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Hypoglycaemia in children and adults with type 1 diabetes: clinical implications

A thesis by

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Dissertation presented for the degree of MD (Doctor of Medicine)

University of Edinburgh

2015

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Declaration

1) This thesis was composed by Alex Graveling

2) Study described in chapter 6 was performed by Dr. Alex Graveling. With the aid of his two supervisors Prof. Brian Frier and Prof. Ian Deary, he wrote the protocol, applied for ethical approval, recruited the participants, executed the glucose clamp procedures, recorded and analysed the data and performed the statistical analysis.

Study described in chapter 7 was performed by Dr. Alex Graveling. Dr. Rohana Wright applied for ethical approval and wrote the protocol which was later amended by Dr. Alex Graveling. With the aid of his supervisors Prof. Brian Frier and Prof. Ian Deary he recruited the participants, carried out the initial interviews, collected the subsequent questionnaires and blood glucose diaries, recorded and analysed the data and performed the majority of the statistical analysis. Dr. Mike Allerhand performed the multinomial logistic regression.

Study described in chapter 8 was conducted by Dr. Alex Graveling. Prof. Brian Frier supervised the study protocol and advised on the data analysis. Dr. Roderick Warren provided assistance with the statistical analysis and drafted the submitted manuscript for publication.

3) Alex Graveling holds the degree MBChB

4) This thesis has not been submitted for any other degree, diploma or professional qualification.

Alex Graveling

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Lay summary

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Abstract of Thesis

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Lay summary

MD Proposal

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The proposed thesis will examine three areas of research: (1) the effects of hypoglycaemia on cognitive function in adults with and without T1DM, (2) the symptoms and awareness of hypoglycaemia in children and adolescents with T1DM and (3) hypoglycaemia and driving in people with insulin-treated diabetes: self-treatment and adherence to recommendations for avoidance.

(1) Executive cognitive function governs organisation of thoughts, prioritisation of tasks, and time management. This study examined the effect of acute hypoglycaemia on executive function in adults with and without diabetes. Thirty-two adults with and without type 1 diabetes were studied. Two hyperinsulinaemic glucose clamps were performed at least 2 weeks apart in a single-blind, counterbalanced order. Executive functions were assessed with a validated test suite (Delis-Kaplan Executive Function). A general linear model (repeated-measures ANOVA) was used. Compared with euglycaemia, executive functions (with one exception) were significantly impaired during hypoglycaemia; lower test scores were recorded with more time required for completion. Large Cohen d values (>0.8) suggest that hypoglycaemia induces decrements in aspects of executive function with large effect sizes. In some tests, the performance of participants with diabetes was more impaired than those without diabetes. Executive cognitive function, which is necessary to carry out many everyday activities, is impaired during hypoglycaemia in adults with and without type 1 diabetes.

(2) In children with type 1 diabetes mellitus (T1DM) the prevalence of impaired awareness of hypoglycaemia (IAH) is uncertain. Questionnaires were completed by 98 children with T1DM (mean age 10.6 years) and their parent(s); hospital admission data for the previous year were collected.

Lay summary

Awareness of hypoglycaemia was assessed using two questionnaire-based methods that have been validated in adults. For 4 weeks, participants performed routine blood glucose measurements and completed questionnaires after each episode of hypoglycaemia. The 'Gold' questionnaire classified a greater proportion of the participants as having IAH than the 'Clarke' questionnaire (68.4 vs. 22.4%). Using the 'Clarke' method, but not the 'Gold' method, children with IAH were younger and more likely to require external assistance or hospital admission. In contrast to adults, behavioural symptoms were the best predictors of awareness status. IAH affects a substantial minority of children and impending hypoglycaemia may be heralded by behavioural symptoms. The 'Clarke' method was more effective at identifying those at increased risk.

(3) A clinical survey of an outpatient clinic population to ascertain current knowledge and practice among drivers with insulin-treated diabetes. A representative sample of 202 current drivers with insulin-treated diabetes completed a structured questionnaire. A minimum blood glucose level of 4.0 mmol/L or higher was considered necessary for driving by 74.8%, and 87.1% reported always keeping carbohydrate in their vehicle. However, 38.1% reported never carrying a glucose meter when driving, and 59.9% that they never test blood glucose before driving, or test only if symptomatic of hypoglycaemia. Most participants 89% would stop driving to treat hypoglycaemia although only 13.9% would wait longer than 30 min. Compliance with statutory requirements to inform the licensing authority and motor insurer is good.

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I am completely indebted to Professor Brian Frier who was the principal driving force behind all of the work presented in this thesis. His enthusiasm and willingness to share his knowledge was always appreciated despite his busy work commitments. Without his enthusiasm and commitment this thesis would not exist.

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Abbreviations & dedication

Abbreviations

The below abbreviations are used throughout this thesis:

CGM	Continuous glucose monitoring
IAH	Impaired awareness of hypoglycaemia
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus

Dedication

For Sylvie & Ruby

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Search strategy

Search strategy

Articles were sourced from Google Scholar and Medline searches (English language and human) using relevant keywords. Articles were also sourced from the author's personal collection.

Chapter 1

1.1 Introduction to hypoglycaemia

Hypoglycaemia is derived from the classical Greek words “hypo” (under), “glykys” (sweet) and “haima” (blood) and is used to describe lower than normal blood glucose concentrations. Despite advances in the delivery and type of insulin, along with improved education and support available for people with type 1 diabetes mellitus (T1DM), hypoglycaemia remains a common and feared intermittent side effect of the insulin therapy used in the treatment of T1DM. Hypoglycaemia results in profound physical, cognitive and psychological effects and is therefore an important and clinically relevant area of study.

The Diabetes Control and Complications Trial (DCCT) demonstrated the benefits of intensified insulin therapy in T1DM. Strict glycaemic control was shown to limit the risk of predominantly microvascular but also macrovascular complications and this benefit was shown to be sustained for ten years following the period of tighter glycaemic control (DCCT Research Group, 1993, Nathan et al., 2005, DCCT/EDIC Group et al., 2009). The downside to striving for blood glucose levels closer to those achieved by people without diabetes is the increased incidence of hypoglycaemia; the intensively treated arm of the DCCT experienced a threefold increase in severe hypoglycaemia.

The huge increase in numbers of people with diabetes both in the developed and developing worlds will provide additional strain on many countries healthcare systems (Wild et al., 2004, Shaw et al., 2010, Yang et al., 2010). Scotland is in the unique position of having a national register of people diagnosed with diabetes. The 2012 Scottish Diabetes Survey reported that over 250,000 people in Scotland had a diagnosis of diabetes which represents 4.9% of the total population; 11.2% of these had a diagnosis of T1DM (Scottish Diabetes Survey Monitoring Group, 2014). This compares with around 3% of the population in 2002; 18.2% of these had a diagnosis of T1DM (Scottish Diabetes Survey Monitoring Group, 2003). Other countries are experiencing

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an even greater increase; particularly in people diagnosed with type 2 diabetes mellitus (T2DM). A recent study (2008) of over 46,000 participants reported that 9.7% of the Chinese population is now affected with diabetes in 2008 compared with 2.5% in 1994 (Pan et al., 1997, Yang et al., 2010). The increasing prevalence of diabetes, albeit predominantly T2DM, will result in more people prescribed being prescribed sulfonylurea or insulin therapy with a consequent increased risk of hypoglycaemia.

This thesis is mainly confined to a discussion of hypoglycaemia occurring in humans with T1DM, other causes of hypoglycaemia will not be discussed. To highlight key differences, reference will be made to hypoglycaemia occurring in adults with T2DM.

1.2 Historical aspects of hypoglycaemia

Prior to the discovery of insulin, careful dietetic regulation in people with T1DM helped prolong the inevitable descent into a fatal hyperglycaemic, ketotic coma. In 1889 von Mering and Minkowski reported that a total pancreatectomy would induce diabetes in dogs (Luft, 1989). Subsequent investigators endeavoured to discover the pancreatic extract responsible for moderating blood glucose levels in animals or humans. The pancreatic extract which became known as insulin was first developed by a team based in Toronto in the early 1920s comprising of Frederick Banting, Charles Best, James Collip and John Macleod. In 1921, Banting and Best under the stewardship of Macleod managed to extract insulin from bovine pancreases and successfully treated their first patient Leonard Thompson who had a two year history of T1DM (Banting et al., 1922). Their successful refinement and administration of their pancreatic extract resulted in the award of the Nobel Prize to Banting and Macleod. This is described in the “Discovery of Insulin” by the Canadian historian, Michael Bliss (Bliss, 2000).

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Prior to the first human trials of insulin, Collip had observed that on injecting the pancreatic extract into normal rabbits they became very hungry and would start eating anything put in front of them, further injections of the extract resulted in seizure, coma and then death. If he took a blood sample from the rabbits, mixed it with glucose and then re-injected one of the comatose rabbits they would recover. This is one of the first descriptions of hypoglycaemia and its subsequent treatment (Bliss, 2000); Collip may have been alerted to the idea by a paper demonstrating hypoglycaemia after hepatectomy and the restorative effect of administering glucose (Mann and Magath, 1921). The Toronto team would therefore have been aware of this potentially fatal side effect of insulin therapy prior to commencing human trials.

Shortly after the first people with T1DM were successfully treated with insulin it was recognised that if insulin was administered in sufficient quantities it could result in a lowering of blood glucose to below normal (Maddock and Trimble, 1928). These hypoglycaemic reactions or “insulin shocks” were noted to induce particular symptoms such as tremor and sweating followed by impaired cognitive performance. Williams in Rochester gave this memorable account after treating his second patient with insulin in June 1922; “we threw him into profound insulin shock. He was so lifeless that the chief of our surgical staff pronounced him dead. We immediately restored him by the injection of some glucose, and it was looked upon as a miracle in the hospital.” (Bliss, 2000). The importance of people with T1DM always carrying a supply of carbohydrate for treatment of “insulin shocks” was emphasised the following year (Hinds-Howell, 1923).

The observation that repeated exposure could result in a diminution of these symptoms was first reported a few years later (Maddock and Trimble, 1928). Lawrence noted that as duration of insulin treatment progressed, that the symptoms experienced changed and often diminished in intensity leading to people being unaware of the impending onset of hypoglycaemia (Lawrence, 1941). Many different research teams noted the variable blood glucose threshold at which people experienced symptoms with some experiencing

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hypoglycaemic symptoms at “normal” levels of blood glucose (Maddock and Krall, 1953).

1.3 Definition of hypoglycaemia

In adults with diabetes, hypoglycaemia is defined by ability to self-treat when exposed to low blood glucose. If self-treatment is possible, the episode is termed “mild”, irrespective of the nature or intensity of symptoms experienced. “Severe” hypoglycaemia is defined as any episode that requires external assistance for recovery, and is not confined to the development of coma or a reduced consciousness level (DCCT, 1991, Graveling and Frier, 2009). Whipples’ triad (i.e. presence of typical symptoms, a low blood glucose and amelioration of the symptoms with the ingestion of glucose) was created in the context of pathological spontaneous hypoglycaemia (Whipple, 1938). The American Diabetes Association proposed five classifications of a hypoglycaemic episode (Workgroup on Hypoglycemia, 2005, Seaquist et al., 2013):

1. Severe hypoglycaemia: An event requiring third party assistance to administer carbohydrate.
2. Documented symptomatic hypoglycaemia: an event with typical symptoms of hypoglycaemia and a measured plasma glucose ≤ 3.9 mmol/L.
3. Asymptomatic hypoglycaemia: an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose ≤ 3.9 mmol/L.
4. Probable symptomatic hypoglycaemia: an event with typical symptoms of hypoglycaemia but no measurement of plasma glucose was performed.
5. Relative hypoglycaemia: an event during which the person experiences typical symptoms of hypoglycaemia but the measured plasma glucose is ≥ 4.0 mmol/L.

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The usual definition of severe hypoglycaemia (SH) used in adults (i.e. requiring external help for recovery), cannot be used in young children, as most require assistance to treat hypoglycaemia regardless of severity. Because of this limitation, SH in children has been defined as hypoglycaemia resulting in coma or seizure activity with moderate hypoglycaemia defined as requiring third party assistance (Clarke et al., 2009).

The blood glucose level that defines hypoglycaemia is the subject of topical debate and is a complex issue (Frier, 2009, Cryer, 2009, Amiel, 2013). As a result, there is no single level of plasma glucose concentration that defines hypoglycaemia. If the blood glucose level that defines hypoglycaemia is set too high, then some of the hypoglycaemic episodes captured will have no clinical relevance (Swinnen et al., 2009). The plasma glucose thresholds that result in symptom generation, counter-regulation and cognitive dysfunction are dynamic and show substantial intra- and inter-individual variation. There is the additional complication that the inherent inaccuracy of many capillary blood glucose meters in the hypoglycaemic range means that a “buffer” zone may be appropriate (Graveling, 2010). Falsely high blood glucose readings can lead to a delay in the diagnosis and subsequent treatment of hypoglycaemia (see section 1.5) (Korsatko et al., 2009).

For clinical purposes having different thresholds for different patient groups is awkward and Diabetes UK, the principal British diabetes charity, adopts the pragmatic policy of “make four the floor”. This is also reflected in the UK guidelines for the treatment of hypoglycaemia occurring in hospitalised adults (Walden et al., 2013). This should be regarded as the alert level that may herald the onset of hypoglycaemia, not the biochemical definition.

1.4 Frequency of hypoglycaemia

1.41 Frequency of hypoglycaemia in T1DM

People with T1DM experience around two episodes of mild hypoglycaemia per week (Pramming et al., 1991, Pedersen-Bjergaard et al., 2004). This number

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has not changed over 20 years despite developments in insulin therapy. Differences in the reported frequencies of mild hypoglycaemia between clinical studies may be related to the heterogeneity of the populations studied and differing hypoglycaemia definitions. Changing the glucose cut-off used to define hypoglycaemia has a substantial effect on the reported frequency of hypoglycaemia as can be seen in Figure 1.1 (Swinnen et al., 2009). Raising the biochemical cut-off increases the proportion of asymptomatic evidence as well as increasing the overall number of reported hypoglycaemic episodes. Thirty percent experienced only asymptomatic hypoglycaemia during the 12-week monitoring period when using $<2.9\text{mmol/L}$ as the biochemical cut off compared with around 60% when using $<3.9\text{mmol/L}$ (Swinnen et al., 2009). The clinical significance of an asymptomatic episode of hypoglycaemia measured at 3.8mmol/L is debateable. Many research groups examining rates of hypoglycaemia find it difficult to find a biochemical cut-off that captures clinically significant events without including too many events that are not significant.

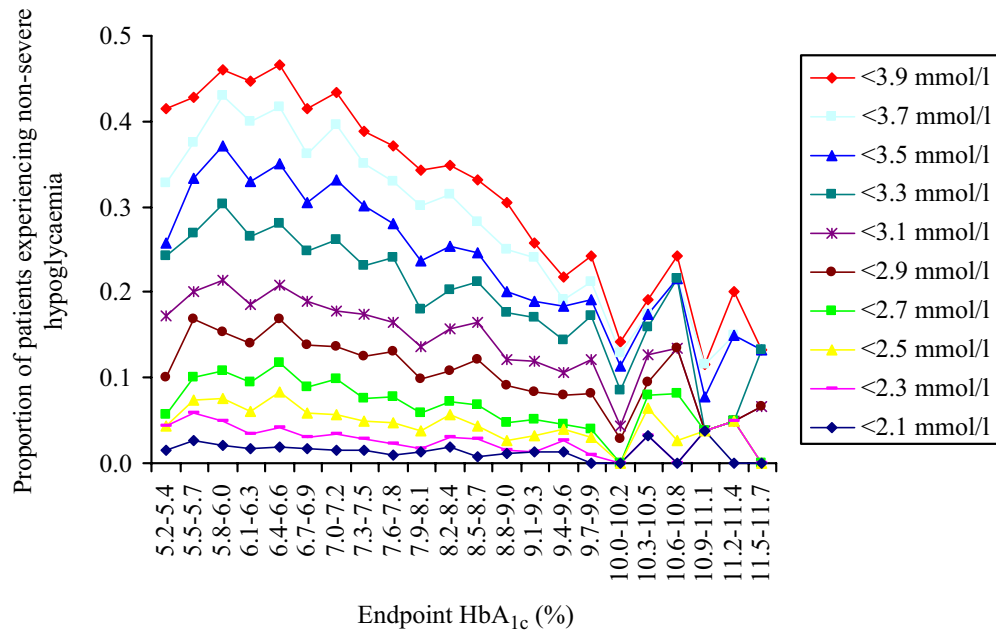


Figure 1.1: Proportion of participants experiencing at least one non-severe hypoglycaemic episode over 12 weeks according to pre-defined glucose cut-off points for the definition of hypoglycaemia plotted against endpoint HbA_{1c} categories (Swinnen et al., 2009).

The annual prevalence of severe hypoglycaemia in unselected populations (i.e. those including anyone, irrespective of risk factors) has been reported consistently at 30-40% in several large studies, with an incidence varying from 1.0 – 1.7 episodes per person per year (Strachan, 2014). This rises to more than 3 episodes per person per year in those with T1DM of > 15 years duration (UK Hypoglycaemia Study Group, 2007). Figure 1.2 shows the proportion of each group experiencing severe hypoglycaemia over the 9-12 month monitoring period; 22% of those with short duration T1DM (<5 years) increasing to 45% of those of longer duration T1DM (>15 years) (UK Hypoglycaemia Study Group, 2007) (Figure 1.2).

