-researching the device the patient decided that the therapy could improve his life. Unfortunately (or fortunately depending on the viewpoint) Patient L003’s glycaemic control was well managed, thus automatically falling short of NICE criteria meaning he was ineligible for NHS CSII funding. Nonetheless the colleague suggested a Diabetologist who may listen and the patient made the case that due to his keen interest in sport and that his future career would likely involve working abnormal shift patterns he was concerned that his glycaemic control may decline as he leaves university and embarks on chaotic full-time employment. This ‘preventative’ slant gained the approval of both the Diabetologist and the Commissioning group

and the patient received funding for the device. Although this is a positive result it poses an interesting juxtaposition with the perceptions of CSII described by other patients through a lack of knowledge of the therapy and it begs the question of whether if patients were fully informed would they too press for funding? Even if they were informed would they be adequately equipped to negotiate the commissioning process in the efficient manner Patient L003 did with the assistance of expert support? That said it should also be remembered that a recent audit of NHS Trusts offering CSII found many to be severely understaffed with insufficient resources to enrol and manage patients and that there exists an unofficial nationwide 'postcode lottery' for pump funding (White, 2014; Dudley, 2014). As such, although this particular patient's experience was positive it is unlikely representative of the nation, or even the hospital as a whole, where CSII funding can in some cases be a difficult proposition (White, 2014). Although the true representativeness of this particular example is unknown, and despite it likely to be an exception rather than a rule, still serves to illustrate some of the inequalities which exist regarding the approval process.

From a clinical perspective, the decision to recommend CSII to a patient is not always straightforward and as shown in the present study, many patients may have underlying psychological issues regarding T1D as well as other complex conditions and CSII may be contraindicated despite documented physiological benefits. Physicians may therefore find themselves in difficult situations where they may have to use their experience to determine the optimum treatment for patients on a case-by-case basis as best-practice guidelines cannot address such issues. After a physician has considered a patient and decided that they would be an ideal candidate for the therapy the process of instigating CSII then starts, for all practical purposes, with approval from an NHS commissioning body; however, this study revealed that sentiments regarding the therapy typically develop in patients long before this day arrives.

A principle example of this was when various patients reported their initial perceptions of the device upon hearing of it for the first time. Many explained how they recoiled in horror when discovering that the pump is a permanent commodity, with the only opportunity for respite being the ability to detach the device for a maximum of an hour to allow active sports or swimming etc. To many patients this

fusion between body and machine was perceived as an act of cementing their relationship with T1D, from which there can be no escape. Conversely, it was mentioned how when using injections after insulin is administered the pen can be placed into its case until next time, effectively shutting the patient off from the disease; albeit temporarily, whereas being attached to a machine would be a permanent reminder of T1D. Work by Saarinen (2014) also found similar concerns in patients and described the pump as 'diabetes made visible', which in the context of the present study refers to a 'visibility' observed by not only others, but by the patient as well.

Some issues were also raised in addition to the physical aspect of the pump, with patients expressing concern that the move onto the treatment may be overwhelming. Furthermore, others reported anxieties about giving control of their diabetes, albeit temporarily, to doctors and nurses. An anxiety further exacerbated as some had developed a mistrust towards Healthcare Professionals as a result of previous negative experiences. It was therefore intriguing to see how over time, as the patients developed an understanding of the device and incorporated the therapy into their lives, these initial hesitations were often dispelled. It was frequently mentioned that, despite minor inconveniences, the pump came to be regarded by the patients almost as a part of their body in much the same way a wristwatch might; a concept again reiterated by Saarinen (2014). Furthermore, this union between body and machine went one step further than patients simply feeling comfortable with the device. Some mentioned how others had asked what the device was, confusing it for a Walkman or mobile phone and when told it was an insulin pump often asked for further explanation. Rather than shying away from this patients described their delight and took it as an opportunity to inform people about their diabetes and the role of the pump and it was clear that the device provoked a great deal of dialogue. This represents a polar shift from patients' perceptions prior to the commencement of the therapy. Whereas beforehand the patients were wary of the device bringing unwanted interest and saw it as little more than an 'aide-memoire' of their condition, after commencing the therapy it came to be regarded almost as a 'medal of honour' to be worn with pride. This sharp contrast is a positive one and rather than trying to attain another life regarded as 'normal', the comments made after the commencement of CSII are

more suggestive of a group of individuals who have come to accept their life with diabetes. Furthermore, rather than the pump being a visual reminder of the condition which should be worn with shame and regret, it in fact became a motif of success over diabetes and a method of promoting awareness which should be outwardly presented with pride and confidence. This imagery ran throughout the study period and appeared to be a long-term metaphor and although being difficult to quantify represented a seismic shift in the quality of life of patients.

If anything, the contradictions and paradoxes presented by both the perceptions and physiology of patients with T1D, whether they are planning to commence CSII or not, highlight the complexity of the disease in general. This is an extremely important factor and one which is has been highlighted in the literature as being imperative to consider during the transition onto CSII. In particular adequate education and ongoing support must be in place and facilitated by trained professionals; a requirement also outlined in NICE best practice guidelines (NICE, 2015). This integral part of commencing the therapy appeared to be highly regarded in the present study, with participants detailed in the case studies reporting how the comprehensive the sessions were (Morrison, 2013). Although this is obviously positive feedback, there was an undercurrent running beneath these practical aspects; primarily embodied within the consistency they provided and the ability to develop a Healthcare Professional / Patient relationship. Many of the patients mentioned how they appreciated the regularity that they associated with CSII and which brought increased levels of predictability to the services provided by Healthcare Professionals. Examples of this were more regular appointments, seeing the same doctor or nurse at every session and whereas some felt they had been previously pushed ‘from pillar to post’ they now described a sense of ‘grounding’. Others detailed how they enjoyed the newfound rapport with someone who recognised their name, their background and who could offer a ‘guiding hand’. This area regarding the consistency of care is under-researched in CSII therapy specifically; however, there is a body of literature revealing how, from a patient perspective, uniformity of care is highly favoured, especially in those with chronic conditions (aside from the important exception of mental illnesses where discontinuity may be more appropriate) (Freeman, 2010).

10.3 Limitations and recommendations for further work

Despite revealing some interesting aspects of CSII therapy it would be unrealistic to suggest that this study is not without its limitations; many of which ultimately stem from its design. This research was observational and therefore has fundamental flaws which should be highlighted. Principally observational studies by their very nature, although being useful to elucidate the risks and benefits of a treatment, can be subject to bias (Jepsen, 2004). For example, when considering the complexities in patients' lives revealed by the case studies it is easy to see how other, often unseen, aspects could have impinged upon not only the findings, but also the recruitment and collection of data. Unfortunately, it is very difficult to control for free-living subjects in the research design apart from choosing a more robust design such as a randomised control trial (RCT) to investigate some of the quantitative aspects; however, the resources and cost required to perform such an endeavour would be considerable. Furthermore, little previous research has been carried out specifically focusing on the areas of concern and therefore a pilot study to gather some preliminary data was considered by the research team to be more appropriate at this stage, rather than pursuing a full scale RCT.

Similarly, it should also be remembered that to perform a robust study a properly powered sample size would be required. As CSII therapy is relatively rarely used this would mean having to recruit participants from multiple sites. As the Royal Liverpool Hospital Diabetes Centre has the largest clinic in the North West national recruitment would have been required. A study using multiple centres throughout the UK was out of scope of the available resources and is likely to be the reason why so little literature exists from RCTs originating from the UK investigating the use of CSII.

With regards to recruitment for the present study, there were also a number of issues which should be raised. Unfortunately, there were unavoidable staffing issues described in the Recruitment Feasibility chapter (see page 65) which initially prevented adequate recruitment to the longitudinal study (with the participants ultimately being used as case studies). Despite this inconvenience it would be unfair to place blame for poor recruitment solely on this issue as it became obvious as the study went on that there was a large participation burden.

Although some of the patients had complicated issues unrelated to the study which caused them to withdraw, the author noted that completing five sets of food diaries and participating in five interviews in addition to the other study requirements was time consuming. Although no complaints were made directly to the author in hindsight perhaps the study could have been made less burdensome with fewer appointments. These compromises could also have been possibly supplemented with some form of incentive. Given that some of the participants, particularly those recruited to the longitudinal section, completed the study they should be thoroughly commended for their efforts.

Furthermore, with regards to the actual sample recruited it should be acknowledged that to be eligible for CSII patients must typically meet NICE criteria and this automatically means that the sample may differ in some ways from patients with T1D in general. For example, they are more likely to possess a certain level of discipline having had to meet the strict criteria. Furthermore, by default they are also highly likely to have poor glycaemic control prior to the commencement of the therapy (which unsurprisingly was shown in the findings). Similarly, those using MDI who participated in the study were also likely to be those of an altruistic nature and therefore arguably 'different' than those who did not agree to take part, as well as being more likely to gravitate towards opportunities which may improve their own health (McCann, 2010). Indeed, the act of simply being a research participant has been shown to alter behaviour. This long-known phenomenon called the 'Hawthorne effect' has been shown in a recent systematic review to impact upon health studies and may well have contributed towards the findings of the present study unbeknown to the author (McCambridge, 2014). In addition to this, the patients with MDI also appeared to be generally a well-managed group and it is difficult to say in the light of this if they are truly representative of MDI patients as a whole. Furthermore, it is unknown if patients recruited from the Royal Liverpool Hospital are truly representative of those with T1D in the UK as a whole.

In addition to these issues of representability, the study also had some limitations with regards to the actual methods used. For example, surveys such as food diaries were completed by the participants at home and therefore, despite best efforts (such incorporating brief interviews to confirm the responses), it is difficult

to truly know the accuracy of results. The energy intake data and findings from the Goldberg equations were also indicative of bias and this is well-known when using assessment method such as food dairies in an overweight and obese population (Livingstone, 1990). Aside from amending the study design and monitoring food intake in more controlled surroundings (which was out of the remit of available resources) little can be done about this; however, food diaries are a commonly used assessment method and it is hoped that a reader will accept and understand their shortcomings and appreciate the findings in the light of this.

In a similar way the patient medical records which were assessed both during the clinical audit and the cross-sectional study also had limitations. Although these issues have already been alluded to previously within this thesis, it is important to reiterate that the data was retrospective and not originally documented with research in mind. As such there is no record of the protocols used to collect the data and the environment in which the measurements were taken is unknown. This could pose issues with regards to the quality of the data. Furthermore, the author was told that after patients began CSII they would see a Healthcare Professional at 3 month intervals where basic clinical markers would be recorded. Unfortunately, as the study progressed it became apparent that this did not always occur and therefore explains some of the missing data which can be seen, especially in the case studies. In hindsight the author should have taken these measurements and acquired additional funding to run tests himself for markers such as HbA_{1c} which would have almost certainly improved the quality of the data in areas.

Furthermore, with regards to the qualitative aspects of the study it is difficult to determine with certainty if the data is reliable. The author made best efforts to ensure that all participants felt comfortable and relaxed and incorporated techniques such as active listening to facilitate the interview process. Despite this, some of the participants, especially those who took part in the cross-sectional study had never met the author before and were expected to answer questions about their life with a chronic condition. Although no particularly sensitive questions were asked, the conversations frequently deviated onto personal and emotional topics and it is unknown just how comfortable the participants were about opening up. The author tried to build rapport as best possible in the short

time prior to the interview commencing; however, in hindsight perhaps it may be best in future to offer pre-study briefing sessions to assist in this rapport building process.

It should also be noted that there were some practical issues which the author encountered during the study. These particularly relate to the laboratory analysis of plasma samples as described in detail in chapter 7. It should be noted; however, that these issues had little bearing upon the results and so will not be discussed further, although for future studies using good quality apparatus is imperative to ensuring good quality results.

With regards to future studies, a number of suggestions became apparent, mainly stemming from the regret of not measuring certain variables. For example it would be useful to determine the frequency of hypoglycaemic episodes during the commencement of CSII. This would have been beneficial as although HbA_{1c} is a useful measure of average glycaemic control, it tells very little of the day-to-day variances which can impact greatly upon patients quality of life. Furthermore, the present study did not measure physical activity levels. This was in hindsight an error because although many patients explained in the interviews how the therapy had allowed freedom to perform physical activity the author had no way of quantifying this and when considering that this aspect was often described as an important part of many participants' lives it would have been beneficial to have investigated this further. Similarly, no measures of lean mass were taken. Although BMI data was gathered from the medical records of patients these showed little change, despite those using CSII mentioning an uptake in physical activity and as such it could be hypothesised that changes in lean mass may instead be occurring. Also, the findings revealed an interesting paradox whereby patients who commenced CSII failed to take advantage of the dietary flexibility inferred by the therapy. This was surprising and the qualitative data suggested that patients preferred to remain attached to their old habits due to an underlying fear of the metabolic disruptions which previously occurred when using MDI. This is an under-researched area and if these behaviours are in fact occurring Healthcare Professionals will need to take heed and ensure that patients are adequately supported to not only take advantage of the flexibility of CSII, but to also make healthful food choices. A further aspect which should also be considered for future

research is that regarding the quality of care and support which patients receive. Numerous times throughout this thesis the profound impact that consistency and quality of care may infer has been hypothesised, yet little research has been performed in this area. Therefore, it would be useful for future studies to investigate this further and although potentially difficult to measure is a gap in the literature which requires confronting. Also, the lipid and lipoprotein analysis carried out in the study, although showing little quantitative differences between those using CSII and MDI shows subtle differences in some areas, such as the Apo-A1 / Apo-B ratio. This could perhaps be indicative of small but important qualitative differences. Indeed the literature suggests that there are qualitative benefits which can be enjoyed by improving glycaemic control and therefore perhaps it may be useful in future research to investigate other aspects of lipoprotein quality (Vergès, 2009). Principle examples being low density lipoprotein (LDL) discordance, oxidation and glycation, as well as HDL functionality, which have all been shown to be sensitive to glycaemic control (Vergès, 2009). Finally, the audit and cross-sectional studies both revealed, for the first time, a novel decrease in blood pressure in those using CSII both over time and compared to those using MDI. The research team are unsure why this may be occurring; however, a future study is planned to investigate the blood pressure of CSII patients more robustly to confirm this finding.

10.4 Summary and relevance of findings

This study shows that the impact of CSII far exceeds the device itself. It is a complex intervention for the treatment of T1D which comprises of a plethora of inter-related factors including technology, education, support, physician attitude and patient self-responsibility. Despite this complex convergence of indispensable elements, very little modern research has been performed focusing on the areas outside of glycaemic control. This study therefore, for the first time, offers an insight into the some of these currently under-researched aspects and amd has revealed often subtle but important differences pertaining to the eating behaviours, quality of life and cardiometabolic risks of adult patients with T1D who are well established with CSII. Furthermore, it also offers not only an albeit brief insight into the transitionary period through a number of case studies, but a more long-term

overview through an 8 year retrospective audit of patient medical records. In fact an audit of this length has never been previously attempted investigating patients residing in the UK.

In addition to making an original contribution to the literature this study, through novel investigation, has also elucidated findings which may have greater value than simply enhancing the knowledge base alone. It is hoped that the findings, published through both a university repository and in a subsequent series of peer-reviewed journal papers will allow Healthcare Professionals to make better judgements regarding patients using both CSII and MDI. In particular, it is hoped that these findings will emphasise the importance of ensuring that patients are well informed of all their treatment options. Using the case study of Patient L003 as an example, it can be seen that after being informed in more detail about CSII he decided it could be of benefit and with assistance of an expert colleague developed a strategy to successfully apply for the treatment. Other patients do not have this luxury and might be unaware of the device and its benefits and may only become mindful after a crisis has happened. In the light of this perhaps Healthcare Professionals should also consider not only *how* they educate their patients but also *when* and aim to prevent rather than treat issues.

As well as being useful to Healthcare Professionals it is also hoped that the findings will be beneficial to patients alike and will hopefully encourage individuals to ask for the treatment they want and need. For example, the case study of Patient L004 illustrated how she was initially lacking in self-confidence and meanwhile her diabetes related issues were intensifying to the point she broke down in a clinic appointment. This got the attention of her consultant who immediately said she would be ideal for CSII. This begs the question that perhaps if she had previously voiced her concerns more assertively would her requests have been taken more seriously? This may have also prevented the culmination of her anxieties and it is hoped that patients in a similar predicament may be able to take some strength from this patient's story and apply it to their own situation. Furthermore, it is also hoped that the findings from this study might also prompt patients to independently take responsibility and self-research their condition and to work in conjunction with, rather than under the control of Healthcare Professionals. Referring back to the case study of Patient L003, his motivated and

proactive approach to self-researching CSII after initially being informed about the therapy was the stepping stone he needed to decide that the treatment could be of benefit; whereas previously he hadn't even considered CSII as a treatment option.

In addition to assisting both Healthcare Professionals and patients, the benefit these findings may have upon society should also not be underestimated. It could initially be suggested by a 'devil's advocate' that comments made in the previous two paragraphs may encourage more patients to ask for CSII and for more physicians to recommend the therapy, which may in turn have cost implications for an already overburdened NHS. However, in reality it is likely these additional costs would be counterbalanced against the money saved from treating the complications associated with poor glycaemic control. Indeed, a recent systematic review of studies investigating the cost effectiveness of CSII compared to MDI found that although higher direct treatment costs were associated with CSII, these were compensated by reductions in costs required for the treatment of complications (Roze, 2015). Despite this a the recent insulin pump service audit illustrated a lack of adequately staffed pump services to induct substantial quantities of new patients and those services which exist are already overburdened with the management of existing patients (White, 2014). Unfortunately, this evidence perhaps serves to highlight that an ever greater problem may lie not with the physicians or hospitals but rather the governing bodies who fund the time of Healthcare Professionals. With 39% of consultant, 61% of diabetes specialist nurse and 60% of dietitian time unfunded it is likely to remain difficult to persuade governing bodies that extra Healthcare Professional time is needed to grow a service which will cost even more in short-term direct costs; despite the fact that the long-term financial benefits have been documented (White, 2013; Roze, 2015). The solutions to these issues are out of the remit of this study; however, it is hoped that the findings may contribute somewhat towards a larger case outlining the benefits of CSII and the positive impact that it may have upon patients, the NHS and society as a whole.

Overall, to summarise, this study has, despite limitations, produced a variety of novel findings in currently under-researched areas, as well as positioning the foundations for a number of successive research studies. It has also created valuable information which can be used directly used by Healthcare Professionals

and which the author hopes may ultimately go some way toward improving the lives of those with T1D.

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Appendices

Appendix 1

NRES ethical approval letter

The Royal Liverpool and
Broadgreen University Hospitals
NHS Trust

Royal Liverpool University Hospital
Prescot Street
Liverpool
L7 8XP

Tel: 0151 706 2000
Fax: 0151 706 5806

TRUST APPROVAL LETTER FOR NON-CTIMP STUDIES

Mr Richard Webb
Liverpool John Moores University
98 Mount Pleasant
Liverpool
L3 5UZ

REC: **13/NW/0122**
NIHR: **Non NIHR**
Date: **15/04/2013**

Dear Mr Webb

RD&I No: 4525
CS11 in T1 diabetes: Diet, quality of life and cardiometabolic risk

The above study is a Non-Commercial, Procedure study, sponsored by Liverpool John Moores University and funded by Self Funded. The Trust is now happy for you to commence work on this study, using the following ethically approved documents.

Document	Version	Dated
Participant Contact Details Form	V1	31 January 2013
Lone Working		
Flow Chart for Study Activities	V1	31 January 2013
Semi Structured Interview Theme Brainstorming	V1	31 January 2013
Participant Consent Form	V2	19 March 2013
Participant Consent Form: Interview Informed Consent	V1	19 March 2013
Participant Information Sheet	V2	19 March 2013
Protocol	V1	31 January 2013
Questionnaire: EQ-5D-3L Health Questionnaire		
Questionnaire: Food Diary	V1	31 Janauary2013
Summary/Synopsis	V1 Methodology Flowchart	31 January 2013

May I to take this opportunity to remind you of your responsibilities as PI for this study to:-

- Report SAE's as per protocol and Trust policy and record total number on OSIRIS
- Ensure that all screening and recruitment activity is updated on OSIRIS every Friday (training can be obtained if required by phoning Ext 3782)
    - Department of Health target for this study was for the first patient to be recruited by **11 April 2013.**

- Please provide a timely response to requests for information regarding achievement of this target
- For Trust sponsored studies, provide RD&I with copies of regulatory annual progress and safety reports to Ethics
- Complete and return the RD&I annual report form in a timely manner
- Comply with the Research Governance Framework 2nd Ed 2005 including but not limited to the Medicines for Human use (Clinical Trials) 2004 act plus it's appendices and the Data Protection Act 1998
- Read, disseminate to research team and acknowledge to RD&I, Trust research SOP announcements (details of relevant SOP's can be found at http://staffintranet/departments_and_services/corporate_services/research_and_development/documents/documents.aspx)
- Inform RD&I of any amendments to, or changes of status in, the study.
- Ensure any conditions to approval stipulated by the MHRA/ REC have been addressed prior to implementation of approved changes
- Maintain the study site file (if not provided by the sponsor a template is available on the Trust intranet)
- Provide copies of publications

Investigators who do not comply with the above will be dealt with in accordance with the Trust Disciplinary policy and/or will have their research stopped.

I wish you every success with your research. Please contact the RD&I Department if you require any advice on the above points.

Yours sincerely

Julia West
Operational Director RD&I

cc Head of Directorate
Liverpool John Moores University

.....

I agree to the terms and conditions of the Trust research approval for RD&I **4525, CS11 in T1 diabetes: Diet, quality of life and cardiometabolic risk** and am aware of my responsibilities under the Research Governance framework and Trust Research SOP's.

Signed: ..... Dated: .....

Please return a copy of this letter to the RD&I Department, 4th Floor Linda McCartney Centre, Royal Liverpool Hospital, Prescot Street, Liverpool, L7 8XP
Thank you

Appendix 2

Participant information sheets (all studies)

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

A Mixed Methods Investigation into the Eating Behaviours, Quality of Life and Cardiometabolic Risks in Adults with Type-1 Diabetes using Continuous Subcutaneous Insulin Infusion Therapy.

Researcher – Richard Webb

Researcher's Email address – R.Webb2009@LJMU.ac.uk

PARTICIPANT INFORMATION SHEET

A Mixed Methods Investigation into the Eating Behaviours, Quality of Life and Cardiometabolic Risks in Adults with Type-1 Diabetes using Continuous Subcutaneous Insulin Infusion Therapy.

Richard Webb – Liverpool John Moores University (Faculty of Education, Community and Leisure)

You are being invited to take part in a research study. Before you decide it is important that you understand why the research is being done and what it involves. Please take time to read the following information. Ask us if there is anything that is not clear or if you would like more information. Take time to decide if you want to take part or not.

1. What is the purpose of the study?

The purpose of this study is to gain knowledge about how insulin pump therapy may affect your eating behaviours, quality of life and cardiovascular disease risks (and markers relating to metabolism). This information will be used to assess the effectiveness of pumps in relation to these factors and to improve the advice we give to people on CSII.

2. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do you will be given this information sheet and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw will not affect your rights/any future treatment/service you receive. (It should also be noted that permission for your participation in this study will also be asked from your health professional – if permission is not given you may be excluded from the study. Additionally, you may also be excluded if you have recently been involved in another study – you should make the researcher aware of this).

3. What will happen to me if I take part?

If you agree to take part you will be asked to:

- *Be involved with the study for its duration (approximately 5 days max).*
- *Complete 1 food intake questionnaire outlining recent food consumption and 1 short quality of life questionnaire.*
- *Allow the research team to contact your GP to make them aware of your participation in the study.*
- *Allow the research team to access your medical records to gather information regarding your current age, gender, weight, height, lipid profile, HbA1c level and blood pressure.*

You may also be asked to:

- *Be interviewed. This will occur once and will last for approximately 1-2 hours and will ask you questions relating to the quality of your life.*
- *Complete 1 food diary for 5 consecutive days (the contents will be reviewed with you during a short interview upon completion).*
- *Agree to an extra 4 teaspoons of blood being drawn after fasting for 12hr in addition to your regular diagnostic sample.*

A flow chart has been attached to this information sheet for you to look at. This visually outlines these activities.

4. Are there any risks / benefits involved?

This study may also pose various risks and burdens to you as a participant. These are outlined below:-

- ***Inconvenience -*** *Some aspects of this study may demand a small investment of your own time. Examples are the 5 day food diaries and interviews. To help minimise the inconvenience caused by this, the food diaries have been designed to be as user friendly as possible.*
- ***Interviews -*** *Additionally, to minimise any impact occurring from the interviews you will be offered the choice of participating either at your regular clinic location at a time of your choice, or alternatively they can take place in your own home.*
  Although the interviews will only be concerned with the impact that insulin pumps have had on your quality of life, it should be noted that the diabetes team from the Royal Liverpool Hospital will be on hand, either at the

clinic sessions or over the phone to offer support and help on any issues.