People with a history of severe hypoglycaemia are at higher risk of experiencing further events, with a median of 2-3 events per year (Lammert et al., 2009). The distribution of severe hypoglycaemia is therefore skewed in that most people do not experience any episodes while a small number of

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individuals experience multiple events (Pedersen-Bjergaard et al., 2004). Recall of severe hypoglycaemia is robust with almost 90% correctly recalling whether than had experienced severe hypoglycaemia in the preceding year (Pedersen-Bjergaard et al., 2003b). For a variety of reasons, many episodes of severe hypoglycaemia are not coded (e.g. using ICD-9) and so do not appear in health service statistics; in one survey 5% of participants reported an episode of severe hypoglycaemia in the preceding month but only 1% had a compatible ICD-9 diagnosis (Libby et al., 2010).

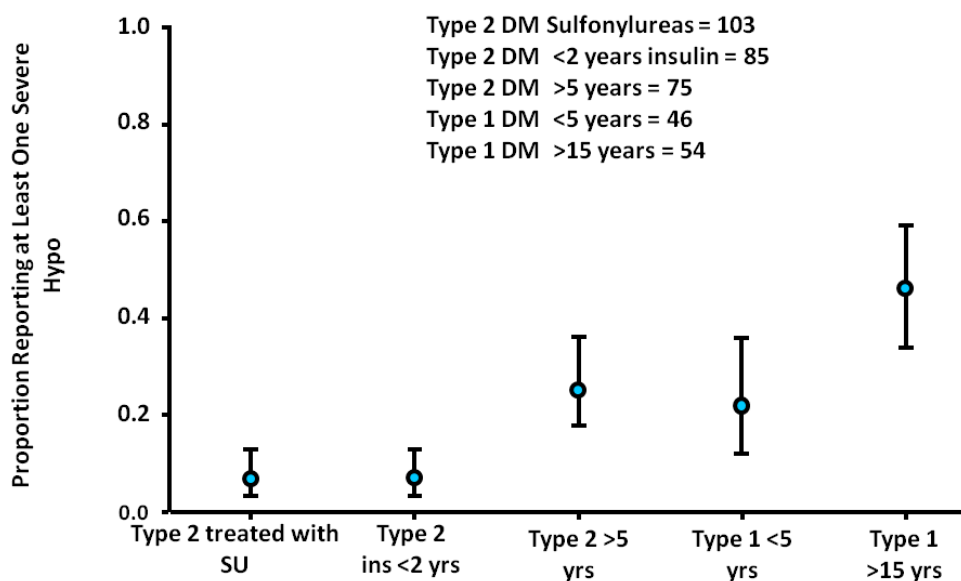


Figure 1.2: Proportion of each group experiencing at least one severe hypoglycaemia episode during 9-12 months of follow up (UK Hypoglycaemia Study Group, 2007).

1.42 Frequency of hypoglycaemia in the paediatric population with T1DM

Varying definitions of hypoglycaemia make it difficult to compare observed frequencies in the paediatric population. However, large, well-conducted studies show similar rates of severe hypoglycaemia. Severe hypoglycaemia in

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the paediatric population is usually defined as hypoglycaemia leading to altered consciousness or seizure resulting in hospital attendance or admissions. An Australian study of 1335 children with T1DM reported an incidence of 16.6 severe events per 100 patient-years (Bulsara et al., 2004). A follow up paper reported that the incidence of severe hypoglycaemia had fallen over time from around 17 per 100 patient-years in 2001 to 6 per 100 patient years in 2009 (O'Connell et al., 2011). A large American study of 1243 children with T1DM reported an overall incidence of severe hypoglycaemia of 19 per 100 patient-years (Rewers et al., 2002). Given the skewed distribution of severe hypoglycaemia within the patient population, patient selection is crucial and may account for some of the variance in the reported incidence.

Nocturnal hypoglycaemia is more frequently associated with improved glycaemic control and younger age, with one third of those under five years experiencing nocturnal hypoglycaemia once every three nights (Porter et al., 1997). Hypoglycaemia can mimic a number of other conditions. In children, non-disclosure of the hypoglycaemic event led to elevated suspicion of drug or alcohol misuse (Berlin et al., 2005).

1.43 Frequency of hypoglycaemia in T2DM

Many trials of insulin-treated T2DM have documented very low rates of severe hypoglycaemia, partly because of patient selection (excluding those at high risk) and short periods of study. Severe hypoglycaemia is less common in people with insulin-treated T2DM, but still represents a substantial clinical problem, with between 7% and 25% of people experiencing at least one severe episode annually; the frequency increases with longer duration of insulin therapy (Henderson et al., 2003b, Leiter et al., 2005, UK Hypoglycaemia Study Group, 2007). As with people with T1DM, the distribution of severe hypoglycaemia is very skewed, in one study 5% of participants accounted for 57% of events (Akram et al., 2009). People with insulin-treated T2DM are more likely to require assistance from the medical services for severe hypoglycaemia than those with T1DM (30% vs. 10% of episodes) (Donnelly et al., 2005). Dementia and an inability to self-manage medications are strong

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risk factors for severe hypoglycaemia requiring the assistance of the healthcare services (hazard ratios of 3.0 and 4.2 respectively) (Bruce et al., 2009). Because of the much larger number of people with insulin-treated T2DM compared with T1DM, the overall number of hypoglycaemic events is greater for the population with T2DM.

Sulfonylureas cause much more hypoglycaemia than is generally recognised, with the annual prevalence of severe episodes in people with well-controlled diabetes being 7% (UK Hypoglycaemia Study Group, 2007). Long-acting agents such as glibenclamide are associated with a higher risk of hypoglycaemia and are particularly dangerous in the elderly (Lassmann-Vague, 2005, Campbell, 2009).

1.5 Biochemical detection of hypoglycaemia

Self-monitoring of capillary blood glucose using a glucose meter is an integral part of diabetes management for people treated with insulin (Hirsch et al., 2008). Whether used at home or hospital, the performance of most glucose meters is compared against an International Organization for Standardization (ISO) standard. Below 4.2 mmol/L, glucose meters are considered accurate if 95% of measurements obtained are within 0.8 mmol/L of the actual concentration (International Organization for Standardization, 2003). A glucose meter is therefore considered to be accurate provided it measures an actual glucose concentration of 3.6 mmol/L as any value between 2.8 mmol/L and 4.4 mmol/L) on 95% of occasions. Above 4.2 mmol/L a glucose meter is considered accurate if its readings are within 20% of the actual concentration on 95% of occasions. In an evaluation of glucose meter accuracy four different glucose meter systems were tested with glucose samples <4.2 mmol/L. None of these meters met the relatively lax ISO criteria as they were out of range on more than 95% of occasions, with the worst performing meter within range on only 62.5% of occasions (Kost et al., 2008). Perhaps in recognition of the need for stricter standards in 2013 the ISO standards were updated (International

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Organization for Standardization, 2013). Below 4.2mmol/L the standards remain unchanged; above 4.2 mmol/L the readings must be within 15% (rather than 20%) of the actual glucose concentration on 95% of occasions.

Two types of erroneous readings of clinical importance have been identified (Kost et al., 2008). The first occurs when the reference measurement is <4.2 mmol/L but the glucose meter reads >6.1 mmol/L; this may lead to clinical decisions that could worsen hypoglycaemia. The second type occurs when the reference measurement is >6.1 mmol/L but the glucose meter reads <4.2 mmol/L, encouraging clinical decisions that could aggravate hyperglycaemia. Other sources of diagnostic inaccuracy include hypotension, body temperature, and abnormalities of haematocrit, oxygenation or acid-base balance (Dungan et al., 2007). Test strips using glucose dehydrogenase pyrroloquinolinequinone (GDH-PDQ) are susceptible to cross-contamination from other forms of carbohydrate. The resultant inaccurate readings have been associated with fatal hypoglycaemia in people receiving peritoneal dialysis using icodextrin (Olansky and Kennedy, 2010). User-related errors include inadequate cleansing of the skin or meter, failure to obtain an adequate blood sample or to use a quality control solution, and improper storage of test strips (Montagnana et al., 2009).

1.51 Continuous Glucose Monitoring

Continuous Glucose Monitoring (CGM), which measures interstitial tissue glucose, has been investigated as a potential tool to detect hypoglycaemia. Interstitial glucose is known to lag behind plasma glucose during euglycaemia by approximately 15-17 minutes (Wei et al., 2010, Kulcu et al., 2003). Interstitial glucose lags even further behind capillary glucose during the descent into hypoglycaemia, in one study by an average of 26 minutes (Boyne et al., 2003, Melki et al., 2006). There was also a delay in return to euglycaemia following hypoglycaemia in interstitial glucose compared with plasma glucose (Aussedat et al., 2000). A more recent study, using microdialysis catheters rather than CGM to measure interstitial glucose, found a shorter lag period of 5-6 minutes suggesting a processing delay when using

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CGM (Basu et al., 2013). This delay means that calibration of CGM devices should be avoided when blood glucose levels are changing rapidly.

In a group of people with T1DM and mean HbA1c of 6.6%, CGM gave lower readings than paired whole blood samples analysed using a (Beckman) glucose analyser on 74% of occasions. The lowest nocturnal reading was $38\% \pm 15\%$ lower using CGM compared with the glucose analyser (McGowan et al., 2002). Placement of glucose sensor may have an impact with lower values obtained from the abdomen compared with forearm (von Döbeln et al., 2005).

When CGM meters are evaluated using ISO standards (i.e. below 4.2 mmol/L, glucose meters are considered accurate if 95% of measurements obtained are within 0.8 mmol/L of the actual concentration (International Organization for Standardization, 2003)) only 32-48% readings meet this standard (Klonoff, 2005, Guerci et al., 2003). CGM has been proposed as a tool to alert people with T1DM to the presence of hypoglycaemia (glucose < 3.9 mmol/L), however CGM only detected 38% of measurements in the hypoglycaemic range. CGM falsely alerted people that their blood glucose was low on 72 out of 135 of occasions, meaning that CGM was only predicting true hypoglycaemia on 47% of occasions (Zijlstra et al., 2013).

Taking these issues into account, CGM has shown that asymptomatic mild hypoglycaemia occurs more frequently than is apparent using conventional intermittent measurements of capillary blood glucose (De Keulenaer et al., 2012). Despite reservations concerning the accuracy of CGM in the hypoglycaemic range, it is reasonably reliable (Caplin et al., 2003). CGM detected asymptomatic episodes of hypoglycaemia in 63% of T1DM and 47% of insulin-treated T2DM over a three-day period (Chico et al., 2003). Over six days, 90% of people with T1DM had at least one episode of biochemical hypoglycaemia, but only 15% experienced symptoms, even in those with normal hypoglycaemia awareness (Hoi-Hansen et al., 2005). The clinical significance of these asymptomatic episodes is unclear but they may induce counter-regulatory hormonal deficiencies and impaired awareness of hypoglycaemia (IAH).

1.52 Detection of nocturnal hypoglycaemia

Approximately 55% of severe hypoglycaemic events occurred at night in the Diabetes Control and Complications Trials (DCCT) (DCCT, 1991). Even in people with poorly controlled T1DM, nocturnal hypoglycaemia has been shown to be common and often prolonged (Gale and Tattersall, 1979). Conventional laboratory blood glucose analysis showed that nocturnal hypoglycaemia (laboratory glucose $<3.5\text{mmol/L}$) occurred in 47% of children with T1DM admitted for observation with hourly blood glucose measurements (without waking the children); almost half (49%) of these episodes were asymptomatic (Beregszaszi et al., 1997). The prevalence of nocturnal hypoglycaemia differs according to biochemical cut-off; when hypoglycaemia was defined as blood glucose $<3.9\text{mmol/L}$ one third of participants experienced nocturnal hypoglycaemia, this reduced to about a quarter with hypoglycaemia defined as $<3.0\text{mmol/L}$ (Wentholt et al., 2007).

A high prevalence of nocturnal hypoglycaemia has been demonstrated using CGM; 67% of participants with T1DM experienced an episode of nocturnal hypoglycaemia (blood glucose $<4.0\text{mmol/L}$) during a 3 night experimental period (around 22% per night); morning hyperglycaemia was negatively associated with nocturnal hypoglycaemia (odds ratio 0.7, $p<0.001$) (Guillod et al., 2007). This would suggest that the Somogyi phenomenon (i.e. morning hyperglycaemia following nocturnal hypoglycaemia through counter-regulatory hormone release) does not occur; this will be discussed further in section 1.7. The largest CGM study was the JDRF (Juvenile Diabetes Research Foundation) study that included 42 participants aged 15-24 years and 70 aged over 25 years. The prevalence of nocturnal hypoglycaemia (blood glucose $<3.3\text{mmol/L}$) was lower at 8.5% of nights; there was no difference between those with CSII or basal bolus insulin regimens (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010).

Asymptomatic hypoglycaemia is common with only 20-33% of nocturnal episodes of hypoglycaemia detected by CGM also being detected by the person with diabetes (Guillod et al., 2007, Woodward et al., 2009). A study of T1DM

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and insulin-treated T2DM showed that 74% of episodes of undetected hypoglycaemia occurred during sleep when symptoms are undetected. People with T1DM were exposed to proportionately more nocturnal episodes than people with insulin-treated T2DM (Chico et al., 2003). The risk of nocturnal hypoglycaemia is greatest when bedtime blood glucose is below 7.0mmol/L; more than one third develop nocturnal hypoglycaemia if their bedtime blood glucose is below 4.0mmol/L (Guillod et al., 2007).

Using CGM in the paediatric population, 10.1% of all values recorded were in the hypoglycaemic range at <3.5mmol/L. The majority of hypoglycaemic episodes were nocturnal with 18.8% of values recorded at night compared with 4.4% of values recorded during the day. Only 9% of nocturnal episodes were symptomatic compared with 56% during the day (Amin et al., 2003). Nocturnal hypoglycaemia was most strongly predicted by a pre-bedtime blood glucose of <5.6 mmol/L (Shalwitz et al., 1990).

1.6 Clinical features of hypoglycaemia

Fletcher and Campbell documented the clinical features during hypoglycaemia following the administration of insulin shortly after the discovery of insulin (Fletcher and Campbell, 1922). One of the earliest hypoglycaemia symptom questionnaires was administered to 179 consecutive patients attending a diabetes clinic in London. Two-thirds had experienced hypoglycaemia and the most common clinical features were sweating (82%), weakness (74%), tremor (73%), visual disturbance (71%) and dizziness (67%) (Cooke, 1934).

“While it must be admitted that hypoglycaemia symptoms are often unpleasant to the sufferer ... and a clear understanding of the early symptomatology by patient and doctor gives at once a sense of confidence and a means of anticipating the more serious manifestations.” (Cooke, 1934)

In adults, hypoglycaemia symptoms show substantial inter-individual variation and can be categorised into autonomic, neuroglycopenic and non-specific groups; children are unable to distinguish autonomic from neuroglycopenic symptoms (McCrimmon et al., 1995, Ross et al., 1998, Tupola and Rajantie, 1998, Deary et al., 1993). The blood glucose levels at which these symptoms are generated are associated with inter- and intra-individual variation according to factors such as prevailing glycaemic control and exposure to antecedent hypoglycaemia (McAulay et al., 2001). Symptoms differ in children compared to adults, particularly with respect to age and pubertal status (Ross et al., 2005, McCrimmon et al., 1995). Behavioural changes, such as becoming naughty or irritable, often alert parents to the presence of hypoglycaemia (Ross et al., 1998, McCrimmon et al., 1995). Increasing duration of diabetes showed a reduction in autonomic symptoms with neuroglycopenic symptoms becoming more prominent although it is unclear whether age was controlled for (Dammacco et al., 1998).

1.61 Clinical assessment of hypoglycaemic symptoms

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A simple 7-point Likert scale has been developed to assess the symptom intensity experienced during hypoglycaemia (Deary et al., 1993).

1.62 Physiological methods of symptom classification

Symptoms are generated by activation of the sympatho-adrenal system (autonomic) and the direct effects of glucose deprivation on the brain (neuroglycopenic) (Deary et al., 1993). Maddock observed two symptom subgroups of autonomic or “adrenaline like” and neuroglycopenic or “central-nervous system like” in the 1950s (Maddock and Krall, 1953). In addition to observations in people with diabetes, studies were performed in people with impaired autonomic nervous systems. People who have cervical cord transections have a preganglionic sympathectomy and exhibit tetraplegia. During acute hypoglycaemia they experience neuroglycopenic, but not autonomic symptoms (Corrall et al., 1979). People who have undergone bilateral adrenalectomy or splanchnicectomy do not secrete adrenaline in response to hypoglycaemia but retain autonomic symptoms (Ginsburg and Paton, 1956, Altorfer et al., 1981, French and Kilpatrick, 1955). Their autonomic neural pathways remain intact allowing normal end-organ stimulation that demonstrates that secretion of adrenaline is not essential in the generation of autonomic symptoms. A pharmacological pan-autonomic blockade with phentolamine, propranolol and atropine) has been shown to affect the awareness of hypoglycaemia and to decrease autonomic but not neuroglycopenic symptom scores (Towler et al., 1993).