- ***Blood Samples -*** *There is also a risk that you may feel a slight discomfort during the drawing of the additional 4 teaspoon volume of blood needed by the study; although this will be no more uncomfortable than any of your other regular blood visits. To minimise the risks of this all blood will be drawn by a trained phlebotomist and will be only be taken in addition to your regular diagnostic sample if needed.*

5. Will my taking part in the study be kept confidential?

All your data collected from this study will be kept confidential. This will be done by:-

- *Ensuring that your name will not be used in any of the data derived from food diaries, food intake questionnaires and quality of life surveys as well as any results from tests carried out on your blood samples.*
- *Ensuring all data will be stored on a secure NHS and university server (apart from your contact details which will be stored separately).*
- *Interviews will be audio recorded and transcribed and stored anonymously on a secure NHS computer.*
- *After transcribing is complete the audio tapes will then be destroyed and the transcribed copy will be stored on the secure NHS server for the duration of the study; after which it will be destroyed within 5 years using appropriate data destruction software.*
- *The only data collected from you which will not be anonymised will be your personal contact details to allow the researcher to keep in touch with you throughout the study. These will be stored in a locked filing cabinet in an NHS location with restricted access. This will be destroyed within 3 months of the study ending.*
- *We will also ensure that outside of the direct healthcare team, only the student (Richard Webb), Academic Supervisor 1 (and Chief Investigator) (Dr Julie Abayomi), Academic Supervisor 2 (Dr Ian Davies) and Academic Supervisor 3 (Professor Andrew Sparkes) will have access to your personal data during the study.*

We will also ensure your blood samples remain confidential by:-

- *Making sure all samples are anonymised before they are made available to the study. It should also be noted that access will be under the control of the Chief Technician, Dr Julie Abayomi and Dr Ian Davies.*

- *Most testing and analysis will take place at LJMU, however some anonymised samples will be prepared at LJMU and then transported on ice to Northumbria University for analysis by Dr John Lodge.*

We would also like to keep with your permission any of your plasma samples that are left over at the end of the study. Left over blood samples will be anonymised and stored for a maximum of 5 years under Liverpool John Moores University policy and may be used in further research projects pending ethical approval.

6. Who can I contact for independent advice to help me decide whether or not to be involved in the study?

- *If you would like independent advice to help you decide whether nor not to be part of the study you can contact your diabetes specialist nurse, GP or Diabetes UK (www.Diabetes.org.uk).*

7. Who can I contact in the event of a complaint regarding the study?

- *If you have a complaint to make regarding the study you can contact the Chief Investigator to discuss your issue further. The Chief Investigator's contact details are shown at the end of this form.*

Contact Details of Researcher

Richard Webb (R.Webb@2009.ljmu.ac.uk)
Liverpool John Moores University (IM Marsh Campus)
Barkhill Road
Aigburth
Liverpool
L17 6BD

Contact Details of Chief Investigator

Dr Julie Abayomi (Senior Lecturer) (J.C.Abayomi@ljmu.ac.uk)
Liverpool John Moores University (IM Marsh Campus)
Barkhill Road
Aigburth
Liverpool

L17 6BD

Note: A copy of the participant information sheet should be retained by the participant with a copy of the signed consent form.

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

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Researcher – Richard Webb

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Richard Webb – Liverpool John Moores University (Faculty of Education, Community and Leisure)

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8. What is the purpose of the study?

The purpose of this study is to gain knowledge about how insulin pump therapy may affect your eating behaviours, quality of life and cardiometabolic risks. This information will be used to assess the effectiveness of pumps in relation to these factors and to improve the advice we give to people on CSII.

9. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do you will be given this information sheet and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw will not affect your rights/any future treatment/service you receive. (It should also be noted that permission for your participation in this study will also be asked from your health professional – if permission is not given you may be excluded from the study. Additionally, you may also be excluded if you have recently been involved in another study – you should make the researcher aware of this).

10. What will happen to me if I take part?

If you agree to take part you will be asked to:

- *Be involved with the study for its duration (13 months).*
- *Complete a food diary every 3 months for 13 months (the contents will be reviewed with you during a short interview after the completion of each diary).*
- *Complete a food intake questionnaire every 3 months for 13 months.*
- *Complete a short quality of life questionnaire every 3 months for 13 months.*
- *Agree to an extra 4 teaspoons of blood being drawn after 12hr fasting in addition to your regular diagnostic sample every 3 months for 13 months.*
- *Allow the research team to contact your GP to make them aware of your participation in the study.*
- *Allow the research team to access your medical records to gather information regarding your current age, gender, weight, height, lipid profile, HbA1c level and blood pressure at each study time point.*

You may also be asked to:

- *Be interviewed 5 times. This will occur every 3 months for 13 months assessing your quality of life. (Each interview will last for approximately 45-60 minutes (apart from the first interview, which may last 1-2 hours).*

A flow chart has been attached to this information sheet for you to look at. This visually outlines these activities.

11. Are there any risks / benefits involved?

This study may also pose various risks and burdens to you as a participant. These are outlined below:-

- ***Inconvenience -*** *Some aspects of this study may demand a small investment of your own time. Examples are the 5 day food diaries and interviews. To help minimise the inconvenience caused by this, the food diaries have been designed to be as user friendly as possible.*
- ***Interviews -*** *Additionally, to minimise any impact occurring from the interviews you will be offered the choice of participating either at your regular clinic location at a time of your choice, or alternatively they can take place in your own home.*
  Although the interviews will only be concerned with the impact that insulin pumps have had on your quality of life, it should be noted that the diabetes team from the

Royal Liverpool Hospital will be on hand, either at the clinic sessions or over the phone to offer support and help on any issues.

- ***Blood Samples -*** *There is also a risk that you may feel a slight discomfort during the drawing of the additional 4 teaspoon volume of blood needed by the study. To minimise the risks of this all blood will be drawn by a trained phlebotomist and will be only be taken in addition to your regular diagnostic sample if needed.*

12. Will my taking part in the study be kept confidential?

All your data collected from this study will be kept confidential. This will be done by:-

- *Ensuring that your name will not be used in any of the data derived from food diaries, food intake questionnaires and quality of life surveys as well as any results from tests carried out on your blood samples.*
- *Ensuring all data will be stored on a secure NHS and university server (apart from your contact details which will be stored separately).*
- *Interviews will be audio recorded and transcribed and stored anonymously on a secure NHS computer.*
- *After transcribing is complete the audio tapes will then be destroyed and the transcribed copy will be stored on the secure NHS server for the duration of the study; after which it will be destroyed within 5 years using appropriate data destruction software.*
- *The only data collected from you which will not be anonymised will be your personal contact details to allow the researcher to keep in touch with you throughout the study. These will be stored in a locked filing cabinet in an NHS location with restricted access. This will be destroyed within 3 months of the study ending.*
- *We will also ensure that outside of the direct healthcare team, only the student (Richard Webb), Academic Supervisor 1 (and Chief Investigator) (Dr Julie Abayomi), Academic Supervisor 2 (Dr Ian Davies) and Academic Supervisor 3 (Professor Andrew Sparkes) will have access to your personal data during the study.*

We will also ensure your blood samples remain confidential by:-

- *Making sure all samples are anonymised before they are made available to the study. It should also be noted that access will be under the control of the Chief Technician, Dr Julie Abayomi and Dr Ian Davies.*

- *Most testing and analysis will take place at LJMU, however some anonymised samples will be prepared at LJMU and then transported on ice to Northumbria University for analysis by Dr John Lodge.*

We would also like to keep with your permission any of your blood samples that are left over at the end of the study. Left over blood samples will be anonymised and stored for a maximum of 5 years under Liverpool John Moores University policy and may be used in further research projects pending ethical approval.

13. Who can I contact for independent advice to help me decide whether or not to be involved in the study?

- *If you would like independent advice to help you decide whether nor not to be part of the study you can contact your diabetes specialist nurse, GP or Diabetes UK (www.Diabetes.org.uk).*

14. Who can I contact in the event of a complaint regarding the study?

- *If you have a complaint to make regarding the study you can contact the Chief Investigator to discuss your issue further. The Chief Investigator's contact details are shown at the end of this form.*

Contact Details of Researcher

Richard Webb (R.Webb@2009.ljmu.ac.uk)
Liverpool John Moores University (IM Marsh Campus)
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Dr Julie Abayomi (Senior Lecturer) (J.C.Abayomi@ljmu.ac.uk)
Liverpool John Moores University (IM Marsh Campus)
Barkhill Road
Aigburth
Liverpool
L17 6BD

Note: A copy of the participant information sheet should be retained by the participant with a copy of the signed consent form.

Appendix 3

Informed consent forms (all studies)

INFORMED CONSENT FORM

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

A Mixed Methods Investigation into the Eating Behaviours, Quality of Life and Cardiometabolic Risks in Adults with Type-1 Diabetes using Continuous Subcutaneous Insulin Infusion Therapy.

Research Student: Richard Webb (Faculty of Education, Community and Leisure)

Please proceed to initial each box if you agree to each statement and sign at the end of the form.

1. I confirm that I have read and understand the information provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect my treatment at the hospital. ☐

3. I understand that any personal information collected during the study will not identify me and will remain confidential. ☐

4. I agree to take part in the above study and I understand that it will involve me completing a food frequency questionnaire and a quality of life questionnaire. ☐

5. I will allow the research team access to my medical records to gather information regarding my current age,
gender, height, weight, HbA1c level, lipid profile and blood pressure. ☐

6. I agree to complete a weighed food diary for a 5 day period (this is optional). ☐

7. I am happy to be contacted with more information about taking part in an interview (this is optional). ☐

8. I consent to the removal and storage of 4 teaspoons of blood volume, after fasting (this is optional). ☐

9. I agree for any blood samples left over at the end of the study to be used for future undefined research pending ethical approval. ☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature
Name of Person taking consent *(if different from researcher)*	Date	Signature

Note: When completed 1 copy for participant, 1 copy for researcher and 1 copy for patient notes.

INFORMED CONSENT FORM

The Royal Liverpool and Broadgreen University Hospitals NHS Trust

A Mixed Methods Investigation into the Eating Behaviours, Quality of Life and Cardiometabolic Risks in Adults with Type-1 Diabetes using Continuous Subcutaneous Insulin Infusion Therapy.

Research Student: Richard Webb (Faculty of Education, Community and Leisure)

Please proceed to initial each box if you agree to each statement and sign at the end of the form.

10. I confirm that I have read and understand the information provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

11. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect my treatment at the hospital. ☐

12. I understand that any personal information collected during the study will not identify me and will remain confidential. ☐

13. I agree to take part in the above study and I understand that it will involve me completing food diaries, food intake questionnaires, quality of life questionnaires. ☐

14. I will allow the research team access to my medical records to gather information regarding my current age,
gender, height, weight, HbA1c level, lipid profile and blood pressure at each study time point. ☐

15. I am happy to be contacted with more information about taking part in an interview. ☐

16. I consent to the removal and storage of 4 teaspoons of blood volume, after 12hr fasting. ☐

17. I agree for any blood samples left over at the end of the study to be used for future undefined research pending ethical approval. ☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature
Name of Person taking consent *(if different from researcher)*	Date	Signature

Note: When completed 1 copy for participant, 1 copy for researcher and 1 copy for patient notes.

Appendix 4

EQ-5D quality of life questionnaire

Health Questionnaire

English version for the UK (validated for Ireland) (v1)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

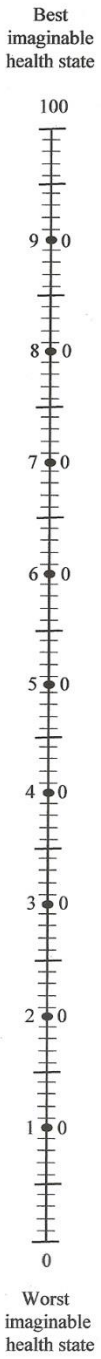
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 4

EPIC food frequency questionnaire

FOOD FREQUENCY QUESTIONNAIRE

This questionnaire asks for some background information about you, especially about what you eat.

Please answer every question. If you are uncertain about how to answer a question then do the best you can, but please do not leave a question blank.

1. **YOUR DIET LAST YEAR**

For each food there is an amount shown, either a "medium serving" or a common household unit such as a slice or teaspoon. Please put a tick (✓) in the box to indicate how often, **on average**, you have eaten the specified amount of each food **during the past year**.

EXAMPLES:

For white bread the amount is one slice, so if you ate 4 or 5 slices a day, you should put a tick in the column headed "4-5 per day".

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
BREAD AND SAVOURY BISCUITS (one slice or biscuit)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread and rolls								✓	

For chips, the amount is a "medium serving", so if you had a helping of chips twice a week you should put a tick in the column headed "2-4 per week".

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
POTATOES, RICE AND PASTA (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Chips				✓					

For very seasonal fruits such as strawberries and raspberries you should estimate your average use when the fruits are in season, so if you ate strawberries or raspberries about once a week when they were in season you should put a tick in the column headed "once a week"

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
FRUIT (1 fruit or medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Strawberries, raspberries, kiwi fruit			✓						

Please estimate your average food use as best you can, and please answer every question - do not leave ANY lines blank. PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
MEAT AND FISH (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Beef: roast, steak, mince, stew or casserole									
Beefburgers									
Pork: roast, chops, stew or slices									
Lamb: roast, chops or stew									
Chicken or other poultry eg. turkey									
Bacon									
Ham									
Corned beef, Spam, luncheon meats									
Sausages									
Savoury pies, eg. meat pie, pork pie, pasties, steak & kidney pie, sausage rolls									
Liver, liver paté, liver sausage									
Fried fish in batter, as in fish and chips									
Fish fingers, fish cakes									
Other white fish, fresh or frozen, eg. cod, haddock, plaice, sole, halibut									
Oily fish, fresh or canned, eg. mackerel, kippers, tuna, salmon, sardines, herring									
Shellfish, eg. crab, prawns, mussels									
Fish roe, taramasalata									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
BREAD AND SAVOURY BISCUITS (one slice or biscuit)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
White bread and rolls									
Brown bread and rolls									
Wholemeal bread and rolls									
Cream crackers, cheese biscuits									
Crispbread, eg. Ryvita									
CEREALS (one bowl)									
Porridge, Readybrek									
Breakfast cereal such as cornflakes, muesli etc.									
POTATOES, RICE AND PASTA (medium serving)									
Boiled, mashed, instant or jacket potatoes									
Chips									
Roast potatoes									
Potato salad									
White rice									
Brown rice									
White or green pasta, eg. spaghetti, macaroni, noodles									
Wholemeal pasta									
Lasagne, moussaka									
Pizza									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
DAIRY PRODUCTS AND FATS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Single or sour cream (tablespoon)									
Double or clotted cream (tablespoon)									
Low fat yogurt, fromage frais (125g carton)									
Full fat or Greek yogurt (125g carton)									
Dairy desserts (125g carton)									
Cheese, eg. Cheddar, Brie, Edam (medium serving)									
Cottage cheese, low fat soft cheese (medium serving)									
Eggs as boiled, fried, scrambled, etc. (one)									
Quiche (medium serving)									
Low calorie, low fat salad cream(tablespoon)									
Salad cream, mayonnaise (tablespoon)									
French dressing (tablespoon)									
Other salad dressing (tablespoon)									
The following on bread or vegetables									
Butter (teaspoon)									
Block margarine, eg. Stork, Krona (teaspoon)									
Polyunsaturated margarine (tub), eg. Flora, sunflower (teaspoon)									
Other soft margarine,dairy spreads (tub), eg. Blue Band, Clover (teaspoon)									
Low fat spread (tub), eg. Outline, Gold (teaspoon)									
Very low fat spread (tub) (teaspoon)									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
SWEETS AND SNACKS (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Sweet biscuits, chocolate , eg. digestive (one)									
Sweet biscuits, plain, eg. Nice, ginger (one)									
Cakes eg. fruit, sponge, home baked									
Cakes eg. fruit, sponge, ready made									
Buns, pastries eg. scones, flapjacks, home baked									
Buns, pastries eg. croissants, doughnuts, ready made									
Fruit pies, tarts, crumbles, home baked									
Fruit pies, tarts, crumbles, ready made									
Sponge puddings, home baked									
Sponge puddings, ready made									
Milk puddings, eg. rice, custard, trifle									
Ice cream, choc ices									
Chocolates, single or squares									
Chocolate snack bars eg. Mars, Crunchie									
Sweets, toffees, mints									
Sugar added to tea, coffee, cereal (teaspoon)									
Crisps or other packet snacks, eg. Wotsits									
Peanuts or other nuts									
SOUPS, SAUCES, AND SPREADS									
Vegetable soups (bowl)									
Meat soups (bowl)									
Sauces, eg. white sauce, cheese sauce, gravy (tablespoon)									
Tomato ketchup (tablespoon)									
Pickles, chutney (tablespoon)									
Marmite, Bovril (teaspoon)									
Jam, marmalade, honey (teaspoon)									
Peanut butter (teaspoon)									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
DRINKS	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Tea (cup)									
Coffee, instant or ground (cup)									
Coffee, decaffeinated (cup)									
Coffee whitener, eg. Coffee-mate (teaspoon)									
Cocoa, hot chocolate (cup)									
Horlicks, Ovaltine (cup)									
Wine (glass)									
Beer, lager or cider (half pint)									
Port, sherry, vermouth, liqueurs (glass)									
Spirits, eg. gin, brandy, whisky, vodka (single)									
Low calorie or diet fizzy soft drinks (glass)									
Fizzy soft drinks, eg. Coca cola, lemonade (glass)									
Pure fruit juice (100%) eg. orange, apple juice (glass)									
Fruit squash or cordial (glass)									
FRUIT **For seasonal fruits marked *, please estimate your average use when the fruit is in season**									
Apples (1 fruit)									
Pears (1 fruit)									
Oranges, satsumas, mandarins (1 fruit)									
Grapefruit (half)									
Bananas (1 fruit)									
Grapes (medium serving)									
Melon (1 slice)									
* Peaches, plums, apricots (1 fruit)									
* Strawberries, raspberries, kiwi fruit (medium serving)									
Tinned fruit (medium serving)									
Dried fruit, eg. raisins, prunes (medium serving)									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
VEGETABLES Fresh, frozen or tinned (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Carrots									
Spinach									
Broccoli, spring greens, kale									
Brussels sprouts									
Cabbage									
Peas									
Green beans, broad beans, runner beans									
Marrow, courgettes									
Cauliflower									
Parsnips, turnips, swedes									
Leeks									
Onions									
Garlic									
Mushrooms									
Sweet peppers									
Beansprouts									
Green salad, lettuce, cucumber, celery									
Watercress									
Tomatoes									
Sweetcorn									
Beetroot									
Coleslaw									
Avocado									
Baked beans									
Dried lentils, beans, peas									
Tofu , soya meat, TVP, Vegeburger									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

YOUR DIET LAST YEAR, continued

2. Are there any **OTHER** foods which you ate more than once a week? Yes ☐ No ☐

If yes, please list below

Food	Usual serving size	Number of times eaten each week

3. What type of milk did you most often use?

Select one only

Full cream, silver ☐ Semi-skimmed, red/white ☐
Skimmed/blue ☐ Channel Islands, gold ☐
Dried milk ☐ Soya ☐
Other, *specify* ☐ None ☐

4. How much milk did you drink each day, including milk with tea, coffee, cereals etc?

None ☐ Three quarters of a pint ☐
Quarter of a pint ☐ One pint ☐
Half a pint ☐ More than one pint ☐

5. Did you usually eat breakfast cereal (excluding porridge and Ready Brek mentioned earlier)? Yes ☐ No ☐

If yes, which brand and type of breakfast cereal, including muesli, did you usually eat?

List the one or two types most often used

Brand *e.g. Kellogg's*	Type *e.g. cornflakes*

6. What kind of fat did you most often use for frying, roasting, grilling etc?

Select one only

Butter ☐ Solid vegetable fat ☐
Lard/dripping ☐ Margarine ☐
Vegetable oil ☐ None ☐

If you used vegetable oil, please give type eg. corn, sunflower ☐

7. What kind of fat did you most often use for baking cakes etc?

Select one only

Butter ☐ Solid vegetable fat ☐
Lard/dripping ☐ Margarine ☐
Vegetable oil ☐ None ☐

If you used margarine, please give name or type eg. Flora, Stork ☐

8. How often did you eat food that was fried at home?

Daily ☐ 1-3 times a week ☐ 4-6 times a week ☐
Less than once a week ☐ Never ☐

9. How often did you eat fried food away from home?

Daily ☐ 1-3 times a week ☐ 4-6 times a week ☐
Less than once a week ☐ Never ☐

10. What did you do with the visible fat on your meat?

Ate most of the fat ☐ Ate as little as possible ☐
Ate some of the fat ☐ Did not eat meat ☐

11. How often did you eat grilled or roast meat? ☐☐ times a week

12. How well cooked did you usually have grilled or roast meat?

Well done /dark brown ☐ Lightly cooked/rare ☐
Medium ☐ Did not eat meat ☐

13. How often did you add salt to food while cooking?

Always ☐ Rarely ☐
Usually ☐ Never ☐
Sometimes ☐

14. How often did you add salt to any food at the table?

Always ☐ Rarely ☐
Usually ☐ Never ☐
Sometimes ☐

15. Did you regularly use a salt substitute (eg LoSalt)? Yes ☐ No ☐

If yes, which brand? ☐

16. During the course of last year, on average, how many times a week did you eat the following foods?

Food type	**Times/week**	**Portion size**
Vegetables (not including potatoes)	☐☐	medium serving
Salads	☐☐	medium serving
Fruit and fruit products (not including fruit juice)	☐☐	medium serving or 1 fruit
Fish and fish products	☐☐	medium serving
Meat, meat products and meat dishes (including bacon, ham and chicken)	☐☐	medium serving

17. Have you taken any vitamins, minerals, fish oils, fibre or other food supplements during the past year? Yes ☐ No ☐ Don't know ☐

If yes, please complete the table below. If you have taken more than 5 types of supplement please put the most frequently consumed brands first.

Vitamin supplements	**Average frequency** Tick **one** box per line to show how often on average you consumed supplements									
Name and brand Please list full name, **brand** and strength	**Dose** Please state number of pills, capsules or teaspoons consumed	Never or less than once a month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Thank you for your help

Appendix 6

Interview structures (all studies)

Qualitative Interview Outline (Cross-Sectional Pump User)

Complete interview consent form!!!!!!!!

Hello there, I'd just like to welcome you here and say thank you for giving up your time to participate in this interview. It is very much appreciated.

My name is Richard Webb and I am a research student from Liverpool John Moores University. I am studying for a PhD in nutrition and I am looking at the impact that diabetes and insulin pumps have had on you. I am not a medic or a healthcare professional and I do not work for any medical company. I should also make you aware that by taking part in this interview your access to treatments and services will not be affected and I am not here to judge you or your service.

The reason I am running these interviews with patients is to try and understand patients' thoughts and feelings surrounding diabetes and how insulin pumps may impact upon patients' quality of life. The information collected from these interviews will be analysed to give an insight into quality of life, which may hopefully help with future service improvements.

Before we begin I would just like to go over the food diary you have filled in (if required) to ensure it is completed correctly and we will then commence with the interview.

(Then proceed to discuss the accuracy of the food diaries with the participant if required).

Introduction to Quality of Life Interview

- Could you please tell me you name and age?

- Thinking back, what was life like before diabetes?

Probe: Tell me about when you found out that you had diabetes – How was that?

Probe: What is it like living with your diabetes?

- How did you first become associated with the diabetes clinic?

Probe: Think back to when you were first diagnosed – could you please tell me about your experience with treatments?

- How did you find the transition onto a pump?

Activities (Regular / Leisure activities / Work / Mobility)

Thinking about since receiving the pump:

- How do you think the pump has affected your regular day to day activities, such as work and house chores etc.?
- In what ways do you think the pump has affected your mobility? (For example, running errands or getting to and from places).
- How do you feel the pump has impacted upon your quality of life with regards to your leisure activities (such as socialising, sports and holidays etc.)?

Diet (Day to day eating behaviours / Appetite)

Since receiving the pump:

- Have you noticed any change in your day to day eating habits?
- How has your appetite been since using the pump?

Health (General health / Self-care / Self-esteem)

Again, thinking about when you were given the pump:

- How do you feel the pump has affected your health, in terms of your diabetes control?
- What pain or discomfort have you found to be associated with it?
- Did you look forward to receiving and using the pump?

Probe: Why was this?

Relationships (Partner / Healthcare Professional / Family)

- Do you think the pump has affected the relationship you have with your healthcare professional in any way at all?
- How about your relationship with your family?

Probe: Could you perhaps give a little more detail about that please?

- Have you noticed any changes in the relationship between you and your partner after receiving the pump?

- What about with your friends?

Ending Questions

- Thinking back over the interview and your thoughts and feelings, what would you say to others considering going onto insulin pump therapy.
- We would like to help other patients with Type 1 diabetes in the future. From your experiences, have you any other advice for us on how to make the transition onto the pump therapy any better?
- How do you feel about the future in general?
- Have we discussed everything? Are there any questions or have you got anything else to add?

- *Thank you for your time. It is much appreciated.*

Qualitative Interview Outline (Cross-Sectional Non - Pump User)

Complete interview consent form!!!!!!!!

Hello there, I'd just like to welcome you here and say thank you for giving up your time to participate in this interview. It is very much appreciated.

My name is Richard Webb and I am a research student from Liverpool John Moores University. I am studying for a PhD in nutrition and I am looking at the impact that diabetes and insulin pumps have had on you. I am not a medic or a healthcare professional and I do not work for any medical company. I should also make you aware that by taking part in this interview your access to treatments and services will not be affected and I am not here to judge you or your service.

The reason I am running these interviews with patients is to try and understand patients' thoughts and feelings surrounding diabetes and how insulin pumps may impact upon patients' quality of life. The information collected from these interviews will be analysed to give an insight into quality of life, which may hopefully help with future service improvements.

Before we begin I would just like to go over the food diary you have filled in (if required) to ensure it is completed correctly and we will then commence with the interview.

(Then proceed to discuss the accuracy of the food diaries with the participant if required).