1.63 Statistical methods of symptom classification

The 11 most common symptoms have been utilised to form the basis of a scoring system for hypoglycaemic symptoms, the Edinburgh Hypoglycaemia Scale (Deary et al., 1993, McAulay et al., 2001). Principal components analysis (PCA) was used to partition the symptoms into the 3 main groups, namely autonomic, neuroglycopenic and general malaise (Table 1.1). A further sub-classification of neuroglycopenic symptoms has also been proposed into cognitive dysfunction (inability to concentrate, blurred vision, anxiety,

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confusion, difficulty speaking, diplopia) and neuroglycopenia (drowsiness, tiredness, hunger, weakness) categories (McCrimmon et al., 2003). Symptom scores (i.e. intensity) declined with age (Henderson et al., 2003a). PCA has also been used to reveal similar underlying subgroups in T2DM, although a general malaise category did not clearly emerge and neuroglycopenic symptoms were more prominent than with younger people (Jaap et al., 1998).

Autonomic	Neuroglycopenic	General malaise
<ul style="list-style-type: none">• Sweating• Palpitations• Shaking• Hunger	<ul style="list-style-type: none">• Confusion• Drowsiness• Odd behaviour• Speech difficulty• Incoordination	<ul style="list-style-type: none">• Headache• Nausea

1.64 Do autonomic or neuroglycopenic symptoms herald the onset of hypoglycaemia?

Studies of hypoglycaemia in subjects without diabetes using a stepped glucose clamp found that autonomic symptoms commenced before neuroglycopenic symptoms; the mean difference between the onset of autonomic symptoms and neuroglycopenic symptoms was 0.5mmol/L (Schwartz et al., 1987, Mitrakou et al., 1991). A study using a non-stepped approach (insulin intravenous infusion technique) found no difference in symptom intensity between autonomic and neuroglycopenic symptoms at the onset of hypoglycaemia (Hepburn et al., 1991). Outside of the experimental setting when people in the community were asked about their initial warning symptoms of hypoglycaemia they reported autonomic and neuroglycopenic symptoms with equal frequency (Cox

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et al., 1993b). Similarly, when asked to report which symptoms appear in the early stages of hypoglycaemia both autonomic and neuroglycopenic symptoms are commonly reported (e.g. trembling, sweating, tiredness, difficulty concentrating and hunger) (Hepburn, 1993).

1.65 Variability of symptoms

There is considerable variation between individuals of symptoms experienced during hypoglycaemia. The symptom profile provoked by hypoglycaemia is idiosyncratic and thus varies in character, pattern and intensity between individuals (Pennebaker et al., 1981, Cox et al., 1983). A more recent study that included participants with both T1DM and T2DM demonstrated substantial intra-individual variation in symptom reporting between different episodes of hypoglycaemia (Zammit et al., 2011). Some participants were more consistent than others with men being more consistent than women. Consistency is clinically relevant because subjects with 4 or more reliable symptoms detect 75% of episodes; this drops to 50% if they only have 1 reliable symptom (Cox et al., 1993a). Although no single symptom is present consistently during hypoglycaemia in all people with diabetes, some symptoms are more common than others (Cox et al., 1983).

The release of counter-regulatory hormones, the generation of symptoms and the development of cognitive dysfunction are triggered at specific levels of blood glucose, indicating that glycaemic thresholds exist for responses to hypoglycaemia. These differ between individuals, and while reproducible in non-diabetic volunteers, in people with diabetes these thresholds can be modified by various factors. These factors include the duration of diabetes, the prevailing degree of glycaemic control (as estimated by HbA1c) and recent exposure to hypoglycaemia (antecedent hypoglycaemia) (McAulay et al., 2001).

Improved glycaemic control is associated with a reduction in autonomic symptom intensity and reduction in tense arousal during hypoglycaemia compared with those with poorer glycaemic control (Weinger et al., 1995).

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Individuals with poorer glycaemic control (HBA1c >10%) experience symptoms of hypoglycaemia at higher blood glucose levels than people without diabetes ($4.3 \pm 0.3 \text{ mmol/L}$ compared with $2.9 \pm 0.1 \text{ mmol/L}$) (Boyle et al., 1988). Symptoms of hypoglycaemia also change in nature and diminish in intensity with advancing age (Prasanna et al., 1991). Although a difference in counter-regulatory responses has been observed between genders (discussed later) there was no difference in hypoglycaemia symptom scores between 160 male and female participants (Geddes et al., 2006).

1.66 Alteration of physical symptoms

The emergence and perception of symptoms is referred to as interoception. Preconceptions affect the symptoms experienced during hypoglycaemia (Pohl et al., 1997). Healthy volunteers with no experience of hypoglycaemia were given one of four possible treatments:

1. Informed that they would be given insulin & given insulin
2. Informed that they would be given saline & given insulin
3. Informed that they would be given saline & given saline
4. Informed that they would be given insulin & given saline

Both autonomic and neuroglycopenic symptom scores were higher in those expecting to receive insulin and getting insulin. Even those expecting to receive insulin and getting saline instead had higher symptom scores than those expecting saline and receiving saline. Figure 1.3 summarises these results. Higher levels of anxiety at baseline have also been shown to increase symptom intensity scores and increase the accuracy of blood glucose estimation (Ryan et al., 2002). Conversely acute stress (e.g. being asked to prepare and then give a speech) has been shown to reduce the increment in symptom scores (perhaps as a result of starting from a higher baseline symptom intensity) and therefore attenuates awareness of hypoglycaemia (Pohl et al., 1998).

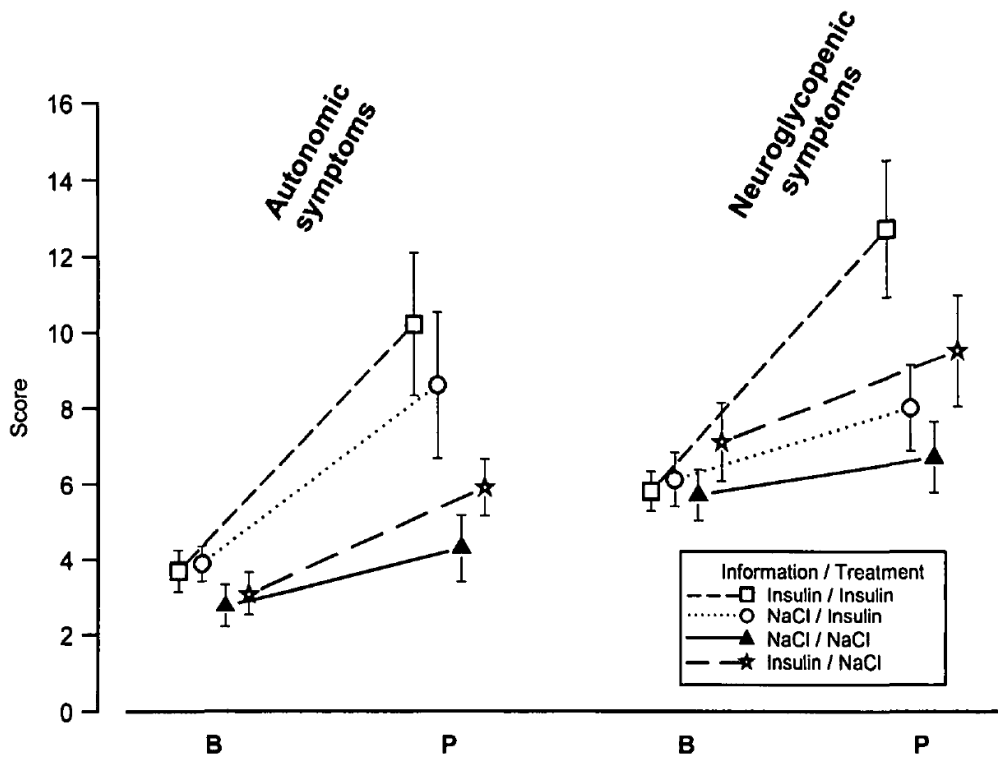


Figure 1.3: Mean±SE baseline (B) and peak (P) sum scores of autonomic and neuroglycopenic symptoms (Pohl et al., 1997)

1.67 Altered ability to detect symptoms

Inability to detect prevailing hypo (or hyperglycaemia) can obviously be potentially dangerous. Sixteen percent of participants estimated their blood glucose as 4.4mmol/L or higher when hypoglycaemic (2.1 mmol/L) during a glucose clamp study; conversely 32% estimated their blood glucose at 4.4mmol/L or less when it was 21.1mmol/L (Weinger et al., 1995). Cox *et al* (1985) categorised the errors that may occur and the likelihood of clinical harm (e.g. treatment of presumed hyperglycaemia with extra insulin when in fact the person with diabetes is in the hypoglycaemic range). Figure 1.4 displays these errors in an error grid analysis graph which categorises estimates of blood glucose into 1 of 5 categories which describe the clinical implications of any estimation error (Cox et al., 1985). This chart has been further refined to avoid small changes resulting in sudden transitions from a blood glucose that is considered safe to one that is considered harmful (Parkes et al., 2000).

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Inability to detect episodes of hypoglycaemia will be discussed further in chapter 4.

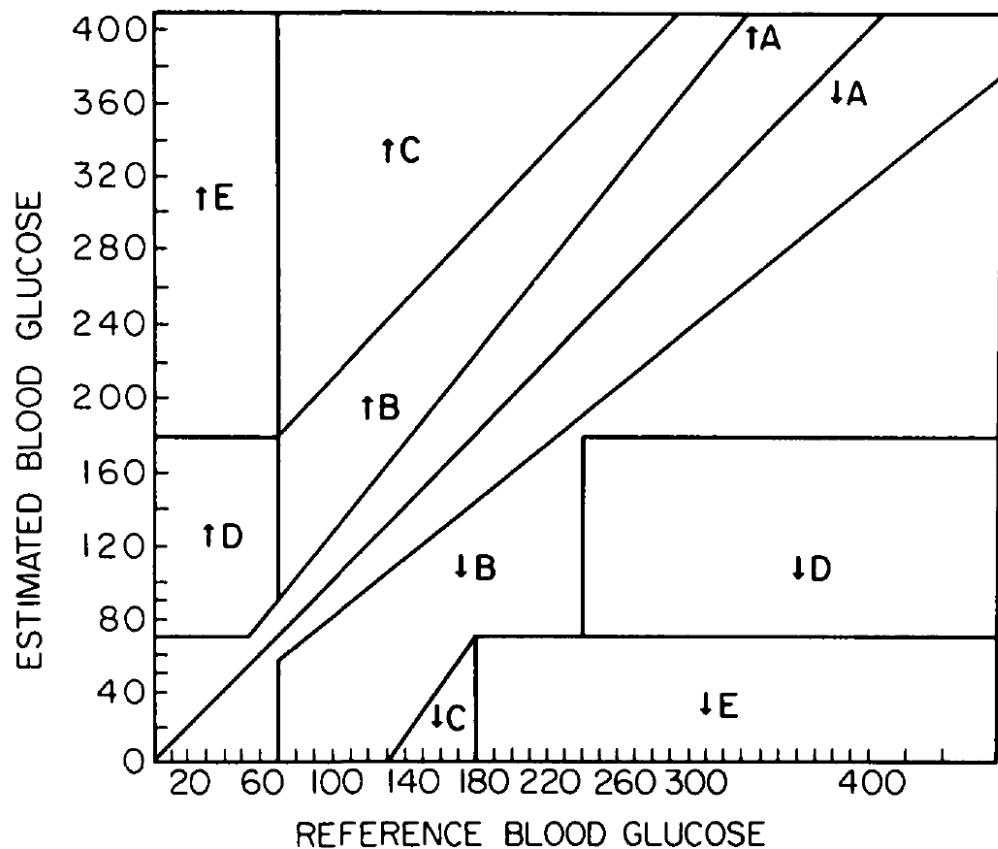


Figure 1.4: Error Grid Analysis graph. Zone A represents accurate estimates; Zone B, clinically neutral or benign errors; Zone C, unnecessary correction of acceptable glucose; Zone D, dangerous failure to treat and Zone E, erroneous treatment (Cox et al., 1985).

1.7 Causes and risk factors for hypoglycaemia

The causes of hypoglycaemia are usually multifactorial and should be distinguished from risk factors; both are listed in table 1.2. Severe hypoglycaemia (ascertained prospectively) in people with T1DM is associated with age, duration of diabetes, awareness of hypoglycaemia and history of severe hypoglycaemia (i.e. hypoglycaemia begets hypoglycaemia) (Gold et al., 1997). A German group found that severe hypoglycaemia was more likely in

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those with a previous history of severe hypoglycaemia, a lower HbA1c, a larger insulin dose per kilogram, lower emotional coping ability scores and a longer duration of diabetes (Bott et al., 1997). Using the DCCT data set, lower mean blood glucose and increased glucose variability were predictors of severe hypoglycaemia (Kilpatrick et al., 2007, Kovatchev et al., 2006).

Pregnancy is associated with an increased risk of severe hypoglycaemia, especially during the first trimester; pre-pregnancy planning does not reduce this risk (Evers et al., 2002, Nielsen et al., 2008, Robertson et al., 2009).

Alcohol consumption is a risk factor for severe hypoglycaemia (ter Braak et al., 2000). An early study found that alcohol was a factor in 31% of people admitted with hypoglycaemia (Seltzer, 1972). Moderate alcohol consumption has been shown in both “real world” and experimental studies to increase the risk of hypoglycaemia the following morning in people with insulin treated diabetes; as well as those on sulfonylurea therapy (Burge et al., 1999, Turner et al., 2001, Richardson et al., 2005). A practical and frequently encountered clinical correlate to this would be an evening spent drinking alcohol followed by fasting overnight. Eating a meal before and after alcohol consumption has been suggested to reduce the risk of alcohol related hypoglycaemia; advice that is often given by diabetes teams in clinical practice (Ismail et al., 2006).

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Table 1.2: Causes and risk factors for hypoglycaemia in people with T1DM (Graveling and Frier, 2009, Cryer, 2008, Muhlhauser et al., 1998, Pedersen-Bjergaard et al., 2004, Stephenson et al., 1996)	
Risk factors	Causes
Previous exposure to severe hypoglycaemia	Insulin doses are excessive, ill-timed or of the wrong type of insulin
Impaired awareness of hypoglycaemia	Inadequate exogenous carbohydrate (e.g. missed meal or snack, overnight fast)
Increasing age	Endogenous glucose production is decreased (e.g. following alcohol ingestion)
Increasing duration of diabetes	Glucose utilisation is increased (e.g. during and shortly after exercise)
Strict glycaemic control	Sensitivity to insulin is increased (e.g. in the middle of the night and following weight loss, improved fitness or improved glycaemic control)
C-peptide negativity	Insulin doses are excessive, ill-timed or of the wrong type of insulin
Lower social status	
Peripheral or autonomic neuropathy	
Exercise	
Pregnancy	
Alcohol	

Increased insulin sensitivity in glucose clamp studies has been shown in participants taking Angiotensin Converting Enzyme (ACE) inhibitors suggesting an increased risk of hypoglycaemia (Pollare et al., 1989, Vuorinen-Markkola and Yki-Jarvinen, 1995, Santoro et al., 1992). A nested case control study conducted in Tayside showed an increased risk of severe hypoglycaemia with ACE inhibitor use (Morris et al., 1997). Various other medications (not used for glycaemic control) have been associated with small increased risks of hypoglycaemia; this will not be discussed further.

An association has been described between elevated serum ACE levels and an increased risk of severe hypoglycaemia (Pedersen-Bjergaard et al., 2001, Pedersen-Bjergaard et al., 2003a). In a large cohort of Danish children, increased serum ACE levels were found to increase the risk of hypoglycaemia in girls only (Johannesen et al., 2011). It has been postulated that lower symptom scores during hypoglycaemia observed in a group with higher ACE levels may be responsible for the increased risk of hypoglycaemia (Hoi-Hansen et al., 2009). Later studies performed in different countries have only shown a weak or no relationship between serum ACE and severe hypoglycaemia meaning that the association remains unproven (Bulsara et al., 2007, Zammitt et al., 2007).

1.71 Disproving the “Somogyi” effect

Michael Somogyi postulated that nocturnal hypoglycaemia may result in fasting hyperglycaemia as a result of excessive counter-regulatory hormone release, this became known as the “Somogyi” effect (Somogyi, 1959); the study was performed using glycosuria as a surrogate for plasma glucose levels. The phenomenon of rebound hyperglycaemia continues to be discussed and promoted by diabetes professionals to people with diabetes (Dose Adjustment for Normal Eating (DAFNE), 2012).

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Using CGM data from more than 250 people with T1DM, a Danish group found that fasting blood glucose levels were lower after nocturnal hypoglycaemia compared with nights containing no hypoglycaemic episodes (6.1 ± 0.3 versus 11.5 ± 0.2 mmol/L (mean \pm SEM)) (Hoi-Hansen et al., 2005). A follow on analysis confirmed that there was no association between nocturnal hypoglycaemia and hyperglycaemia the following morning taking into account the other potential determinants of late morning blood glucose levels (Hoi-Hansen et al., 2006). A similar picture was noted in a study analysing CGM data from the UK Hypoglycaemia Group Study showing again that fasting glucose was lower after nights with hypoglycaemia than without (5.5 versus 14.5 mmol/L) (table 1.3) (Choudhary et al., 2013); when the fasting capillary blood glucose was <5 mmol/L there was evidence of hypoglycaemia in 94% of nights.