Introduction to Quality of Life Interview

- Could you please tell me you name and age?
- Thinking back, what was life like before diabetes?

Probe: Tell me about when you found out that you had diabetes – How was that?

Probe: What is it like living with your diabetes?

- How did you first become associated with the diabetes clinic?

Probe: Think back to when you were first diagnosed – could you please tell me about your experiences with different treatments?

- Do you know about insulin pumps at all?
- What are your views about them?

Activities (Regular / Leisure activities / Work / Mobility)

- Does your diabetes affect your regular day to day activities, such as work and house chores etc.?
- Do you think your diabetes affects your mobility at all? (For example, running errands or getting to and from places).
- How do you feel your diabetes impacts upon your quality of life with regards to your leisure activities (such as socialising, sports and holidays etc.)?

Now think about if you were offered an insulin pump:

- Do you think a pump would change any of these things in any way?

Diet (Day to day eating behaviours / Appetite)

- Have you noticed any changes in your day to day eating habits upon using previous treatments since you were diagnosed?
- How has your appetite been using previous treatments?

Now think about if you were offered an insulin pump:

- How do you think using an insulin pump may affect these?

Health (General health / Self-care / Self-esteem)

Again, think if you were offered a pump:

- How do you feel a pump may affect your health, in terms of your diabetes control?
- What pain or discomfort do you think may be associated with it?
- Would you look forward to receiving and using the pump?

Probe: Why might this be?

Relationships (Partner / Healthcare Professional / Family)

- Do you think that your diabetes has ever affected your relationship with anyone; such as friends, family, partner or healthcare professionals?

Probe: Why do you think this is?

- Do you think having a pump might change those in any way?

Probe: Could you perhaps give a little more detail about that please?

Ending Questions

- Thinking back over the interview and your thoughts and feelings, what would you say to others considering going onto insulin pump therapy.
- How do you feel about the future in general?
- Have we discussed everything? Are there any questions or have you got anything else to add?

- *Thank you for your time. It is much appreciated.*

Qualitative Interview Outline (Longitudinal)

Complete interview consent form!!!!!!!!

Hello there, I'd just like to welcome you here and say thank you for giving up your time to participate in this interview. It is very much appreciated.

My name is Richard Webb and I am a research student from Liverpool John Moores University. I am studying for a PhD in nutrition and I am looking at the impact that diabetes and insulin pumps has had on you. I am not a medic or a healthcare professional and I do not work for any medical company. I should also make you aware that by taking part in this interview your access to treatments and services will not be affected and I am not here to judge you or your service.

As part of this study you will be expected to take part in four interviews (once every three months), lasting for no longer than one hour each (apart from the first interview which may last up to two hours, although this may be carried out over two sessions depending on your feelings).

The reason I am running these interviews with patients who have recently been accepted onto insulin pump therapy is to try and understand patients' thoughts and feelings surrounding diabetes and how insulin pumps may impact upon patients' quality of life over the course of a year. The information collected from these interviews will be analysed to give an insight into quality of life, which may hopefully help with future service improvements.

Before we begin I would just like to go over the food diary you have filled in to ensure it is completed correctly and then we will then commence with the interview.

(Then proceed to discuss the accuracy of the food diaries with the participant).

Introduction to Quality of Life Interview

- Could you please tell me you name and age?
- Thinking back, what was life like before diabetes?

Probe: Tell me about when you found out that you had diabetes – How was that?

Probe: What is it like living with your diabetes?

- How did you become associated with the diabetes clinic and your insulin pump?

- Think back to when you were first offered the pump. Why did you opt for the treatment?

Probe: What did you inspect it to involve?

- How have your impressions changed after thinking about it for a while?

Activities (Regular / Leisure activities / Work / Mobility)

Thinking about when you will get the pump:

- How do you think the pump will affect your regular day to day activities, such as work and house chores etc.?
- In what ways do you think the pump will affect your mobility? (For example, running errands or getting to and from places).
- How do you feel the pump might impact upon your quality of life with regards to your leisure activities (such as socialising, sports and holidays etc.)?

Diet (Day to day eating behaviours / Appetite)

When you receive the pump:

- Do you think there will be any change in your day to day eating habits?
- How do you think your appetite will be after using the pump?

Health (General health / Self-care / Self-esteem)

Again, thinking about when you will be given the pump:

- How do you feel the pump will affect your health, in terms of your diabetes control?
- Imagine you already have the pump. What pain or discomfort do you think might be associated with it?
- Are you looking forward to receiving and using the pump?

Probe: Why is this?

Relationships (Partner / Healthcare Professional / Family)

- How do you think the pump will affect the relationship you have with your healthcare professional in any way at all?

- How about your relationship with your family?

Probe: Could you perhaps give a little more detail about that please?

- What changes do you feel may occur in the relationship between you and your partner after receiving the pump?

Ending Questions

- Thinking back over the interview and your thoughts and feelings, what would you say to others considering going onto insulin pump therapy.
- We would like to help other patients with type 1 diabetes in the future. From your experiences, have you any other advice for us on how to make the transition onto the pump therapy any better?
- Have we discussed everything? Are there any questions or have you got anything else to add?

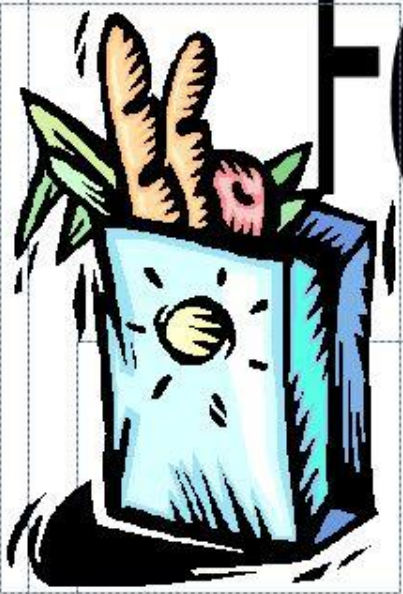
- *Thank you for your time. It is much appreciated.*

Appendix 7

Food diary

liverpool JMU

Food Diary



Food Diary ID

Volunteer ID

Date Started

Details of how to fill in the diary

It is very important that you do not change what you normally eat and drink just because you are keeping this record. **Please keep your usual food habits for a full 5 days, ensuring that 2 of the days fall over a weekend.**

Each day is divided into sections, from the first thing in the morning to late evening and through the night.

When recording your food include the **brand name** (if known), **portion size** (using household measures, **weights** from labels or the picture examples to help), any additions to the food (fats, oils, sugars/sweeteners, sauces, salt, pepper etc), **cooking methods** (fried, grilled, baked, roasted etc) and any **leftovers**. **Please weigh all food items where possible!**

Please record everything at the time of eating, **not from memory** at the end of the day. The diary covers a 24h period for each day, so please include any food or drinks that you may have had during the night. You may have had some foods and drinks between meals (snacks), or food that you have not recorded earlier, so please include these in the extras section.

It helps a great deal if you enclose labels from any unusual foods and also from any supplements you take when returning your completed food diary.

Overleaf you can see an example of how we would like you to record your food and drink intake.

EXAMPLE

Day of Week Date

BEFORE BREAKFAST

Time	Food/Drink	Description & Preparation	Amount
7.30	Water	Tap water, no additions	

BREAKFAST

Time	Food/Drink	Description & Preparation	Amount
8.00am	Toast Margarine Marmalade	Hovis, wholemeal, pre sliced, thin cut Flora original Robetson's low sugar, thin cut orange and lime	2 slices (left crusts) 2 medium spread 2 thin spread
8am	Tea Milk Sugar	Medium strength Tetley Semi skimmed pasteurized White castor	1 mug (incl milk) Dash in tea 1 teaspoon in tea (drank all)
8am	Breakfast Cereal Milk	Kellogg's cornflakes Semi skimmed pasteurized	1 pict 1 b (ate all) Approx 1/3 pint

MID-MORNING—between breakfast time and lunch time

Time	Food/Drink	Description & Preparation	Amount
10.30 am 10.30 am	Coffee Milk Biscuit	Nescafe original caffeinated Full fat pasteurized McVities chocolate digestive	1 cup, drank all 1 average in coffee 2 biscuits, ate all

EXAMPLE

Day of Week Date

LUNCH

Time	Food/Drink	Description & Preparation	Amount
1.15 pm	Ham Salad Sandwich		
	Bread	Tesco's own brand, medium sliced white	2 slices
	Mayonnaise	Hellman's ordinary mayonnaise	2 thin spreads on bread
	Ham	Bernard Matthews thin slices lean ham	2 thin slices
	Lettuce	Iceberg Lettuce	1 leaf
	Cucumber	Including Skin	3 thin slices
	Seasoning	Black Pepper, coarse ground	from mill
1.15 pm	Can of cola	Pepsi Max	1 can, 20% extra free (396ml) drank all
1.30 pm	Crisps	1 average pack, Walkers cheese and onion flavour	1 25g packet left half

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount
4.00 Pm	Coffee	Same as mid morning	2 cups
4.10 Pm	Apple	Golden Delicious	1 with skin peeled Didn't eat core
4.15 pm	Banana	Small	1

EXAMPLE

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount
6.30 pm	*Lamb*	*Roast*	*3 thin slices*
	Potatoes	*Old, boiled in salt water, mashed with semis skimmed milk and anchor butter*	*Picture 4b*
	Cabbage	*Green, boiled in salt water*	*Picture 7a*
	Carrots	*Boiled in salt water*	*2 tablespoons*
	Potatoes	*Old, boiled in salt water, roasted in meat fat*	*3 medium potatoes, 1 left*
	Gravy	*Bisto Gravy granules made with veg water*	*4 tablespoons left approx 1/4*
	Water	*Highland spring carbonated water*	*1 tumbler drank all*
6.50 pm	*Ice cream*	*Tesco's vanilla non-dairy*	*2 scoops*

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount
7.30 pm	Tea	Same as breakfast	2 mugs
9.15 pm	Whiskey	Blackbush	2 shots in average size glass
	Lemonade	Diet own brand lemonade	To top of glass
9.30 pm	Chocolates	Cadburys roses	2 from box
12-6am	water	Tap water	1 average glass

EXAMPLE

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount
8.30 pm	*Coffee*	*1 mug with cream, 1 tsp sugar*	*1 mug incl cream (drank all)*

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons
Sanatogen	*1 a day gold A-Z*	*1*
Boots own brand	*Cod liver oil capsule (normal strength)*	*1 500mg capsule*

Use the pictures to help you to indicate the size of the portion you have eaten. Write on the food record the picture number and size A, B or C nearest to your own helping.

The pictures could also be used for foods not shown i.e. pasta shapes similar to spaghetti, ham pie similar to quiche and peas similar to baked beans.

Remember that the pictures are much smaller than life size. The actual size of the dinner plate is 10 inches (25cm), the side plate, 7 inches (18cm) and the bowl 6.3 inches (16cm).

1. Rice

A	B	C

2. Spaghetti

A	B	C

3. Cheese

A	B	C

4. Boiled Potatoes

A	B	C

5. Chips

A	B	C

6. Baked Beans

A	B	C

7. Broccoli

A	B	C

8. Quiche / Pie

A	B	C

9. Sliced Meat

A	B	C

10. Stew

A	B	C

11. Battered Fish

A	B	C

12. Cornflakes

A	B	C

13. Fruit Cake

A	B	C

14. Sponge Cake

A	B	C

15. Ice Cream

A	B	C

Day of Week Date

BEFORE BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

MID-MORNING—between breakfast time and lunch time

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

LUNCH

Time	Food/Drink	Description & Preparation	Amount

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons

Day of Week ..... Date .....

BEFORE BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

MID-MORNING—between breakfast time and lunch time

Time	Food/Drink	Description & Preparation	Amount

Day of Week ..... Date .....