Table 1.3: Number of nights with different nadir sensor glucose (lowest sensor glucose for at least 20 min) based on fasting capillary blood glucose (total nights = 89) (Choudhary et al., 2013)

Lowest sensor glucose	Fasting capillary glucose (following morning)		
	< 5 mmol/L	5-10 mmol/L	> 10 mmol/L
< 3.5 mmol/L	16	14	2
3.5-5.0 mmol/L	1	14	4
5.1-10 mmol/L	0	18	13
>10.1 mmol/L	0	1	6

1.72 Risk factors for hypoglycaemia in the paediatric population

The impact of different variables on the risk of severe hypoglycaemia is unclear, studies have often reported apparently conflicting results (table 1.4).

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Many of these studies are not directly comparable looking at differing age groups or duration of diabetes. Severe hypoglycaemia in children is often associated with improved glycaemic control and sometimes with increasing age (Allen et al., 2001). A large Australian study reported that risk factors for severe hypoglycaemia altered with increasing age. In children aged 0-6 years there were no significant associations with severe hypoglycaemia. In children aged 6-12 years increasing disease duration was a risk factor for severe hypoglycaemia but not HbA1c, gender or treatment regimen. In children aged >12 years duration of diabetes was again noted to be a strong risk factor with a 10 fold risk of severe hypoglycaemia in those with >6 years of diabetes compared to those in their first year of diagnosis. (Cooper et al., 2013). An inappropriate response to hypoglycaemia (i.e. by checking for ketones or taking no corrective action) was noted in 38% of hypoglycaemic episodes reported by adolescents (Johnson et al., 2000).

<i>Table 1.4: Risk factors for severe hypoglycaemia in the paediatric population</i>		
<i>Risk factor</i>	<i>Positive (significant) association</i>	<i>No (significant) association</i>
Diabetes duration	Increased with duration (Rewers et al., 2002, O'Connell et al., 2011, Blasetti et al., 2011, Wagner et al., 2005)	(Bognetti et al., 1997). No significant difference after 1 years duration (Davis et al., 1997).
Age	Decreased rate with younger age in girls (Rewers et al., 2002). Increased rate with younger age (Wagner et al., 2005, Bulsara et al., 2004). Increased with age (Bognetti et al., 1997)	
Glycaemic control	Increased rate with lower HbA1c (Davis et al., 1998)	No relationship (O'Connell et al., 2011, Blasetti et al.,

		2011)
Gender	Increased in males (Bulsara et al., 2004)	
Insulin regimen	Pump therapy associated with reduced rate (O'Connell et al., 2011, Cooper et al., 2013)	No relationship (Blasetti et al., 2011). No difference with analogue insulin compared with human insulin (Wagner et al., 2008).

1.72 Risk factors for hypoglycaemia in T2DM

Hypoglycaemia in people with T2DM results from similar causes and risk factors to people with T1DM; a Scottish study identified previous hypoglycaemia and duration of insulin therapy as independent predictors (Donnelly et al., 2005). A large study of people in North America with T2DM has shown that limited health literacy (i.e. problems learning, help reading, not confident with forms) increased the likelihood of severe hypoglycaemia over the preceding 12 months (Sarkar et al., 2010).

1.73 Risk factor case study: Exercise

Exercise and hypoglycaemia has recently been extensively reviewed (Gallen, 2014). Exercise has been shown to increase the risk of hypoglycaemia, both during the event itself and for up to 18 hours following the event (MacDonald, 1987). Late onset hypoglycaemia has been demonstrated in the paediatric population with children more likely to develop nocturnal hypoglycaemia on nights following exercise than following sedentary days (Tsalikian et al., 2005). Hypoglycaemia is common during endurance exercise such as marathon running, and is multifactorial in aetiology (Lumb and Gallen, 2009).

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The warning symptoms of hypoglycaemia may be confused with those induced by exercise *per se*, and may delay its recognition and treatment.

At rest and during low intensity exercise free fatty acids are used as the principal source of energy. With exercise of at least moderate intensity, carbohydrate metabolism becomes an increasingly important source of fuel (Perry and Gallen, 2009). Working groups of skeletal muscle initially obtain glucose for energy from muscle glycogen stores, but once depleted, a balance develops between glucose production (primarily via hepatic glycogenolysis) and glucose uptake by exercising muscle (Petersen et al., 2004). Energy consumption and production during endurance exercise differs from that during intermittent high intensity exercise. The increase in catecholamines is considerably greater with intermittent high intensity exercise (Sigal et al., 1996), which increases glucose production and protects against hypoglycaemia.

Extreme sporting events such as marathons can result in severe hypoglycaemia, especially in the setting of preceding nocturnal hypoglycaemia with associated seizure activity (Graveling and Frier, 2010). In this case report, glycogen stores would have been severely depleted during the preceding nocturnal seizure and their replenishment would have been delayed due to post-hypoglycaemia insulin resistance associated with the secretion of counter-regulatory hormones (Orskov et al., 1996). At rest, blood flow to skeletal muscle increases during hypoglycaemia (Hoffman et al., 1999), but during exercise, the blood flow to skeletal muscle is already maximal, so no further protective increase in blood flow can occur to maximise delivery of circulating glucose. The reduced hepatic glycogen stores would have compounded the severity of the subsequent exercise-induced hypoglycaemia. Storage of glycogen is reduced during hypoglycaemia (Orskov et al., 1996), but with adequate ingestion of oral carbohydrate it can be replenished within 12-14 hours (Steppel and Horton, 2003).

Because insulin is administered exogenously to treat diabetes, plasma levels do not fall when commencing endurance exercise as in a non-diabetic person. Indeed, exercise *per se* can accelerate insulin absorption by increasing blood

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flow to contracting muscles (Hopkins, 2004). Heat produced by working muscle groups is dissipated via an increase in subcutaneous blood flow; this increases insulin absorption from adjacent injection sites. The increased ratio of insulin to glucagon results in less hepatic glucose production (Lumb and Gallen, 2009). The exogenous administration of insulin also reverses the usual portal: systemic ratio of insulin levels. The relatively higher peripheral concentrations promote peripheral muscle glucose uptake and predispose to hypoglycaemia.

Delayed hypoglycaemia can occur for up to 15 hours after exercise, and is associated with increased uptake and storage of glucose by skeletal muscle, inadequate repletion of hepatic glycogen and increased insulin sensitivity (MacDonald, 1987). Antecedent exercise blunts the counter-regulatory hormonal response and warning symptoms of impending hypoglycaemia (Sandoval et al., 2004). The fall in blood glucose after exercise is bimodal, decreasing for around 90 minutes immediately after exercise with a further decrement after 7 to 11 hours (McMahon et al., 2007). More than 30 minutes of moderate to vigorous activity during the afternoon increased the risk of hypoglycaemia by 31% the following day in adolescents with T1DM (Metcalf et al., 2014).

1.8 Chapter summary

Hypoglycaemia is a common and feared complication of insulin therapy and the main obstacle to achieving good glycaemic control. The frequency and symptoms vary widely between individuals. The detection of hypoglycaemia may be made easier with new technologies such as CGM although it does have some limitations. The main risk factor for hypoglycaemia is antecedent hypoglycaemia. It is important to identify any contributing risk factors (e.g. exercise) that can result in hypoglycaemia after each episode.

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Chapter 2 Hypoglycaemia: Mechanisms, morbidity and mortality

2.1 Pathophysiology of hypoglycaemia

2.11 Introduction

Acute hypoglycaemia provokes pronounced physiological responses, the important consequences of which are to maintain the supply of glucose to the brain and promote the hepatic production of glucose. Blood flow is reduced to organs that are not important for counterregulation, such as the spleen and the skin. By contrast blood flow is increased to the myocardium, splanchnic circulation (carrying 3-carbon precursors to the liver) and the brain. Autonomic activation, principally of the sympatho-adrenal system, results in end-organ stimulation and a profuse release of adrenaline, which provokes the haemodynamic changes listed in Table 2.1 (Cryer, 2013).

Table 2.1: Haemodynamic changes during hypoglycaemia (Laing et al., 1999b, Hilsted et al., 1984, Fisher et al., 1990)
• Increased heart rate
• Increased peripheral systolic blood pressure
• Decreased central blood pressure
• Increased myocardial contractility with an increased ejection fraction
• Decreased peripheral resistance (resulting in a widened pulse pressure)

2.12 Defences against hypoglycaemia

The normal defence against falling blood glucose levels is the ingestion of oral carbohydrate. As blood glucose levels fall in healthy individuals insulin secretion from pancreatic beta-cells is inhibited (at around 4.4mmol/L); this

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fall in insulin levels results in stimulation of pancreatic alpha-cells thus increasing glucagon secretion (Cooperberg and Cryer, 2010, McCrimmon, 2008). If glucose levels continue to fall then adrenaline and noradrenaline are released (at around 3.6-3.8mmol/L) (Fanelli et al., 1994). Additional and less immediate responses include increased growth hormone and cortisol secretion (Beall et al., 2012).

2.13 Unregulated hyperinsulinaemia

Humans have evolved to deal with hypoglycaemia in the situation of low insulin and low glucose levels (i.e. periods of prolonged starvation). People with T1DM have high insulin levels from exogenous insulin administration and low glucose levels. This results in conflicting signals and compromises the defence systems against hypoglycaemia in people with T1DM. The elevated insulin concentrations increase glucose uptake into muscle, fat and liver and limit gluconeogenesis. Insulin also inhibits lipolysis, prevents the release of alternative energy stores and suppresses glucagon secretion through direct action on pancreatic alpha-cells (Beall et al., 2012, Garber et al., 1976).

2.14 Counterregulatory deficiencies

Glucagon increases glucose production by the liver through hepatic glycogenolysis, increased gluconeogenesis, increased amino acid transport and increased fatty acid metabolism (ketogenesis) (Fanelli et al., 2006). Blood glucose was previously thought to be the dominant stimulus of glucagon secretion, displaying an inverse relationship with hypoglycaemia resulting in increased glucagon secretion. However, it is the reduced beta-cell secretion of insulin, resulting in decreased inhibition of alpha-cells, which leads to an increase in glucagon secretion (Raju and Cryer, 2005, Taborsky and Mundinger, 2012). Glucagon secretion is therefore inversely related to the prevailing intra-islet insulin concentration. Artificially maintaining intra-islet insulin concentrations with a sulfonylurea markedly attenuates the glucagon response (Peacey et al., 1997, Banarar et al., 2002). The glucagon response is therefore not dependent on innervation and people with pancreas transplants or

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spinal cord transections have normal glucagon secretion (Diem et al., 1990, Palmer et al., 1976).

Glucagon secretion in response to hypoglycaemia becomes attenuated and then eventually fails altogether in T1DM and advanced T2DM (Gerich et al., 1973, Bolli et al., 1983, Segel et al., 2002). Glucagon responses to other stimuli are preserved, indicating that the alpha-cells remain functional (Cryer, 2005, Siafarikas et al., 2012). Residual beta-cell function has been shown, in children, to be associated with a lower risk of severe hypoglycaemia (Sorensen et al., 2013).

The next counter-regulatory deficiency to be acquired is a failure of adrenaline and noradrenaline secretion during hypoglycaemia. This defect is not because of classical autonomic neuropathy but is primarily mediated by reduced sympathetic drive. Secretion of adrenaline in response to hypoglycaemia is reduced in magnitude and occurs at a lower glucose concentration in T1DM and advanced T2DM but not those with T2DM of shorter duration (Levy et al., 1998).

2.15 Counter-regulatory deficiencies in children

As in adults, the initial response to a decline in blood glucose in children is suppression of endogenous insulin production, followed by the release of counter-regulatory hormones including glucagon. This is followed by sympatho-adrenal activation, which generates autonomic symptoms (such as pounding heart and trembling) while the cognitive dysfunction associated with neuroglycopenia underlies the development of cognitive symptoms (Matyka, 2014). There is a relative paucity of experimental studies in children, perhaps reflecting concerns from ethical committees about subjecting the developing brain to hypoglycaemia (Ryan, 2009). Glucagon secretion in adolescents, as in adults, is lost early in the disease course (median of 8 months from diagnosis) (Siafarikas et al., 2012). In children, the blood glucose levels at which counter-regulatory hormone secretion occurs will differ according to pubertal stage and level of glycaemic control (Ross et al., 2005, Jones et al., 1991).

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Compared to children without diabetes, adrenaline, cortisol and glucagon incremented to a lesser extent in children with T1DM (mean HbA1c 9.8%) (Bjorgaas et al., 1997). A more recent study of children with T1DM and better glycaemic control (mean HbA1c 7.7%) found blunted counter-regulatory responses to a modest hypoglycaemic nadir (Diabetes Research in Children Network Study et al., 2009). The mean glucose nadir was 3.3mmol/L and only one third mounted a response at >3.3mmol/L with one third mounting a response with blood glucose <3.3 mmol/L and one third exhibited no counter-regulatory response. The authors attributed this finding to hypoglycaemia associated autonomic failure (HAAF) although the hypoglycaemic stimulus may have simply have been insufficient to trigger a counter-regulatory response (Graveling et al., 2010). In children with poorly controlled T1DM (mean HbA1c 10.8%) and moderate disease duration (mean 6 years) the adrenaline increase in response to hypoglycaemia was greater than in adults with T1DM and a similar level of glycaemic control but longer duration of diabetes (mean 11.8 years); the increased duration of diabetes may have been responsible for the attenuated response seen in adults rather than the older age of the participants (Amiel et al., 1987).

During nocturnal hypoglycaemia the counter-regulatory responses are blunted. Pre-pubertal children experiencing nocturnal hypoglycaemia were shown to have significant increases in adrenaline (but not noradrenaline, cortisol or growth hormone) compared to nights when no nocturnal hypoglycaemia was observed (Matyka et al., 1999).

2.2 Detection of hypoglycaemia and utilisation of glucose by the central nervous system

2.21 Central versus peripheral glucose sensing during hypoglycaemia

Glucose sensing cells regulate glucose concentrations throughout the body. Peripherally these cells are present in the portal vein, carotid body, pancreas and gut (McCrimmon, 2008). Centrally they are mostly found in the hypothalamus and brainstem (Jensen et al., 2014, McCrimmon, 2011).

In animal studies, portal vein glucose sensing is necessary for the attenuation of counter-regulatory responses following antecedent hypoglycaemia (Matveyenko et al., 2007). However, it appears to be less important in humans in whom hormonal and symptomatic responses are unaffected by prevention of portal hypoglycaemia (Rossetti et al., 2009) and peripheral glucose sensors do not appear to be important in stimulating the counter-regulatory response to acute hypoglycaemia.

A core network of brain regions, including the hypothalamus, is recruited during hypoglycaemia (Musen et al., 2008). Sites of glucose sensing during hypoglycaemia is an area of on going debate; while the brain is known to play a key role more recently peripheral glucose sensing has been shown to be important (Cherrington, 2008). The hypothalamus and more specifically the ventromedial hypothalamus (VMH) plays a key role in glucose sensing with a two-fold increase in blood flow to the hypothalamus during hypoglycaemia (Page et al., 2009, McCrimmon, 2009). Glucose sensing neurones use glucose not as a fuel but as a signalling molecule to regulate their metabolic activity; there are two main types of glucose sensing neurones, inhibitory and excitatory (McCrimmon, 2008, McCrimmon, 2009). Glucose excited neurones increase their activity as glucose levels increase and glucose-inhibited neurones increase their activity as glucose levels fall (Levin et al., 2004). Glucose sensing neurones in the ventromedial hypothalamus (VMH) use ATP sensitive potassium (K_{ATP}) channels (similar to those found in the pancreatic beta-cell); closing these channels (using a sulfonylurea) results in suppressed counter-regulatory responses to systemic hypoglycaemia (Evans et al., 2004). Mice with knockout mutations for neuronal insulin receptors displayed less hypothalamic activation and impaired counter-regulatory response (Diggs-Andrews et al., 2010).

The dominance of a particular area in glucose sensing may change with the rate of fall of blood glucose; the brain takes a more dominant role with rapid decrements in blood glucose (Saberri et al., 2008). Nitric oxide is necessary to

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detect hypoglycaemia in the VMH and to generate the counter-regulatory response (Fioramonti et al., 2010).

A canine study illustrated the influence of the brain on counter-regulatory hormone secretion. Dogs were rendered peripherally hypoglycaemic with glucose infusions into the carotid and vertebral arteries to prevent cerebral hypoglycaemia and compared with dogs rendered hypoglycaemic both centrally and peripherally. When the cerebral perfusion was kept euglycaemic, the magnitude of hormonal responses were only 14% for adrenaline, 12% noradrenaline, 17% cortisol and 21% glucagon compared with whole body hypoglycaemia (Biggers et al., 1989). A similar study in rats found a similar magnitude of reduction by perfusing the ventromedial hypothalamic nucleus with glucose on a background of peripheral hypoglycaemia (Borg et al., 1997).

2.22 Cerebral energy metabolism during hypoglycaemia

During hypoglycaemia, brain glucose uptake falls by 22-24% in all but those with tightly controlled T1DM (Boyle et al., 1995). Human studies have shown that brain glucose uptake initially falls with hypoglycaemia but with antecedent hypoglycaemia brain glucose uptake is preserved at euglycaemic levels (Boyle et al., 1994). The process of adaptation to hypoglycaemia depends on the degree and duration of previous hypoglycaemia.

2.23 Glucose transporters

The rate-limiting step in cerebral cellular glucose metabolism is glucose transport into cells. Glucose does not freely permeate through the plasma cell membranes and therefore requires transport proteins. Glucose is transported down a concentration gradient by energy-independent facilitative glucose transporters (GLUTs) and up a concentration gradient by energy-dependent sodium-dependent glucose transporters (SGLTs). GLUT1 and GLUT3 are the main glucose transporters in the brain; GLUT1 transports glucose from the peripheral circulation into the brain (i.e. through the blood-brain barrier) and GLUT3 facilitates transport into neurones (Jensen et al., 2014, Reno et al.,

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2013). The expression of glucose transporters is to some extent determined by previous glycaemic experience with a probable increase after hypoglycaemia (Amiel, 1995, McCall et al., 1986).

2.24 Glucose concentrations in the brain during hypoglycaemia compared with euglycaemia

As the brain is unable to store or synthesise glucose in any significant quantity, a continuous supply of glucose is required from the peripheral circulation (Cryer, 2007). Glucose is the obligate fuel for cerebral metabolism under physiological conditions and the brain accounts for about 20%-25% of the total glucose utilised by the body in the resting state despite comprising only 2% of the body's mass (Berg et al., 2002, Bryant et al., 2002, Belanger et al., 2011). In children the relative proportion required by the brain is even higher, suggesting a increased vulnerability to any hypoglycaemic episodes (McCall, 2004).

Microdialysis catheters placed in the cerebral circulation allow direct measurement of cerebral extracellular fluid concentrations of glucose and lactate. Determination of ECF glucose is important as this indicates the prevailing glucose concentration that neurones will be exposed to. Table 2.2 displays this data; concentrations of cerebral ECF glucose were approximately 17% of the systemic circulation during euglycaemia with the percentage remaining unchanged during hypoglycaemia. Changes in ECF cerebral glucose lagged about 30 minutes behind that of plasma glucose; this may help protect the brain against severe hypoglycaemia (Abi-Saab et al., 2002). During euglycaemia, the cerebrospinal fluid concentration is about 50-80% that of the systemic circulation (Owen et al., 1974, Leen et al., 2012).

Table 2.2: Concentrations of plasma and cerebral glucose of conscious human subjects during sequential hyperglycaemic-hypoglycaemic clamps (Abi-Saab et al., 2002).

	Baseline	Hyperglycaemia	Hypoglycaemia
Plasma glucose (mmol/L)	5.50±0.46	11.5±1.27	3.00±0.78
Cerebral ECF glucose (mmol/L)	0.82±0.27	1.56±0.73	0.27±0.10

2.25 Cerebral blood flow during hypoglycaemia

Early studies reported variable effects of acute hypoglycaemia on cerebral blood flow with Porta *et al* (1964) reporting an increased flow (Porta et al., 1964) but two others reporting a decreased flow (Kety and Woodford, 1948, Eisenberg and Seltzer, 1962). In rat studies it has been suggested that the increase in cerebral blood flow occurs when glucose level fall below 2.0mmol/L (Choi et al., 2001). After ten minutes of hypoglycaemia (2.0mmol/L), cerebral blood flow increased by 25% in adults both with and without T1DM (Tallroth et al., 1992, Tallroth et al., 1993). This increased cerebral flow was observed in children at a higher blood glucose level than in adults (Jarjour et al., 1995). A stepped hypoglycaemic clamp was utilised to achieve the more modest hypoglycaemic stimuli of 2.8 mmol/L and 3.3 mmol/L, rather than 2.0 mmol/L used during the studies of Tallroth *et al* (1992 & 1993) (Powers et al., 1996). No change in regional cerebral blood flow was observed. Using more sophisticated measuring techniques more recent work has suggested that overall cerebral blood flow decreases slightly during hypoglycaemia (by ~7%) although the median prefrontal cortex showed increased neuronal activation (Teves et al., 2004). The more complicated picture of regional variation in cerebral blood flow has emerged with more

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sophisticated imaging techniques. Cerebral blood flow increases to the motor cortices and thalamus during hypoglycaemia (Kennan et al., 2005, Mangia et al., 2012, Bie-Olsen et al., 2009).

People with diabetes were shown to have a relatively greater uptake to the frontal cortex, especially in those with a history of severe hypoglycaemia (MacLeod et al., 1994). A subsequent study failed to show any difference in regional blood flow in those with impaired awareness of hypoglycaemia compared to normal awareness; again flow was increased to the frontal cortices and thalamus with reduced flow elsewhere (MacLeod et al., 1996).

2.26 Alternative cerebral energy sources

During euglycaemia, glucose is the obligate metabolic substrate required to maintain cerebral function, although this may not be the case during hypoglycaemia (Wahren J et al., 1999). While glucose remains the primary energy source of the brain, alternative substrates can be used (i.e. ketone bodies during fasting) (Butterworth, 1999).

The likely contribution of other energy sources (e.g. lactate) remains small although there is some evidence that people with T1DM may be better able to utilise these alternative fuel sources (Lubow et al., 2006, Mason et al., 2006). In rodent models, lactate transport during hypoglycaemia is increased by antecedent hypoglycaemia. However the concentrations achieved are insufficient to meet the metabolic demands of the brain, glucose transport is also unregulated however and this may help protect the brain against subsequent hypoglycaemia (Herzog et al., 2013).

Studies using catheters placed in the jugular artery and vein failed to show an increased uptake of lactate or pyruvate (Wahren et al., 1999). Using intracerebral microdialysis catheters, lactate concentrations in the human brain are three times that of the systemic circulation but remain unchanged during hypoglycaemia despite an increase in the systemic circulation (Abi-Saab et al., 2002). In contrast to earlier studies, using functional MRI during

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hypoglycaemia, cerebral lactate concentrations increased five-fold in people with T1DM and impaired awareness of hypoglycaemia (IAH) compared to people without diabetes (De Feyter et al., 2013).

Using magnetic resonance spectroscopy to detect metabolic changes, people with T1DM demonstrate a two-fold increase in monocarboxylic acid transport compared with healthy volunteers during acute hypoglycaemia; this up-regulation in people with previous experience of hypoglycaemia would allow better utilisation of alternative energy sources (Mason et al., 2006). The increased uptake of various free fatty acids (i.e. lactate, alanine and leucine) would not be enough to offset the energy deficit incurred by the reduction in circulating glucose experienced during cerebral hypoglycaemia (Lubow et al., 2006).

Human brain glycogen is primarily localised to the astrocytes (Wiesinger et al., 1997, McCall, 2004). The main storage sites for glycogen are liver and skeletal muscle with the accepted ratio of glycogen storage in liver/skeletal muscle/brain is 100:10:1 (Nelson et al., 1968). Because of the low glycogen content, the central nervous system has very little endogenous fuel.

More recently the role of cerebral glycogen has been re-examined. An intravenous infusion of radiolabelled with nuclear magnetic resonance spectroscopy (^{13}C NMR) allows visualisation of cerebral glycogen metabolism (Oz et al., 2007). Human cerebral glycogen content was estimated at $3.5\mu\text{mol/g}$ with a very slow turnover requiring 3-5 days for complete turnover. The very slow turnover and lack of increase with intense stimulation prompted the conclusion that cerebral glycogen is not extensively utilised under normal physiological condition, however it has subsequently been shown to act as a buffer during hypoglycaemia (Choi et al., 2003, Oz et al., 2009).

2.27 Recovery from hypoglycaemia

A reduced glucose recovery rate in people with T1DM has been shown compared to people without diabetes. This was postulated to be as a result of

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counter-regulatory deficiencies; infusion of glucagon improves the recovery rate but does not return it to normal (Lager et al., 1984). Post hypoglycaemia insulin resistance occurs up to 7-8 hours following acute hypoglycaemia; it is mediated by noradrenaline in the early phase and later by growth hormone and cortisol (Fowelin et al., 1989, Lucidi et al., 2010).

2.28 Factors which modify the counter-regulatory response

The effect of antecedent hypoglycaemia and cerebral adaptation will be discussed in chapter 4 (Sherwin, 2008).

2.3 Hypoglycaemia and cardiovascular function

2.31 Introduction

Wright and Frier (2008) have suggested that while a young healthy individual can tolerate the profound physiological effects of acute hypoglycaemia on the cardiovascular system, when these acute changes are superimposed on a diseased coronary vasculature, they may provoke myocardial ischaemia or an arrhythmia (Wright and Frier, 2008). It would now be considered potentially dangerous and unethical to subject people with established coronary heart disease to experimental hypoglycaemia, but anecdotal case reports have demonstrated a relationship between hypoglycaemia and acute vascular events and sudden death (Miura et al., 1998, Frier et al., 1995, Burke and Kearney, 1999).

2.32 Effect of hypoglycaemia on endothelial and platelet function, coagulation and fibrinolysis

During euglycaemia, insulin has been shown to reduce several key mediators of oxidative and inflammatory stress (Dandona et al., 2010b). However, during hypoglycaemia the increased activity of the sympathetic nervous system and secretion of other hormones and peptides such as the potent vasoconstrictor, endothelin, have pronounced effects on intravascular haemorrhology, coagulability and viscosity (Wright and Frier, 2008).

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Inflammatory markers such as interleukin-6, interleukin-8, tumour necrosis factor and endothelin-1 are increased during hypoglycaemia (Razavi Nematollahi et al., 2009, Wright et al., 2007). Hypoglycaemia results in platelet activation and inflammation with increased CD40 expression and high sensitivity C-reactive protein (Wright et al., 2010, Galloway et al., 2000). Increased plasma viscosity occurs during hypoglycaemia because of an increase in erythrocyte concentration, while coagulation is promoted by platelet activation and an increment in factor VIII and Von Willebrand factor. Endothelial function may be compromised during hypoglycaemia because of an increase in C-reactive protein, mobilisation and activation of neutrophils and platelet activation (Dandona et al., 2010a, Galloway et al., 2000).

Figure 2.1 indicates how these changes could promote vascular occlusion and localised tissue ischaemia leading to vascular complications. Endothelial dysfunction is an early pathological feature in the development of atherosclerosis but the degree of impairment does not always correlate with the extent of coronary arterial disease (Vita and Keaney, 2002, Wykretowicz et al., 2005). Severe endothelial dysfunction, even in the absence of obstructive coronary heart disease, is associated with an increase in cardiac events (Suwaidi et al., 2000).

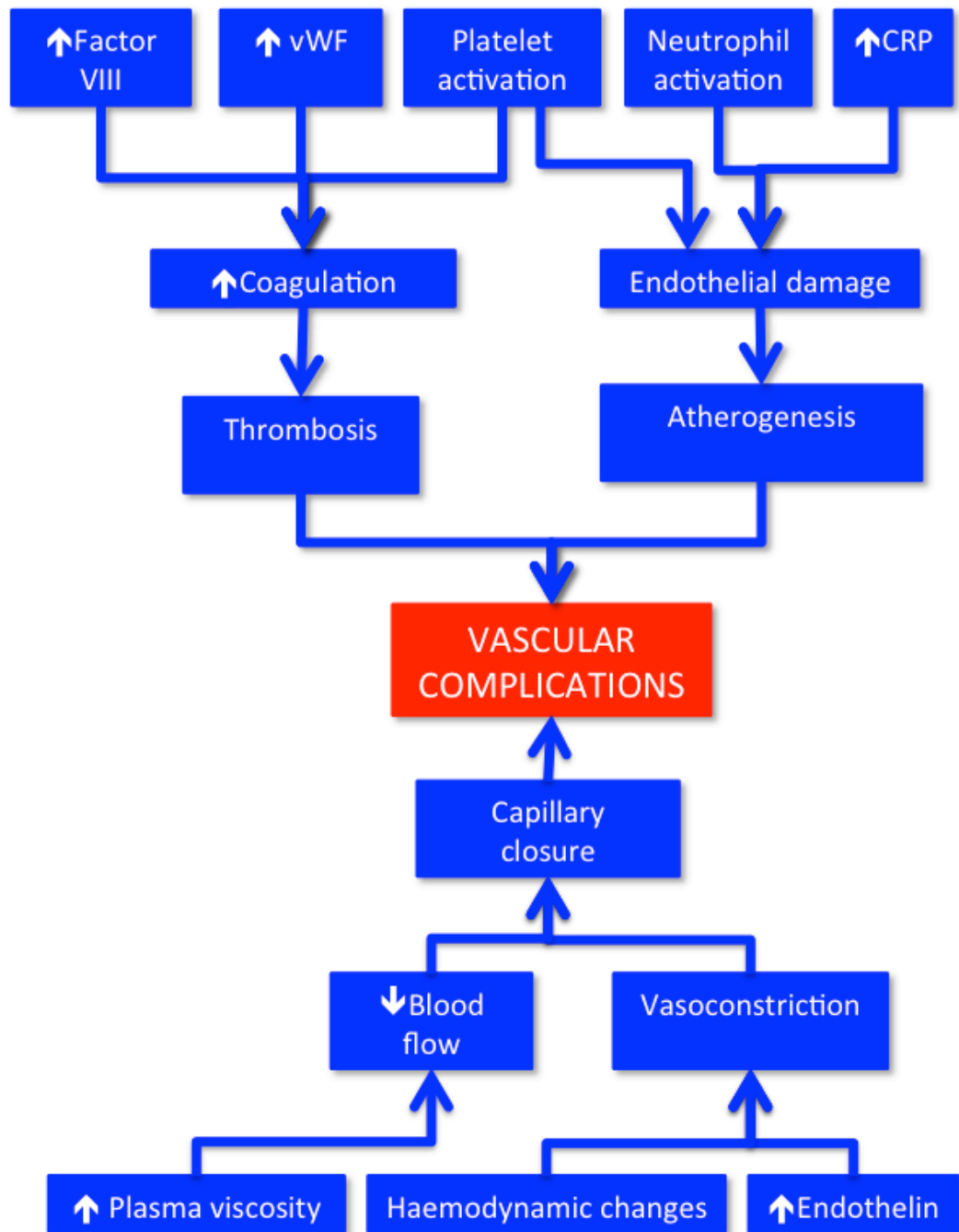
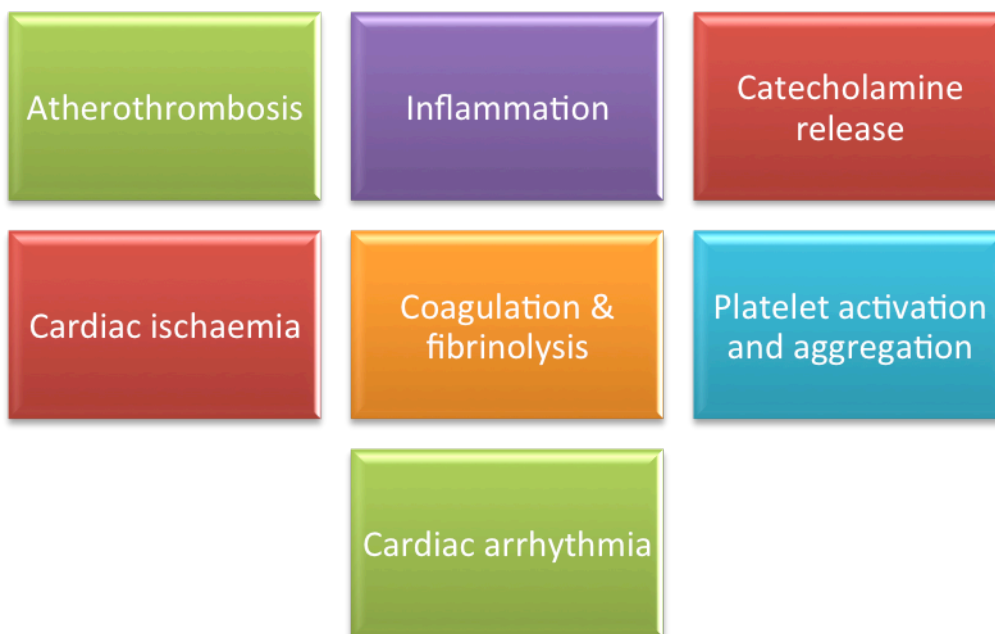


Figure 2.1: Haematological and inflammatory processes induced by hypoglycaemia that may lead to vascular complications (Wright and Frier, 2008)

2.33 Hypoglycaemia and arterial wall stiffness

People with diabetes develop arterial stiffness prematurely, with a significant increase being observed in young adults with T1DM of long duration (> 15 years), as compared with age-matched non-diabetic volunteers and those with a shorter duration of T1DM (<5 years) (Sommerfield et al., 2007). This arterial stiffness has important implications for coronary vascular flow as coronary artery filling mostly occurs during diastole. Normal elasticity of the arterial wall ensures that the reflected pressure wave from the high-pressure arterioles, generated during each myocardial contraction, returns to the heart during early diastole so increasing diastolic pressure and thereby enhancing coronary arterial perfusion (Nicols and O'Rourke, 2005). Progressive stiffening of the arterial wall results in the earlier arrival of the reflected wave during late systole, which may interfere with coronary arterial perfusion (Saito et al., 2008). The increased vascular stiffness that occurs in people with T2DM has been shown to predict cardiovascular mortality (Djaberi et al., 2008).