LUNCH

Time	Food/Drink	Description & Preparation	Amount

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons

Day of Week Date

BEFORE BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

MID-MORNING—between breakfast time and lunch time

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

LUNCH

Time	Food/Drink	Description & Preparation	Amount

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons

Day of Week Date

BEFORE BREAKFAST

Time	Food/Drink	Description & Preparation	Amount

BREAKFAST

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MID-MORNING—between breakfast time and lunch time

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

LUNCH

Time	Food/Drink	Description & Preparation	Amount

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons

Day of Week Date

BEFORE BREAKFAST

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Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

LUNCH

Time	Food/Drink	Description & Preparation	Amount

TEA—between lunch and the evening meal

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

EVENING MEAL

Time	Food/Drink	Description & Preparation	Amount

LATER EVENING—and through the night

Time	Food/Drink	Description & Preparation	Amount

Day of Week Date

BETWEEN MEALS SNACKS & DRINKS if not already written in

Time	Food/Drink	Description & Preparation	Amount

Please name any medication, vitamins, minerals or food supplements and what they were taken with. Please give all details and enclose label(s) if possible

Brand	Name (in full)	Number: pills, capsules, teaspoons

Thank you for completing this diary

Please return it to the study team as requested

Study Contacts

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Appendix 8

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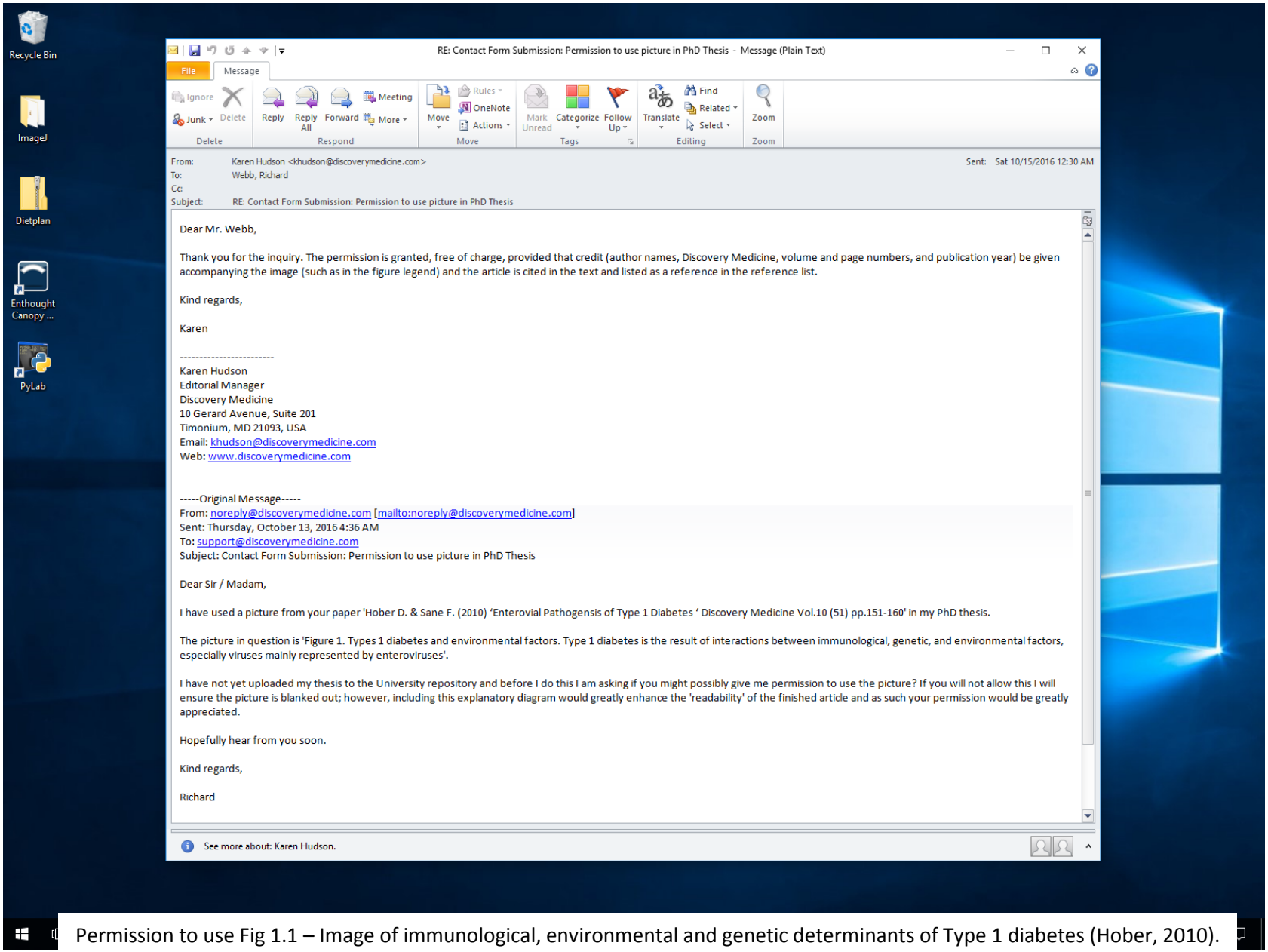

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Kind regards,
Marie-Astrid Thielens

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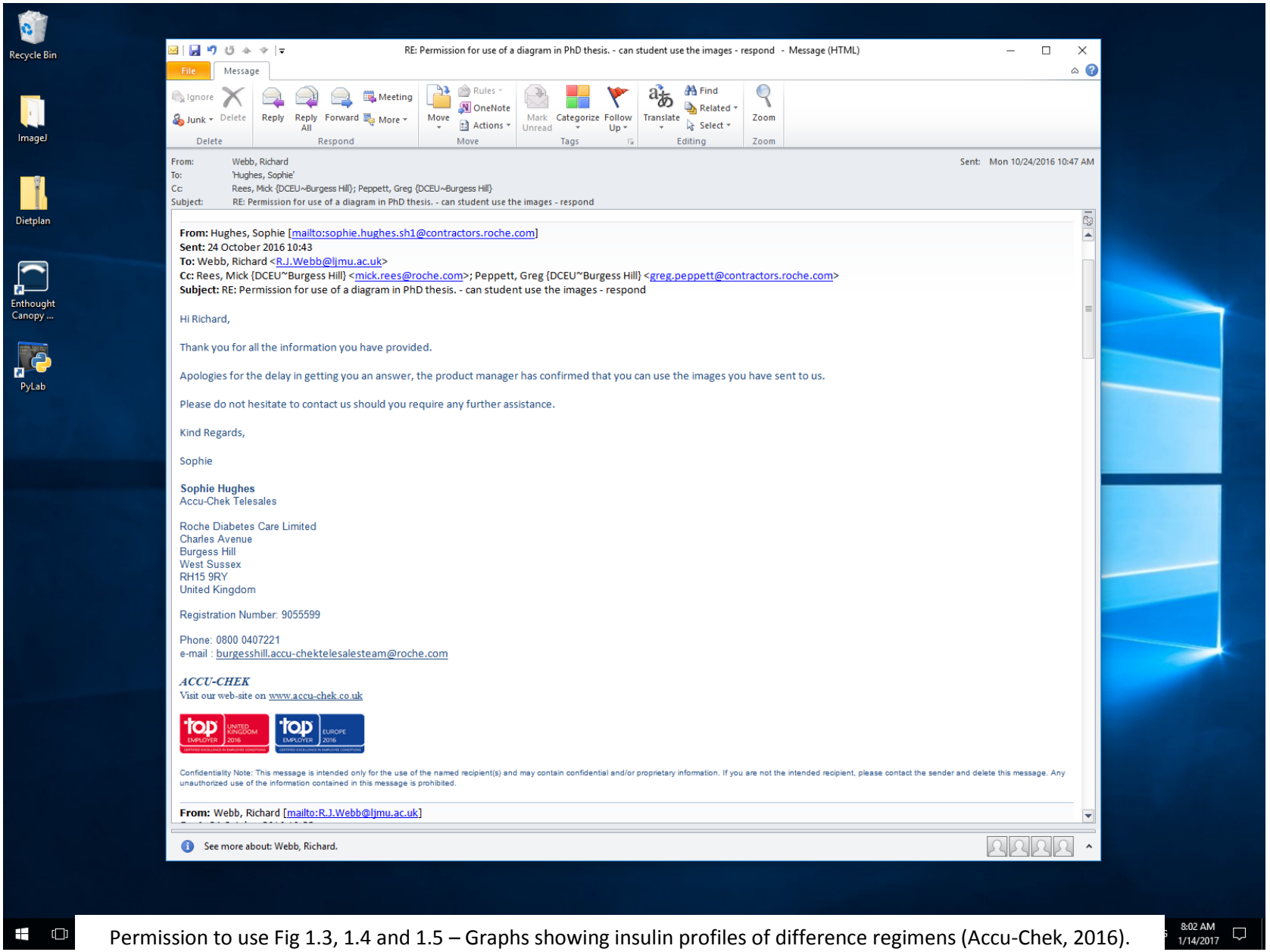

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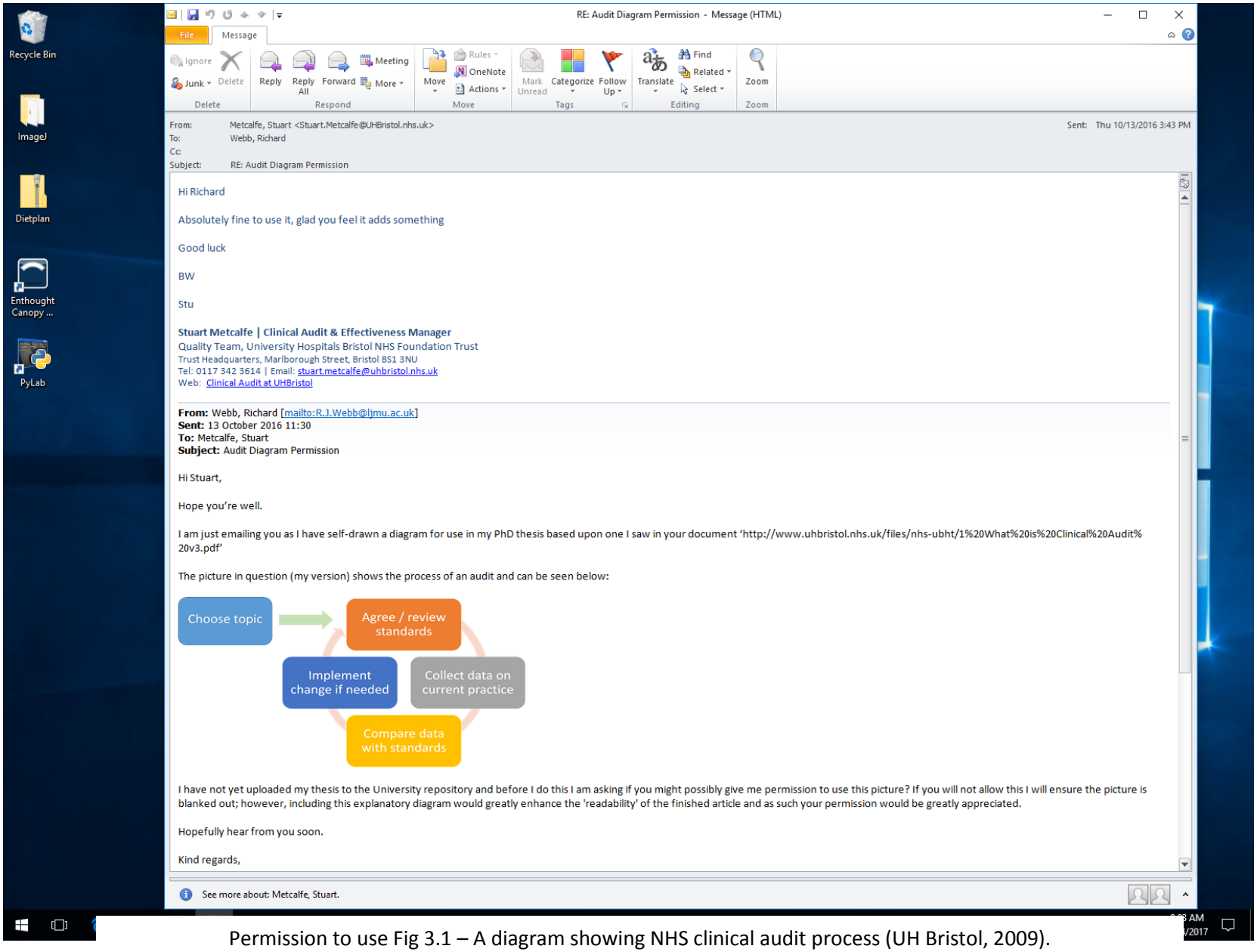