2.34 Hypoglycaemia and cardiac function



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Figure 2.2: Mechanisms that can adversely affect cardiovascular function during hypoglycaemia (Chow and Heller, 2012)

Mechanisms that can adversely affect cardiovascular function during hypoglycaemia are shown in Figure 2.2. Hypoglycaemia has profound effects on cardiac function but these can be difficult to distinguish from the effects of insulin *per se*. Insulin is a coronary vasodilator and has pro-inflammatory actions (Sundell et al., 2002, Dandona et al., 2007). The administration of intravenous insulin has a small, immediate effect to promote sympathetic neural activation and to increase left ventricular ejection fraction, before any fall in blood glucose occurs (Fisher et al., 1990). These changes become more pronounced with a progressive decline in blood glucose; the maximal responses coincide with the glucose nadir. Significant increments in stroke volume and cardiac output also occur during hypoglycaemia (Hilsted et al., 1984).

In an effort to separate the effects of insulin from that of hypoglycaemia, cardiac performance during a hyperinsulinaemic euglycaemic clamp was compared with performance during a hyperinsulinaemic hypoglycaemic clamp. The infusion of insulin resulted in increased left ventricular ejection fraction (LVEF) whereas hypoglycaemia resulted in a further increase in LVEF and also an increase in peak filling rate (PFR) in participants without diabetes. Participants with diabetes demonstrated an increase in LVEF and PFR with insulin but a blunted response to hypoglycaemia (Russell et al., 2001).

Myocardial blood flow (MBF) reserve is calculated as the ratio of peak MBF to resting MBF. MBF reserve is reduced during acute hypoglycaemia in adults with and without T1DM (Rana et al., 2011). The haemodynamic changes during hypoglycaemia observed in non-diabetic adults are attenuated in some people with T1DM, particularly those with strict glycaemic control (Russell et al., 2001). Hypoglycaemia has been shown using CGM and ambulatory blood pressure monitoring to increase blood pressure in “real world” studies in people with T1DM and T2DM (Feldman-Billard et al., 2010).

2.35 Can hypoglycaemia cause myocardial ischaemia?

An early case report described a 58-year-old person with diabetes who experienced angina in association with “insulin shock” (hypoglycaemia) (Turner, 1930), while in a more contemporary case, typical ECG and enzyme changes were associated with an acute coronary syndrome (ACS) that followed a massive insulin overdose and subsequent severe hypoglycaemia (Kamijo et al., 2000). Angiography demonstrated normal coronary vasculature; therefore dynamic changes in the coronary blood vessels may have caused the myocardial ischaemia.

Anecdotal case studies such as these have prompted researchers to examine the association between hypoglycaemia and cardiovascular events. Hypoglycaemia was induced in 7 people with known coronary artery disease, this precipitated angina attacks in 2 out of 7 of the participants with typical electrocardiographic changes (Strouse et al., 1932). The effect of insulin and hypoglycaemia on electrocardiographic (ECG) changes can be seen in Figure 2.3 (Egeli and Berkmen, 1960). Participants with diabetes were rendered hypoglycaemic with insulin (the lowest blood glucose was around 2.5 mmol/L) and ECG changes involving the ST segments and T waves were noted. These changes could be partly ameliorated with beta-blockade or administration of serum potassium (Robinson et al., 2003).

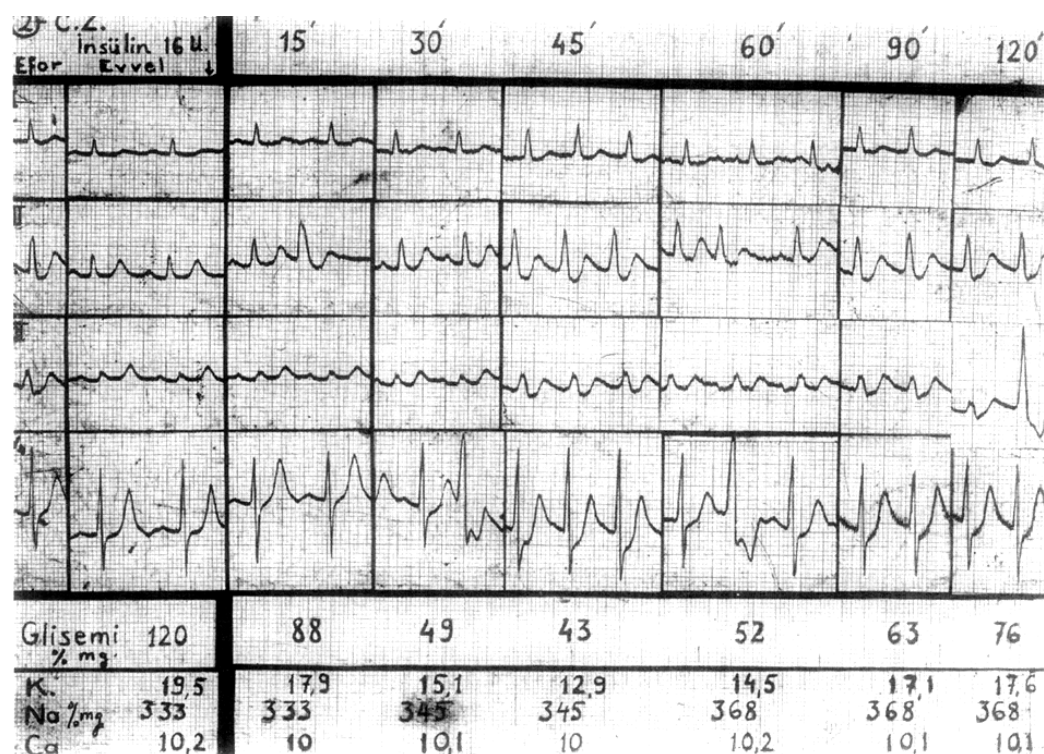


Figure 2.3: ECG alterations under the influence of insulin, maximal ST depression corresponds with the glucose nadir at 45 minutes (Egeli and Berkmen, 1960)

Ischaemic changes were noted in the ECGs of five out of six people with T2DM when they were rendered hypoglycaemic; a bradyarrhythmia occurring in one participant resulted in loss of consciousness (Lindstrom et al., 1992). Continuous blood glucose monitoring and Holter ECG monitoring were performed simultaneously in people with T2DM and known ischaemic heart disease; 54 episodes of hypoglycaemia (blood glucose <3.9mmol/L) were identified, 10 of which were accompanied by chest pain (Desouza et al., 2003). ST segment abnormalities were observed in four of the symptomatic episodes and in two episodes of asymptomatic biochemical hypoglycaemia. By contrast, one solitary episode of chest pain occurred during hyperglycaemia (blood glucose >11.1mmol/L) and none occurred during euglycaemia.

2.36 Electrolyte disturbance during hypoglycaemia

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Hypoglycaemia provokes rapid and rapidly reversible increases in serum sodium, chloride and calcium (Caduff et al., 2011). Hypoglycaemia results in a decrease in serum potassium levels; caused by both the insulin itself and the counter-regulatory secretion of adrenaline (Heller and Robinson, 2000, Petersen et al., 1982). In contrast to the other electrolytes, the recovery of serum potassium is delayed until more than 2 hours after euglycaemia has been restored (Caduff et al., 2011, DeFronzo et al., 1980).

2.37 Can hypoglycaemia result in clinically significant arrhythmia?

Hypoglycaemia may provoke an arrhythmia in 3 main ways; prolongation of the QTc interval (corrected QT interval), rise in intracellular calcium and hypokalaemia (Nordin, 2010). Hypoglycaemia has long been known to affect the electrocardiogram with delayed repolarisation being demonstrated by a prolonged QT interval (Judson and Hollander, 1956, Lee et al., 2003, Marques et al., 1997). The QT interval is dependent on heart rate and the correction method utilised may over or underestimate the actual correct QT interval using a subject specific correction formula (Christensen et al., 2010). Although the finding of a lengthened QTc interval has not been invariable, hypoglycaemia consistently reduces the T wave amplitude (Robinson et al., 2003, Koivikko et al., 2008). These ECG changes may increase the risk of arrhythmia (Robinson et al., 2004).

Ventricular tachycardia and atrial fibrillation have been reported during hypoglycaemia (Chelliah, 2000, Collier et al., 1987). Cardiac arrhythmias have been recorded during spontaneous episodes of nocturnal hypoglycaemia (Gill et al., 2009). Routine ECG screening appears to be of limited use in detecting those at risk as no correlation was shown between QTc prolongation during euglycaemia and QTc prolongation during hypoglycaemia. CGM and ambulatory ECG recording in 25 participants with T2DM demonstrated that bradycardia, atrial and ventricular ectopics were more common during hypoglycaemia (especially nocturnal hypoglycaemia); the incidence of bradycardia was increased eight fold during nocturnal hypoglycaemia compared with euglycaemia (Chow et al., 2014).

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Sudden death during sleep has been described in people with T1DM, the putative mechanism being a significant cardiac arrhythmia induced by nocturnal hypoglycaemia (Tattersall and Gill, 1991, Dahlquist and Kallen, 2005). Many of these people had no evidence of severe hypoglycaemia-induced neuronal damage at autopsy, implying that a cardiac arrhythmia had been triggered by hypoglycaemia, resulting in sudden death (Fisher and Heller, 2007). It is reassuring that despite the high frequency of nocturnal hypoglycaemia in young people with T1DM, sudden nocturnal death (“dead in bed” syndrome) is rare. However, it is possible that the presence of a genetic mutation (e.g. in a cardiac ion channel) or predisposition may be necessary for a cardiac arrhythmia to occur (Start et al., 2007). A German study of 16 adolescents with T1DM observed lengthening of QTc during hypoglycaemia in all subjects with the greatest increase recorded in the sibling of an adolescent who had died from “dead in bed” syndrome (Rothenbuhler et al., 2008).

2.38 Does previous exposure to hypoglycaemia modify the vascular risk?

Antecedent hypoglycaemia induces a reduction in baroreflex sensitivity and sympathetic response to hypotensive stress, which may predispose susceptible individuals to the development of a cardiac arrhythmia (Adler et al., 2009, Arbelaez et al., 2008). Impairment of the autonomic neural control of heart rate is associated with an increased risk of mortality (Maser and Lenhard, 2005).

2.4 Morbidity and mortality of hypoglycaemia

Compared with age-matched individuals, adults with T1DM are at substantially elevated risk of death with an almost four-fold increased risk of mortality (Soedamah-Muthu et al., 2006a). Self-reported severe hypoglycaemia increased the risk of mortality in the next five years in both T1DM and T2DM (McCoy et al., 2012). Under the age of 40, acute diabetes complications (e.g. hypoglycaemia or DKA) remain the most common cause of death for people with T1DM. Over the age of 40, cardiovascular disease accounts for more than half the cause of deaths in people with T1DM (Tu et al., 2008).

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Over 23,000 people with T1DM were followed up for between 4 to 25 years. Overall, the relative risk of death (standardised mortality ratio) was 4.0 for females and 2.7 for males (Laing et al., 1999a). Looking at the specific cause of death, hypoglycaemia was specifically attributed as the cause of death in 18% of men and 6% of women (Laing et al., 1999b). A study in Yorkshire of people with T1DM diagnosed under the age of 30 reported that 7% of deaths were attributed to hypoglycaemia (Feltbower et al., 2008). Unexpected deaths are recognised to occur during sleep in a small number of young adults with T1DM, hypoglycaemia was suspected in many of the cases (Tattersall and Gill, 1991, Weston and Gill, 1999). A recent case report revealed prolonged hypoglycaemia recorded using a CGM device prior to death (Waheed et al., 2013).

While the majority of hypoglycaemia episodes do not result in significant morbidity beyond the acute event the morbidity associated with hypoglycaemia episodes can be substantial and is further detailed in Table 2.3.

Table 2.3: Morbidity associated with severe hypoglycaemia (McAulay et al., 2001, Cryer, 2011)

Cardiovascular (Chelliah, 2000, Koivikko et al., 2008)	Neuropsychological (Carter and Taylor, 2002)	Miscellaneous
Prolongation of QT interval	Focal/generalised convulsion	Fracture of long bones/vertebrae
Atrial fibrillation	Coma	Joint dislocation
Non-sustained ventricular tachycardia	Hemiparesis; TIAs	Soft tissue injury
Silent myocardial ischaemia	Ataxia, choreoathetosis	Head injury
	Focal neurological deficits	Burns

Angina	Decortication	Hypothermia
Myocardial infarction	Cognitive impairment	Hypothermia
Sudden death	Behavioural/personality change	Road traffic accidents
	Automatism/aggressive behaviour	
	Psychosis	

2.41 Morbidity and mortality of hypoglycaemia in children

A British study found an excess mortality in children with T1DM, 83 out of 116 deaths were caused by diabetes with DKA being responsible for 69 and hypoglycaemia in 7 (Edge et al., 1999). Nine were found dead in bed with no cause proven. A Norwegian study looking at mortality in childhood onset T1DM found hypoglycaemia was responsible for 5% of deaths in early adulthood compared with 3-4% in a similar Japanese cohort (Skriverhaug et al., 2006, Morimoto et al., 2013). The Swedish Childhood Diabetes Register showed a significant excess mortality in children with T1DM (Dahlquist and Kallen, 2005). Some deaths were clearly related to diabetes with 20 having died of diabetic ketoacidosis and at least one from hypoglycaemia following alcohol intoxication. Seventeen were found deceased in bed with no cause of death found at autopsy compared with 2 of the control subjects; hypoglycaemia was considered but not proven.

In adults with T1DM nocturnal hypoglycaemia has been shown to increase arousal and disturb sleep; somnambulism (sleep walking) triggered by nocturnal hypoglycaemia has been reported (Bell, 2010, Bendtson et al., 1992). It is concerning that fairly profound (mean glucose nadir 2.0 mmol/L) and prolonged (mean 308 minutes) nocturnal hypoglycaemia did not affect sleep quality in children with T1DM (Matyka et al., 2000). Porter *et al* (1996)

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reported similar findings, in both studies sleep quality was assessed using polysomnography (Porter et al., 1996).

2.42 Neurological sequelae of hypoglycaemia

See table 2.3 for possible neurological consequences of acute hypoglycaemia. The earliest report of hypoglycaemia resulting in transient hemiparesis was published in 1928 (Ravid, 1928). Acute hypoglycaemia has been shown to affect the EEG with a decrease in alpha activity and an increase in delta and theta activities. All changes were reversible on correction of the hypoglycaemia (Hyllienmark and Brismar, 2012).

The vulnerability of different structures within the brain to hypoglycaemia appears to vary; the cerebellum is relatively spared. The hippocampus is thought to be more vulnerable and is enlarged in younger adults with a history of severe hypoglycaemia compared with sibling controls (Hershey et al., 2010). Rat studies have shown that the presence of (untreated) diabetes increases the vulnerability of the brain to hypoglycaemia related neuronal injury, particularly in the hippocampus (Bree et al., 2009).

A number of papers have reported a variety of imaging characteristics seen on MRI after severe hypoglycaemia resulting in altered consciousness level. The lesions described have varied considerably. The outcome of such patients is often poor with a high mortality rate (Witsch et al., 2012). An MRI study of term infants after neonatal hypoglycaemia found a varied pattern of injury with white matter injury not confined to the posterior regions. Early MRI findings were more useful than duration or severity of hypoglycaemia in predicting outcomes (Burns et al., 2008). In neonates with brain damage following severe hypoglycaemia, the occipital and parietal lobes were most severely affected (Yalnizoglu et al., 2007). In young children, the age at which hypoglycaemic brain injury is sustained affects the pattern of injury seen; from birth to 6 months, lesions predominantly involved the posterior white matter; between 6-22 months the basal ganglia, and after 22 months the parietal-temporal cortex (Gataullina et al., 2013).

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Using MRI to look at the structure, rather than function of the brain, has shown some differences in those exposed to hypoglycaemia. In children and adolescents with T1DM and a history of hypoglycaemia there was a reduction in grey matter volume in the left superior temporal region (Perantie et al., 2007). This region has been associated with memory. In adults with T1DM cortical atrophy was more common in those with a history of severe hypoglycaemia (Perros et al., 1997). Human subjects with T1DM will also have had significant exposure to hyperglycaemia, which may be a confounding factor.

2.43 Type 1 diabetes and cardiovascular mortality

Microvascular disease was traditionally considered to be a risk of people with T1DM while those with T2DM were thought to be at risk of developing premature macrovascular disease (Retnakaran and Zinman, 2008). However, although people with T2DM undoubtedly have an increased risk of developing premature cardiovascular disease, people with T1DM have a similar level of risk for cardiovascular disease when matched for age (Libby et al., 2005, Juutilainen et al., 2008).

Many studies examining the impact of diabetes on cardiovascular outcomes either refer to people with T2DM or fail to differentiate between different types of diabetes. The landmark study for people with T1DM was the Diabetes Control and Complications Trial (DCCT). Following 6.5 years of active treatment the intensive arm achieved a mean HBA1c of 7.4% compared with 9.1% in the control group at the cost of a three-fold elevated risk of severe hypoglycaemia (DCCT Research Group, 1993). While the risk of microvascular disease was substantially reduced with intensive control, a follow-up study showed the effect on macrovascular disease was more modest but remained significant (Nathan et al., 2005). From the age of 30, cardiovascular disease is the most common cause of death in both men and women with T1DM (Laing et al., 1999b). The risk of cardiovascular disease is substantially elevated in T1DM compared with matched controls, with hazard ratios of 3.6 in men and 7.7 in women (Soedamah-Muthu et al., 2006b).

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In a large prospective study of people with T1DM, after mean 7.3 years of follow up, self-reported severe hypoglycaemia did not increase the risk of cardiovascular disease (Gruden et al., 2012). An observational study of people with T1DM showed no evidence of a “J” shaped curve; there was no increase in vascular events with lower levels of HbA1c (Eeg-Olofsson et al., 2010).

A direct relationship between hypoglycaemia and cardiovascular events remains difficult to demonstrate as blood glucose and cardiac monitoring are seldom performed simultaneously. Speculation continues as to whether hypoglycaemia is a causative event or whether it is simply a marker of illness.

2.5 Chapter summary

The human body has a number of finely balanced mechanisms aimed at maintaining blood glucose concentration within narrow limits. Acute hypoglycaemia provokes pronounced physiological responses, the important consequences of which are to maintain the supply of glucose to the brain. A multi-layered defence system protects the normal human and their brains from hypoglycaemia; many of these defences are compromised in people with T1DM.

Evidence is accumulating that severe hypoglycaemia can provoke adverse cardiovascular outcomes such as myocardial ischaemia or cardiac arrhythmia. Clinicians should avoid the exposure of seriously ill patients to low blood glucose levels, particularly in those at high risk such as middle-aged people who have multiple cardiovascular risk factors, and in frail elderly people. With the improved survival of people with T1DM (as well as the increasing number of people with T2DM), this becomes increasingly relevant. In younger people the advent of continuous blood glucose monitoring has allowed more accurate documentation of the incidence of hypoglycaemia, particularly at night. This may permit more rational adjustment of insulin regimens to avoid hypoglycaemia and reduce the potential risk of inducing a cardiac arrhythmia.

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Chapter 3: Hypoglycaemia: Effect on cognitive function

3.1 Introduction

The profound effects of hypoglycaemia on cognitive function were recognised and described soon after the discovery of insulin (Banting et al., 1923). Cognitive function involves all aspects of thinking and intellectual activity. The effect of diabetes *per se* on cognitive function has been recently reviewed and is outwith the scope of this chapter (Kodl and Seaquist, 2008, McCrimmon et al., 2012).

3.2 Cognitive function testing during hypoglycaemia and its limitations

In early experiments hypoglycaemia was induced with intravenous boluses of insulin which led to a rapid fall and then rise in blood glucose levels (Russell and Rix-Trott, 1975). Blood glucose levels were not adequately controlled and so the hypoglycaemic stimuli varied, the glucose clamp technique solved this problem (DeFronzo et al., 1979). Numerous studies have subsequently used this technique to examine the effect of hypoglycaemia on cognitive functioning. The stepped clamp does allow multiple blood glucose concentrations to be assessed in a single experimental session but is relatively arduous for the test subject and there is some evidence that during prolonged hypoglycaemia, there may be a degree of acute adaptation (Heller and Macdonald, 1996).

Where most studies now use single-blind, euglycaemia-controlled hyperinsulinaemic clamps a number of issues remain (Inkster and Frier, 2012, Warren and Frier, 2005):

- Lack of consensus over appropriate cognitive tests for measurement of cognitive function (partly as there is no clear consensus on the cognitive processes involved with each)
- Absence of power calculations (inadequate statistical power might result in false negative or type II errors)

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- Heterogeneity of study cohorts
- Variable target blood glucose levels (most have a target blood glucose during hypoglycaemia of 2.0-3.0 mmol/L)
- Many glucose analysers utilise the glucose oxidase method; analysis of plasma produces a glucose value 10-20% higher than that measured in whole blood (Foster et al., 1978).
- It is often difficult to extrapolate experimental conditions to real life scenarios where speed of onset, duration and severity of hypoglycaemia may vary

3.21 Effect of insulin and counter-regulatory hormones

Insulin is known to cross the blood-brain barrier and enhance cognitive function (Park et al., 2000). However, insulin *per se* did not affect cognitive function during hypoglycaemia during a study of healthy volunteers infused with high levels of insulin (2.0 mUnits/kg/hr) compared with low levels of insulin (0.35 mUnits/kg/hr) (Fanelli et al., 1994). This is a point of reassurance when testing cognitive function using hyperinsulinaemic hypoglycaemic clamps.

While the blood glucose level may be “clamped”, the counter-regulatory responses alter over time with increased levels of counter-regulatory hormones but diminished symptom intensity (Kerr et al., 1991). Counter-regulatory hormones such as adrenaline can also act as cognitive enhancers themselves (McNay and Cotero, 2010). Cognitive performance during hypoglycaemia was compared against euglycaemia with an infusion of counter-regulatory hormones released during hypoglycaemia. The deterioration in cognitive function is a result of hypoglycaemia itself and not increased levels of counter-regulatory hormones (Kerr et al., 1993).

3.22 Intra- and inter-individual variation

There is considerable inter-individual variation in cognitive functioning during hypoglycaemia although intra-individual variation is less marked. Substantial

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inter-individual variation has been reported in many studies; this demonstrates the importance of comparing a participant's performance during hypoglycaemia with their own during euglycaemia (Heller and Macdonald, 1996, Gold et al., 1995a). Some commonly used cognitive function tests (e.g. paced auditory serial addition task) have high retest reliability with r values ranging between 0.69 and 0.95 (Schachinger et al., 2003). Repeated attempts at cognitive function tests are likely to improve performance through familiarity until boredom or frustrations occurs (Amiel, 1998, Gonder-Frederick et al., 1994). Whilst batteries of cognitive function tests allow testing of a bigger variety of cognitive functions, fatigue may result in a reduction in performance.

3.23 Ceiling effect

Care must be taken to avoid ceiling effects where the performance of the subjects is at or almost at the maximum achievable level. There may be an element of "cognitive reserve" which then means that any decremental condition (i.e. hypoglycaemia) does not have an appreciable effect on performance. Acute hypoglycaemia failed to induce the expected impairment of performance when completing *Raven's progressive matrices* (RPM) (McAulay et al., 2001, Raven, 1958). This is surprising as RPM is thought to be one of the best indicators of general fluid intelligence, which has a substantial association with working memory that is known to be extremely sensitive to hypoglycaemia (Marshalek et al., 1983, Ackerman et al., 2002, Deary et al., 2003). The uniformly high test scores for the RPM indicated that subjects were achieving close to maximum marks in both hypo- and euglycaemia. By using two more difficult tests (i.e. *Raven's advanced progressive matrices* and the *Alice Heim 5* test), a significant decrement in performance was then noted during hypoglycaemia (Warren et al., 2004). A further ceiling effect was demonstrated during a study of visual memory during acute hypoglycaemia (Warren et al., 2007).

3.24 Determining which particular cognitive process is being examined

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Many cognitive function tests only record the time taken and correct selection of the target object, number or letter. Many of these tests encompass a number of cognitive processes. Figure 3.1 shows the cognitive processes involved in the *letter selection* test; the time taken to complete each step was measured using scalp electrodes to detect event-related brain potentials. A sequence of coloured letters was presented, red letter G requires the right hand button and red letter N requires left hand button with all other red letters and any green letter being ignored. The event-related brain-potential (ERP) response to stimuli starts to differ from the ERP response to irrelevant stimuli (i.e. any green letter) between 120-300ms after stimulus presentation (e.g. selection negativity or SN). Response selection is measured by examining the contralateral motor cortex and subtracting any responses seen in the ipsilateral motor cortex to isolate potentials that are strictly movement related. The resulting potential is referred to as the lateralised readiness potential (LRP) and its onset latency can be assumed to reflect the time at which a unilateral motor response is selected. Hypoglycaemia increased both SN and LRP with LRP being affected to a greater extent. During the recovery period LRP continued to be affected whereas SN returned to its baseline euglycaemia level (Smid et al., 1997).

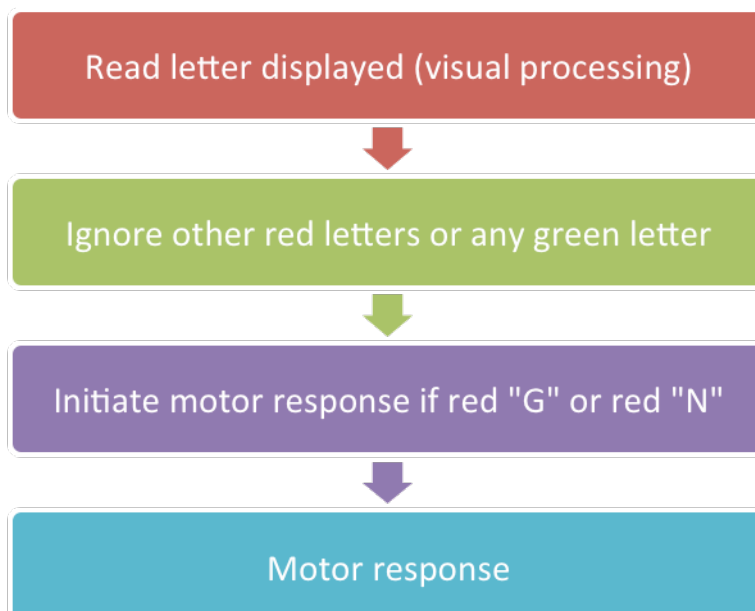


Figure 3.1: Cognitive processes involved in a letter selection test

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A more recent attempt was made to separate a reaction time test into the multiple cognitive and non-cognitive processes. The results were separated into three components, the quality of information on which a decision is made (drift rate), the critical amount of evidence that needs to be accumulated before a decision is made (boundary separation) and the time taken by non-cognitive processes. Hypoglycaemia reduced the drift rate but had no effect on the other two processes. This would indicate that hypoglycaemia affects central processing rather than the quantity of information required to make a decision or peripheral and motor processes (Geddes et al., 2010).

3.3 Onset and recovery of cognitive impairment

In adults without diabetes the threshold for the onset of cognitive impairment lies between 2.7-3.1mmol/L although occasionally reported at higher blood glucose levels (Warren and Frier, 2005). In adults without diabetes there are separate thresholds for symptoms, hormonal counter-regulation and cognitive dysfunction. This is clinically important as it allows individuals to take note of warning symptoms and implement remedial action (e.g. carbohydrate ingestion), prior to the onset of cognitive dysfunction. In healthy volunteers, the onset of hypoglycaemia was followed by immediate cognitive dysfunction although counter-regulatory and symptomatic responses were delayed by 20 minutes; this lag between cognitive dysfunction and symptomatic response is of potential clinical importance (Evans et al., 2000).

Recovery of cognitive function has been shown to lag behind the restoration of euglycaemia despite normalisation of the symptom profile and counter-regulatory response. During the recovery phase, Evans *et al* (2000) only measured cognitive function once, twenty minutes after the restoration of euglycaemia, *four choice reaction time* remained impaired whereas performance on the *Stroop* test had returned to baseline (Evans et al., 2000). A stepped hypoglycaemic clamp resulted in a fairly prolonged period of hypoglycaemia (i.e. at least 1 hour 45 minutes); once euglycaemia had been restored reaction time remained impaired for 45-75 minutes (Blackman et al., 1992). A shorter duration of hypoglycaemia (60 minutes) resulted in more

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rapid recovery of reaction time; complete recovery had occurred 40 minutes after the restoration of euglycaemia (Lindgren et al., 1996).

Following 60 minutes of hypoglycaemia (2.5 mmol/L) recovery of cognitive function in subjects with T1DM and normal awareness was examined. When analysed as a group, recovery times varied according to the cognitive task being performed; the *trail making B* task was impaired for up to 10 minutes after the restoration of euglycaemia whereas the *four choice reaction time* was impaired for up to 40 minutes. Impairment persisted for up to 75 minutes in participants with normal awareness (Zammit et al., 2008). Recovery was faster in people with T1DM than control subjects although the precise time periods are not stated (Lobmann et al., 2000).

Strachan *et al* (2000) examined recovery of cognitive function at 1.5, 9 and 30 days post severe hypoglycaemia that occurred in the community (i.e. not induced in an experimental setting), mostly in subjects with T1DM. A control group with T1DM was also examined with no history of severe hypoglycaemia in the preceding year. Although mood alteration persisted for longer, there was little evidence of a “hangover” effect of the severe hypoglycaemic episode on cognitive function by 1.5 days after the event with only 1 out of 14 cognitive tasks (i.e. block design) still affected (Strachan et al., 2000). Experimentally induced nocturnal hypoglycaemia (2.3-2.7 mmol/L for 1 hour) did not affect cognitive function during euglycaemia the next day (King et al., 1998).

3.4 How rate of descent and duration of hypoglycaemia affects cognitive function

The rate of descent into hypoglycaemia may be important. A rapid descent into hypoglycaemia in subjects with T1DM resulted in greater cognitive impairment than a slow descent (i.e. 30 minutes from 5.7 to 2.4 compared with 90 minutes), although counter-regulatory hormone release was reduced with the rapid descent (Fanelli et al., 2003). Unlike previous studies, subjects were studied in the post-prandial condition.

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The degree of cognitive impairment may be influenced by the duration of hypoglycaemia. During 120 minutes of hypoglycaemia, cognitive function started to improve towards the end. The euglycaemia arm also saw an improvement over time, although it is unclear whether this met statistical significance, and so a practice effect may have contributed to this improvement (Kerr et al., 1989). Gold *et al* (1995b) performed cognitive testing on the same subjects on 3 occasions, in a random order, at least 2 weeks apart. The participants underwent a euglycaemic clamp as a control session, a hypoglycaemic clamp with the cognitive test done immediately after the induction of hypoglycaemia and a further hypoglycaemic clamp with a delay in cognitive testing until 40 minutes after the induction of hypoglycaemia. Although hypoglycaemia predictably impaired cognitive function there was no evidence of short term cerebral adaptation (Gold et al., 1995b).

3.5 Sensitivity of different cognitive processes to hypoglycaemia

Simple cognitive tasks such as finger tapping or reaction time are not significantly affected by hypoglycaemia (Warren and Frier, 2005, Pramming et al., 1986). With many cognitive functions, accuracy is often preserved at the expense of speed. Some evidence of a differential sensitivity does exist with working memory being completely abolished during hypoglycaemia with only deterioration in short- and long-term memory (Deary et al., 2003).

3.51 Attention

Attention can be grouped into 3 major themes: alertness or vigilance (maintenance of attention performing long, boring tasks), selective attention (ability to preferentially select information from a particular source) and orientation which is responsible for engaging, moving and disengaging attention in space (Posner and Petersen, 1990). Using tests of everyday attention both visual and auditory selective attention were significantly impaired during acute hypoglycaemia in people with and without T1DM (McAulay et al., 2001, McAulay et al., 2006a).

3.52 Memory

Memory is the process of storing, encoding and retrieving information and can be sub-classified into short-term, long-term, working and sensory memory (Baddeley, 1997). Working memory is often confused with short term memory; short term memory requires the maintenance of information in the memory over a short period of time (e.g. keeping a telephone number in mind while finding the telephone) whereas working memory requires active manipulation of processing of information (e.g. calculating and adding a tip to a restaurant bill) (Drag and Bieliauskas, 2010).

Hypoglycaemia substantially disrupts memory formation and recall (Deary and Zammitt, 2014). Immediate (verbal & visual), working memory and delayed (verbal & visual) memory were all affected by acute hypoglycaemia in both subjects with and without T1DM; working and delayed memory were most susceptible to the effects of neuroglycopenia (Sommerfield et al., 2003a, Sommerfield et al., 2003b). Participants were asked to remember visual (e.g. line drawing) or verbal (e.g. list of words read aloud) lists both straight after (immediate) and after 1 hour has elapsed (delayed).

Warren *et al* (2007) separated the acquisition and recall phases of memory tasks so that only one occurred during hypoglycaemia. Both prospective memory tasks (where the learning takes places during euglycaemia with the recall during hypoglycaemia) and the delayed verbal memory (where the learning takes place during hypoglycaemia and the recall during euglycaemia) were significantly impaired (Warren et al., 2007). A further study in healthy volunteers assessed whether a period of hypoglycaemia (~60 minutes) between the learning and the recall or recognition phase can affect performance of various memory tasks. There was no difference in memory consolidation whether subjects were rendered hypoglycaemic or continued under “clamped” euglycaemia (Warren et al., 2008). The authors discuss a number of possible explanations, the sample size (n=16) may have been too small according to retrospective power calculations, the degree of hypoglycaemia may not have been low enough and the period of hypoglycaemia may have occurred too late

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(i.e. after consolidation had taken place). In summary hypoglycaemia affects both the acquisition and recall phases of memory tasks.

Functional MRI has been used to demonstrate that regional brain activation is different during working memory tasks in people with T1DM compared to those with no diabetes despite there being no difference in cognitive performance. Several brain regions were activated to a greater degree in T1DM suggesting that recruiting supplementary brain regions may be necessary to preserve cognitive performance in T1DM (Bolo et al., 2011).

3.53 Mood, emotion and motivation

Mood can be assessed in terms of tense arousal (feeling anxious or nervous rather than relaxed or calm) and energetic arousal (feeling lively and active rather than tired and sluggish). Hedonic tone (happiness versus sadness) can also be assessed. The relationship between hypoglycaemia and mood is complex. Most people report negative symptoms in association with hypoglycaemia such as an increase in “tense tiredness” with a decrease in happiness (Gold et al., 1997, Hermanns et al., 2003, Cox et al., 2002a). Hypoglycaemia resulted in a negative mood state with reduced energy levels and increased anxiety levels (McAulay et al., 2006b). A specific problem (e.g. career prospects) may be viewed significantly more negatively during hypoglycaemia (McCrimmon et al., 1999).