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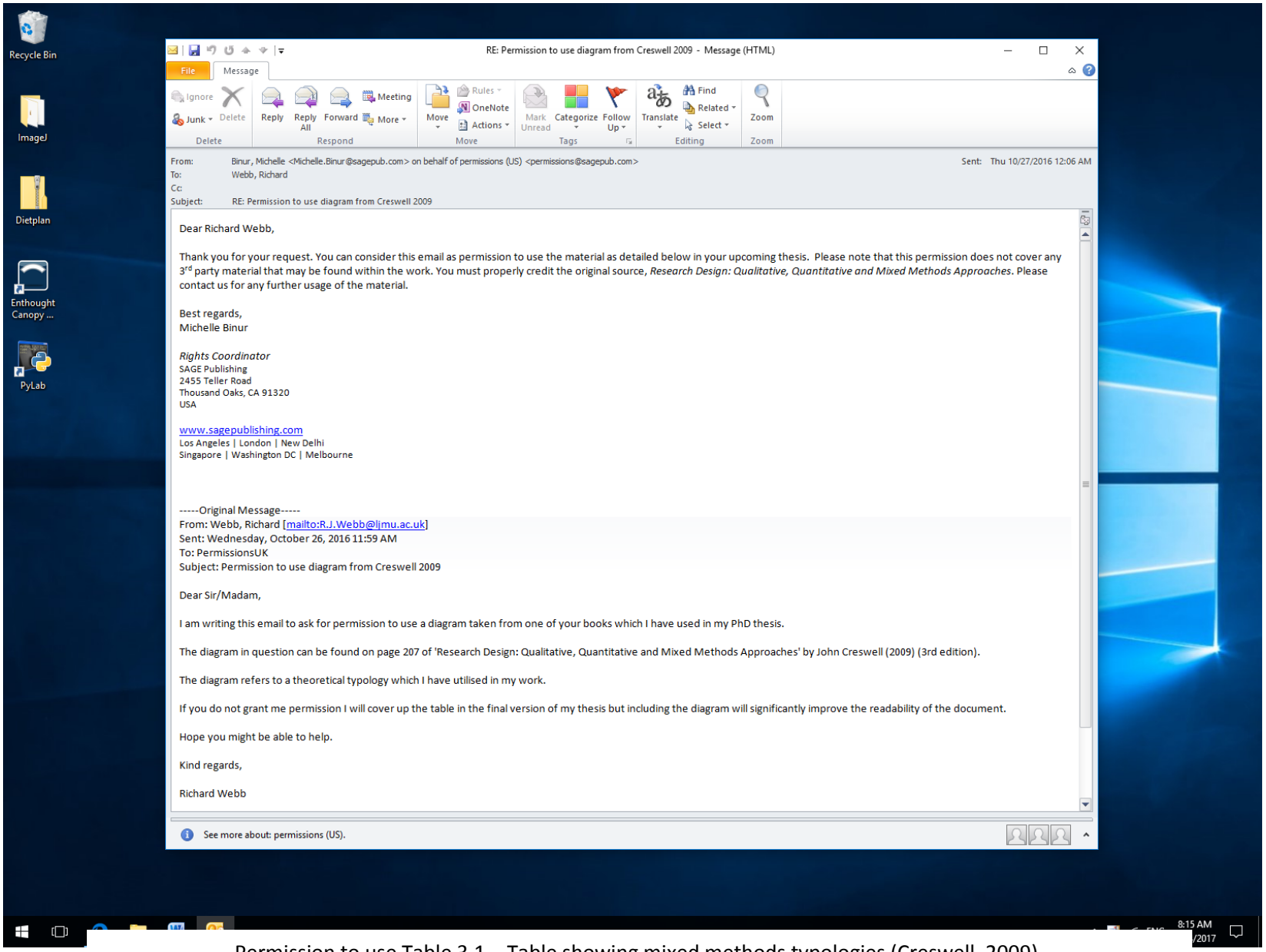

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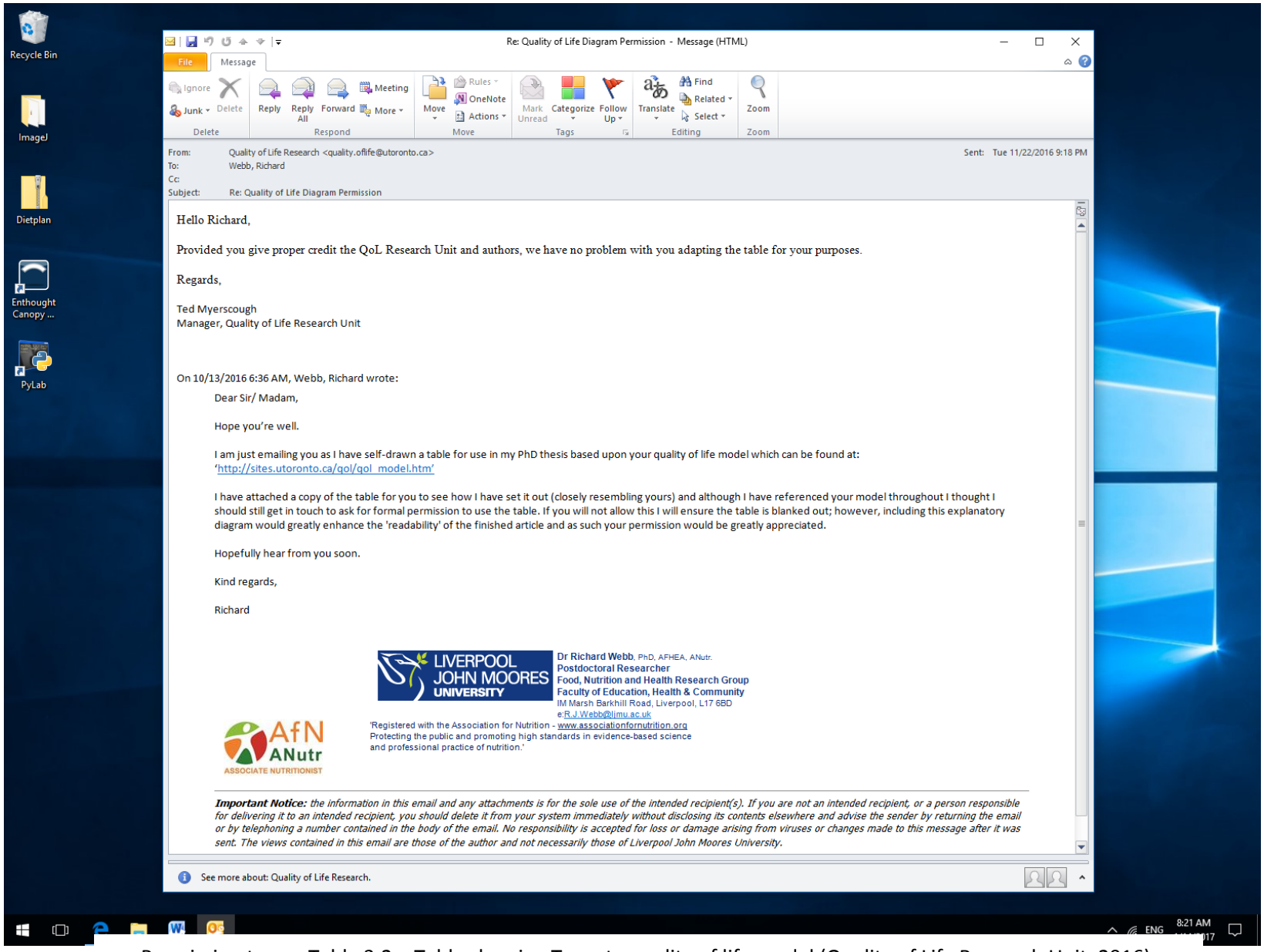

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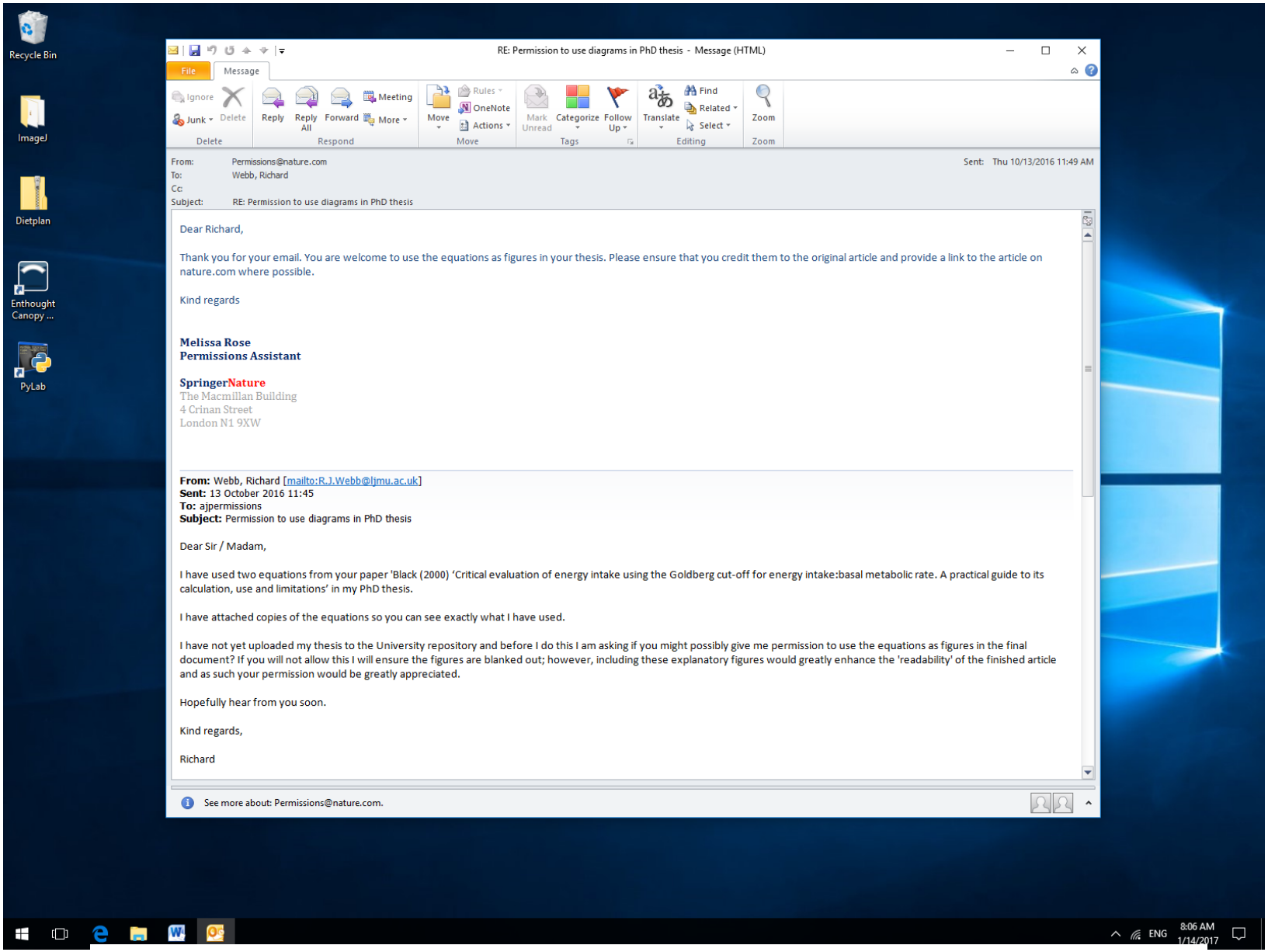

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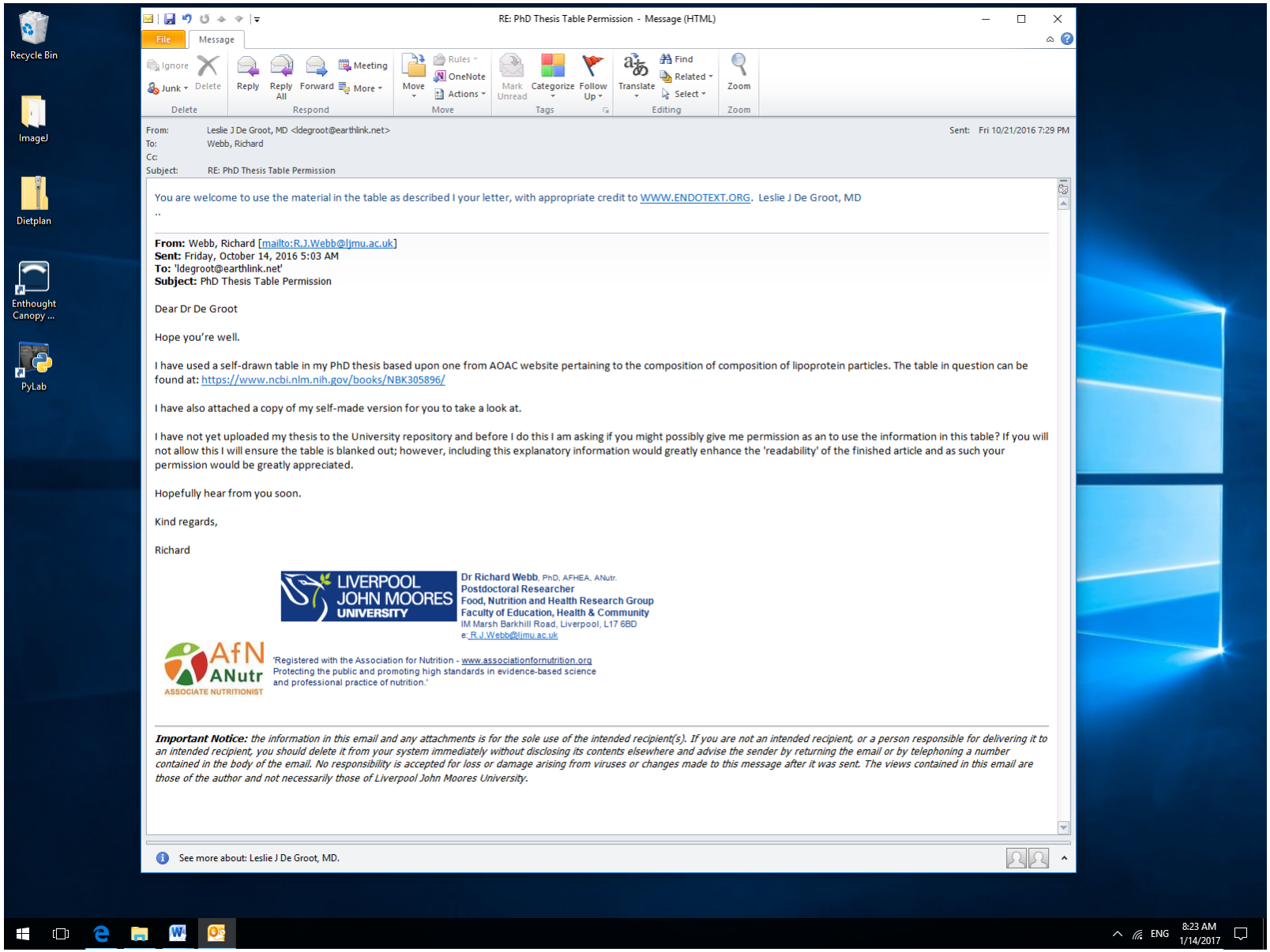

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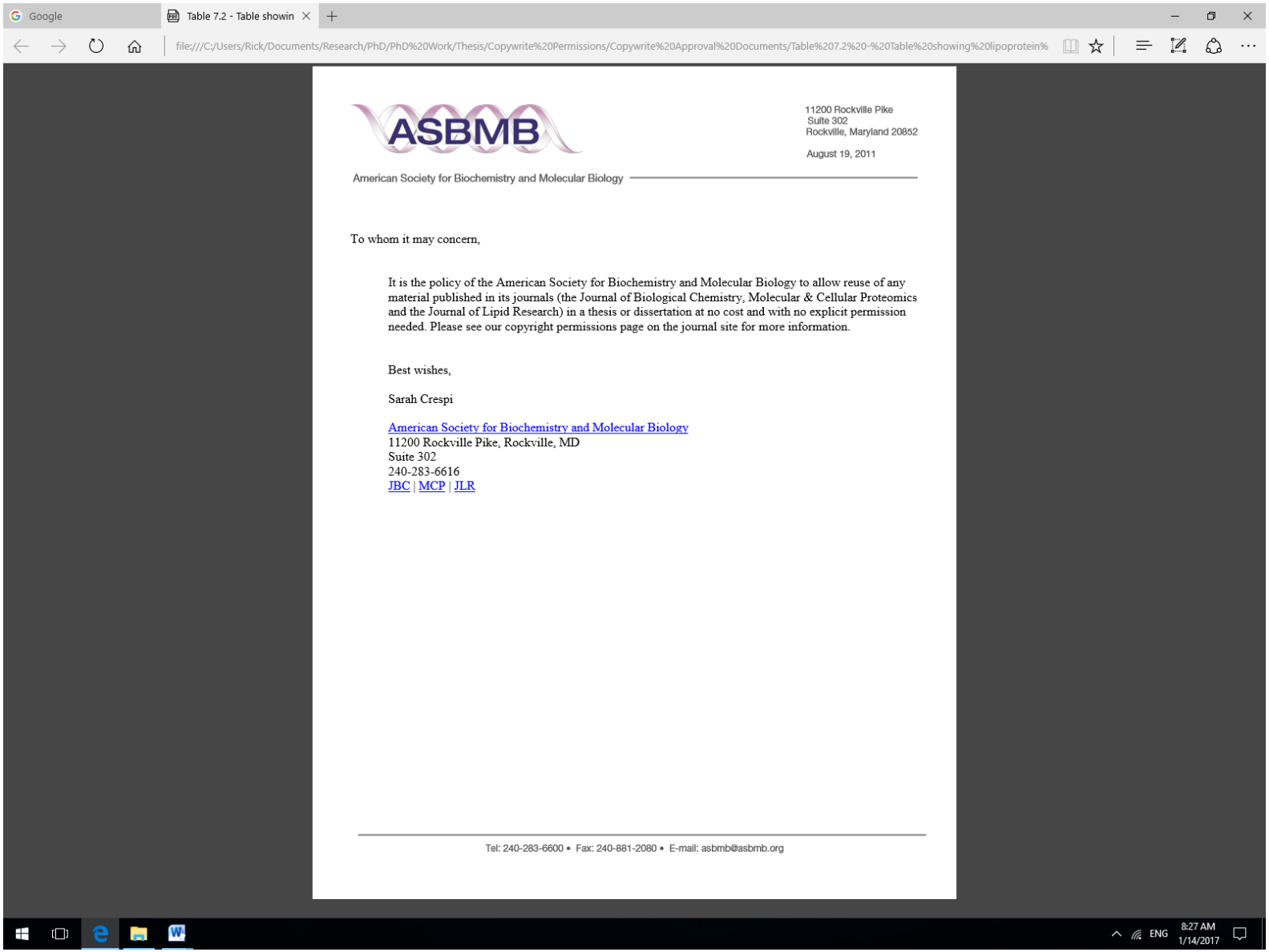

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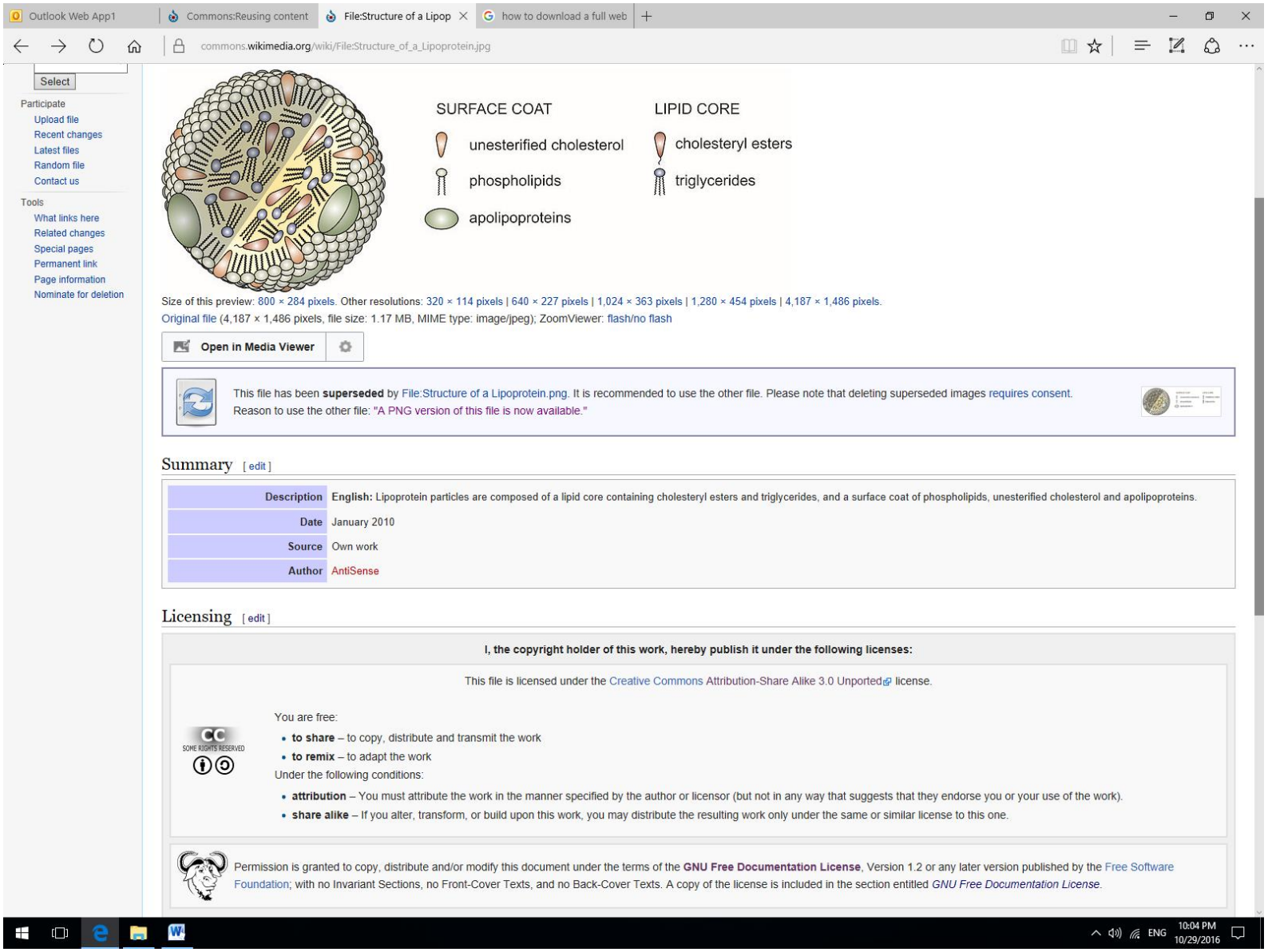

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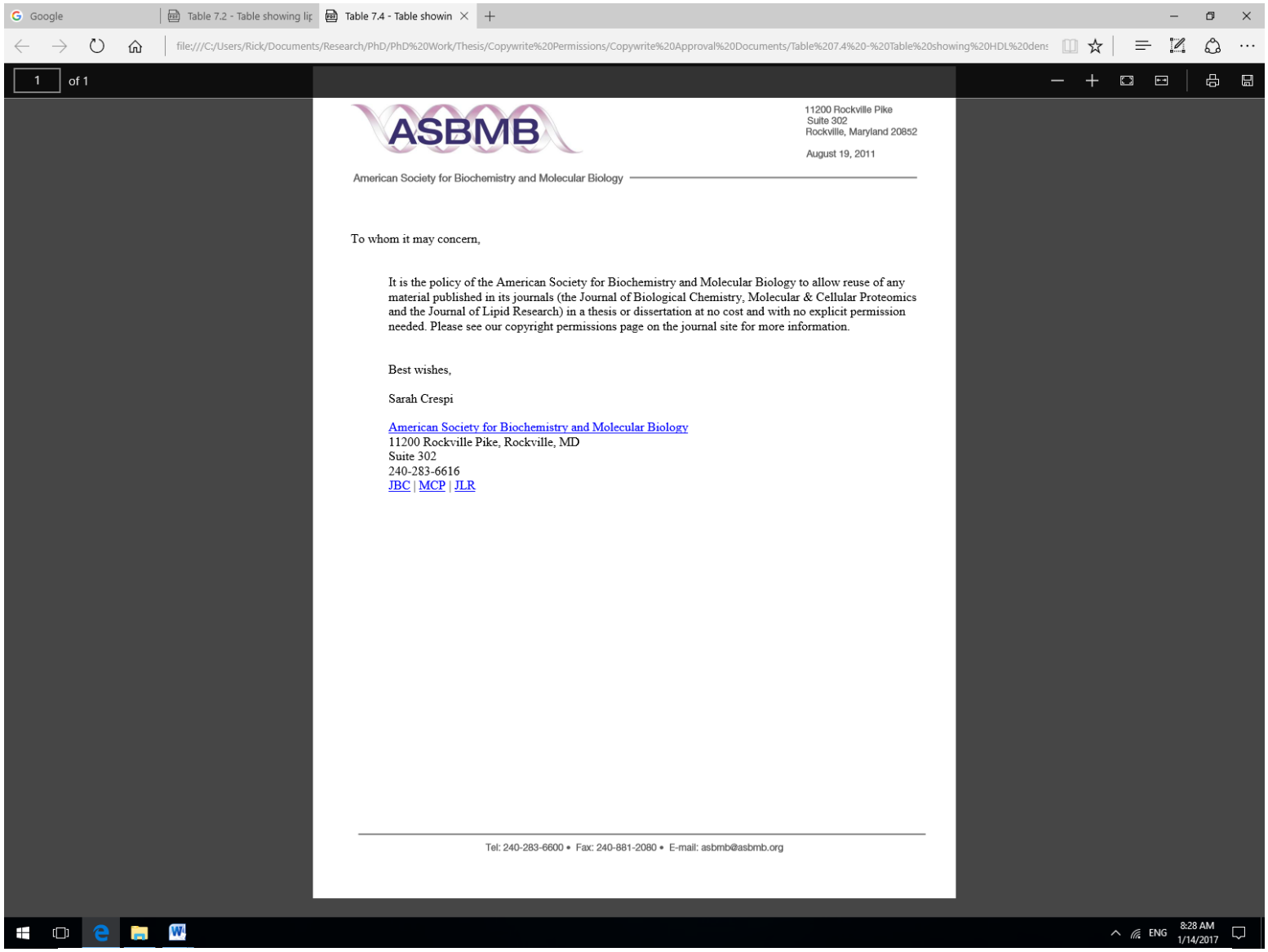

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Permission to use Table 7.4 – Table showing HDL density ranges (Harman, 2013).