To examine the effect of hypoglycaemia on motivation and cognitive interference, the Dundee Stress State Questionnaire was completed before and after tests of cognitive function during acute hypoglycaemia on participants with T1DM (McAulay et al., 2006b). Hypoglycaemia decreased task relevant and increased task irrelevant interference (i.e. during hypoglycaemia subjects were more distracted by matters not relevant to the task in hand). Self-focus of attention was higher during hypoglycaemia; this refers to a state of pre-occupation and reflection.

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Nocturnal hypoglycaemia results in increased fatigue and a reduced sense of well being the following day (King et al., 1998). A recent history of spontaneous, severe hypoglycaemia (up to 30 days ago) resulted in elevated levels of anxiety and depression (Strachan et al., 2000).

3.54 Visual or auditory function

Blurring of vision and diplopia are recognised clinical features of acute hypoglycaemia (Deary and Zammitt, 2014). Visual information processing tasks and contrast sensitivity were disrupted during acute hypoglycaemia in both subjects with and without T1DM (McCrimmon et al., 1996, Ewing et al., 1998). In contrast visual acuity or stereoscopic vision was unaffected. Visual evoked potentials are detected by an electrophysiological recording method involving the placement of scalp electrodes. Electrophysiological studies have demonstrated the prolongation of visual evoked potentials (P100 and P300 latencies) during acute hypoglycaemia (Harrad et al., 1985, Blackman et al., 1990, Blackman et al., 1992).

Acute hypoglycaemia resulted in a significant deterioration in auditory temporal processing and one of three tasks of simple auditory processing (i.e. discrimination of single tone loudness) in participants with and without diabetes. Most auditory event-related potentials (AERPs) (N100, P200 and P300) were not affected by hypoglycaemia although N240 was reduced in amplitude during hypoglycaemia. In these experiments, two tones of different frequencies are delivered through earphones; participants are asked to ignore one and to count the other. The AERP waveforms from the target stimuli were recorded (McCrimmon et al., 1997, Strachan et al., 2003).

3.55 Other cognitive processes

Geddes *et al* (2008) examined the effects of acute hypoglycaemia on psychomotor function. People with T1DM were less affected than those without; psychomotor function was significantly impaired in 2 out of 7 tests in people with T1DM compared with 5 out of 7 for healthy volunteers (Geddes et

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al., 2008). The reduction in counter-regulatory hormonal response seen in those with T1DM may have been beneficial in reducing tremor and improving the fine motor control necessary for many of the tests. An earlier study using a less comprehensive test battery had suggested a similar impairment of psychomotor function (Schachinger et al., 2003).

Spatial ability is also affected during acute hypoglycaemia with 5 out of 6 tests being significantly affected (Wright et al., 2009). Peripheral nerve function (i.e. conduction velocities and amplitudes of motor action potentials) remains intact during hypoglycaemia (Strachan et al., 2001).

3.6 Cognitive function testing during hypoglycaemia in children

Neuropsychological testing is possible in the vast majority of children, even those who are relatively young. Neuropsychological testing was successfully completed in 98% of participants with T1DM aged between 3-10 (Aye et al., 2011). Relatively mild acute hypoglycaemia (3.1-3.6 mmol/L) impairs cognitive function in children using a range of cognitive tests; the *trail making* test was most affected suggesting that tests requiring planning and decision-making would be particularly impaired. Recovery of cognitive function was delayed following the restoration of euglycaemia (Ryan et al., 1990). “Naturally occurring” acute hypoglycaemic episodes (i.e. those occurring in real life rather than an experimental setting) have been shown to impair a child’s cognitive ability when asked to complete two brief cognitive function tests (mental arithmetic and *choice reaction time*) during hypoglycaemia (Gonder-Frederick et al., 2009).

3.7 Factors which may moderate cognitive effects

3.71 Gender and premorbid intelligence

Many studies have not reported on a differential effect of gender on cognitive function during hypoglycaemia (Kodl and Seaquist, 2008). Using a stepped clamp (8.9mmol/L, 5.6 mmol/L and 2.2mmolL), men were more affected than women during the *digit vigilance* test, *trail making* test, word recall and *verbal*

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fluency; these differences persisted after adjustment for confounding factors (Draeos et al., 1995). A greater deterioration in cognitive function during acute hypoglycaemia was shown in men compared to women (Gonder-Frederick et al., 1994).

It has been postulated that a higher IQ might have a protective effect on cognitive functioning during hypoglycaemia because of the concept of “cognitive reserve”. In participants without diabetes there was no difference in overall cognitive functioning during hypoglycaemia in those with high and average IQ scores; indeed one measure of cognitive function showed less of a deterioration in those with average intelligence (Gold et al., 1995a).

3.72 T1DM

The effect of having T1DM on cognitive function during hypoglycaemia is of clinical importance because of the expectation of experiencing repeated episodes of hypoglycaemia as part of everyday life. Some studies have shown a greater decrement in cognitive performance during hypoglycaemia (2.0 mmol/L) in adults with T1DM compared to controls with similar performance during euglycaemia (Wirsen et al., 1992). Many other studies have failed to show a difference between those with and without diabetes in general cognitive function during hypoglycaemia (Herold et al., 1985, Widom and Simonson, 1990, Ferguson et al., 2003). Studies examining specific cognitive processes have also shown no difference between those with and without T1DM. Functional MRI showed no difference in regional brain changes during hypoglycaemia during passive auditory and visual stimuli in subjects with T1DM compared with matched controls (Driesen et al., 2007). As noted earlier, psychomotor function is less affected by hypoglycaemia in participants with T1DM, perhaps as a result of reduced counter-regulatory hormone release with a reduction in tremor and sweating (Geddes et al., 2008).

No difference in cognitive performance during hypoglycaemia was observed in people with T1DM who had proliferative diabetic retinopathy (as a marker of microvascular disease) compared to those without (Wessels et al., 2006).

3.73 Glycaemic control and nocturnal hypoglycaemia

Glycaemic control certainly affects the blood glucose level below which counter-regulatory hormones are released. However there was no difference in cognitive function test scores with varying degrees of glycaemic control (Widom and Simonson, 1990, Maran et al., 1995).

A UK based research group failed to show an effect of nocturnal hypoglycaemia on cognitive function the following day compared with nocturnal euglycaemia in people with T1DM (King et al., 1998). Nocturnal hypoglycaemia following an episode of learning was found to reduce recall the following morning (in a euglycaemic state) in people with and without T1DM. None of the other cognitive tests revealed any effect of antecedent nocturnal hypoglycaemia although mood was significantly lower (Jauch-Chara et al., 2007). An earlier study that showed that some measures of cognitive function during hypoglycaemia showed less deterioration following nocturnal hypoglycaemia than following nocturnal euglycaemia in people with T1DM. This suggests an improvement in cognitive function during hypoglycaemia with antecedent hypoglycaemia; this could be considered as cognitive “preconditioning” (Fanelli et al., 1998b). Antecedent nocturnal hypoglycaemia may benefit selected cognitive functions during subsequent daytime hypoglycaemia, episodes of nocturnal hypoglycaemia prior to performance of the cognitive tasks appear to have little effect on cognitive function and episodes of nocturnal hypoglycaemia in between the learning and recall phase of the cognitive tasks may have a detrimental impact.

3.74 Impaired awareness of hypoglycaemia (IAH)

People with IAH experience less of a decrement in cognitive function with moderate hypoglycaemia (2.5mmol/L) and faster recovery (Zammit et al., 2008). In contrast, an earlier study had shown that subjects with IAH experienced a greater decrement in cognitive function during hypoglycaemia with a slower recovery (Gold et al., 1995c). Another study showed no differences between those with IAH and normal awareness during various

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memory tests (Warren et al., 2007). Methodological differences between the studies may account for these discrepant results. No difference in regional blood flow was seen in subjects with IAH compared to those with normal awareness (MacLeod et al., 1996). IAH is discussed further in chapter 4.

3.75 Sleep, alcohol, illness and medications

Sleep deprivation did not compound the effect of hypoglycaemia on cognitive function (reaction time and auditory evoked potentials) (Jauch-Chara et al., 2010).

The addition of alcohol induces an additional reduction in cognitive performance during hypoglycaemia but its effect is additive rather than synergistic; alcohol induces a similar decrement in cognitive function during both euglycaemia and hypoglycaemia (Cheyne et al., 2004).

Critical illness *per se* has been shown to impair subsequent cognitive function with worse performance across a range of cognitive domains. Experience of hypoglycaemia during critical illness compounds this with worsened visuospatial skills compared with matched subjects with no experience of hypoglycaemia during critical illness (Duning et al., 2010).

Detemir is an analogue, long acting insulin that is more lipophilic than human insulin and thought to cross the blood brain barrier more readily. In healthy volunteers, despite no difference in counter-regulatory responses, the onset of cognitive impairment occurred at a higher blood glucose level with detemir compared with human insulin (Rossetti et al., 2008). The cognitive dysfunction was more marked with detemir in some cognitive domains. It could be speculated that the greater cerebral insulin levels may result in a greater degree of neuroglycopenia.

Erythropoietin (or “epo”) is known for its induction of erythropoiesis but it has also been shown to increase modestly during hypoglycaemia and may have a neuroprotective effect. Low baseline levels of erythropoietin are associated with poorer cognitive function during hypoglycaemia and exogenous

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administration of erythropoietin has been shown to improve performance in choice reaction task but not other commonly used tests of higher cerebral function (i.e. *trail making* test or *Stroop* test) (Kristensen et al., 2009, Kristensen et al., 2013).

3.76 Driving

Experimental laboratory studies have demonstrated that cognitive functions critical to driving (such as attention, reaction times and hand-eye coordination) are impaired during hypoglycaemia (Warren and Frier, 2005, Inkster and Frier, 2012). The changes in visual information processing that occur during hypoglycaemia could affect visual perception under conditions of limited perceptual time and low visual contrast (poor light); this would also have a significant effect on driving performance (McCrimmon et al., 1996). Studies using a sophisticated driving simulator have shown that driving performance is affected adversely by moderate hypoglycaemia, causing problems such as inappropriate speeding or braking, ignoring road signs and traffic lights and not keeping to lanes (Cox et al., 1993, Cox et al., 2000). During simulation studies, driving *per se* required higher dextrose infusion rates to maintain normoglycaemia compared to passively watching a driving video; this increased metabolic demand in drivers will risk promoting hypoglycaemia, particularly if their blood glucose is <5.0 mmol/L (Cox et al., 2002b). Driving and diabetes is discussed further in chapter 8.

3.8 Adaptation to hypoglycaemia

The effect of antecedent hypoglycaemia on cognitive performance during subsequent hypoglycaemia has been the subject of a number of studies (see Table 3.1). The methodology of Boyle *et al* (1994) differs significantly from the other studies listed; 2 stepped hypoglycaemic clamps were performed reaching a nadir of 2.5 mmol/L separated by 56 hours of hypoglycaemia (2.9 mmol/L. Veneman *et al* (1993) found that antecedent hypoglycaemia results in improved cognitive function; in contrast Hvidberg *et al* (1996) found antecedent hypoglycaemia did not affect cognitive function during

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hypoglycaemia (both tested participants without diabetes) (Veneman et al., 1993, Hvidberg et al., 1996). Other studies have reported that cognitive functioning deteriorates less during subsequent hypoglycaemia when preceded by hypoglycaemia (Veneman et al., 1993, Mellman et al., 1994, Fruehwald-Schultes et al., 2000), whereas other have reported no effect (Lingenfelter et al., 1993, Robinson et al., 1995, Hvidberg et al., 1996). Two of these studies subjected their control groups to antecedent hypoglycaemia as well as the intervention group and so their results may be confounded (Lingenfelter et al., 1993, Robinson et al., 1995).

Lead author & year	Subjects studied	Notes	Effect
(Boyle et al., 1994)	Healthy volunteers	Stepped hypoglycaemic clamp	Blood glucose threshold for cognitive impairment was lower with antecedent hypoglycaemia
(Fanelli et al., 1998a)	T1DM	Nocturnal antecedent hypoglycaemia	Selective beneficial effect
(Fruehwald-Schultes et al., 2000)	Healthy volunteers	Antecedent hypoglycaemia on day before	Selective beneficial effect
(Hvidberg et al., 1996)	Healthy volunteers	Antecedent hypoglycaemia	No effect

		day before	
(Lingenfelter et al., 1993)	T1DM	Three short term episodes of antecedent hypoglycaemia	Selective adverse effect
(Mellman et al., 1994)	Healthy volunteers	2 hours of antecedent hypoglycaemia immediately prior	Selective beneficial effect
(Robinson et al., 1995)	Healthy volunteers	Antecedent hypoglycaemia 6 days prior	No effect
(Schultes et al., 2005)	Healthy volunteers	Two hypoglycaemic clamps on 1 st day, further clamp on next day (no euglycaemic clamp)	Some cognitive functions show adaptation to recurrent hypoglycaemia (although no control for practise effect)
(Veneman et al., 1993)	Healthy volunteers	Nocturnal antecedent hypoglycaemia	Beneficial effect

3.9 Preservation of cognitive function during hypoglycaemia

Rosenthal *et al* (2001) attempted to map out brain activation during cognitive function testing. During simpler tasks (e.g. finger tapping) blood oxygen level-

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dependent (BOLD) functional MRI imaging showed decreased BOLD signal in motor related brain areas and increased BOLD signal in left cerebellum and right frontal areas. The more complex *four choice reaction time* test elicited decreased BOLD activation in the motor and visual symptoms with an increased BOLD signal in the parietal area. The increased signals in parietal areas may be compatible with additional recruitment of brain areas involved in planning to limit cognitive dysfunction (Rosenthal et al., 2001). Anderson *et al* (2006) used the same imaging technique but employed passive visual stimulation (e.g. alternating patterns). During hypoglycaemia reduced BOLD signal was observed, particularly in the occipital areas (Anderson et al., 2006).

As discussed in chapter 2, alternative fuels to glucose can be utilised by the brain during hypoglycaemia. Ingestion of medium chain fatty acids has been shown to lessen the cognitive decrement induced by hypoglycaemia in intensively controlled participants with T1DM (Page et al., 2009).

3.10 Psychological consequences of hypoglycaemia

The effect of acute hypoglycaemia on mood and anxiety has been discussed earlier (section 3.53). Fear of hypoglycaemia (FoH) can be assessed using various validated questionnaires; one of the most widely used is the *Hypoglycemic fear survey* (HFS) or the updated version, HFS-II (Cox et al., 1987, Wild et al., 2007). This has been shown to be a reliable and valid measure of FoH in adults with T1DM using both the behaviour and worry subsections of the survey (see tables 3.2 and 3.2) (Gonder-Frederick et al., 2011).

A more recent questionnaire comprises of 15 statements that are rated using a 1-5 Likert scale. Using principal components analysis, the 15 statements can be grouped into 3 categories (fear, avoidance and interference) (Anarte Ortiz et al., 2011). Several of the diabetes specific quality of life questionnaires also include questions to assess fear of hypoglycaemia (e.g. Problems areas in diabetes or PAID) (Watkins and Connell, 2004).

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Fear of hypoglycaemia (FoH) questionnaires compose two subscales; worry and behaviour subscales (Tables 3.2 & 3.3). The worry subscale measures aspects of hypoglycaemia that can induce a fearful state and the behaviour subscale indicates behaviours that people may engage in to reduce the risk of hypoglycaemia. The two subscales allow researchers to identify whether worry actually translates into a change in behaviour (section 4.81 discusses this further). FoH provokes similar levels of anxiety to that of some of the severe long-term complications of diabetes (see Figure 3.2). Hypoglycaemia and particularly severe hypoglycaemia impairs quality of life and provokes anxiety in both people with diabetes and their diabetologists (Bohme et al., 2013, Hendrieckx et al., 2014). Fear of hypoglycaemia has been identified as the strongest barrier to exercise (Brazeau et al., 2008).

Table 3.2: Adult HFS-II Behavioural subscales item examples (Gonder-Frederick, 2013)					
Behaviour Subscale Items	Never	Rarely	Sometimes	Often	Almost always
To avoid low blood sugar and how it affects me, I ...					
Reduce my insulin when my blood sugar is low	0	1	2	3	4
Measure my blood sugar six or more times a day	0	1	2	3	4
Limit my exercise/physical activity	0	1	2	3	4
Make sure there are other people around	0	1	2	3	4
Kept my blood sugar higher than usual when doing an important task	0	1	2	3	4

Table 3.3: Adult HFS-II Worry subscales item examples (Gonder-Frederick, 2013)					
Worry Subscale Items	Never	Rarely	Sometimes	Often	Almost always
Because my blood sugar could go low, I worry about ...					
Not recognising/realising I am having a low blood sugar	0	1	2	3	4
Not having food, fruit or juice available	0	1	2	3	4
Passing out in public	0	1	2	3	4
Having a hypoglycaemic episode while alone	0	1	2	3	4
Making a mistake or having an accident	0	1	2	3	4

Following severe hypoglycaemia, 84% of people with T2DM and 64% of people with T1DM reported increased FoH (Leiter et al., 2005). FoH scores increased in people with T2DM who experience mild or severe hypoglycaemia compared with no experience of hypoglycaemia (Stargardt et al., 2009). Despite the lower incidence of hypoglycaemia in T2DM; there is an association between hypoglycaemia and depressive symptoms along with increased anxiety leading to impairment of activities of daily living such as driving and working with lower treatment satisfaction scores (Barendse et al., 2012, Alvarez Guisasola et al., 2008, Lundkvist et al., 2005).

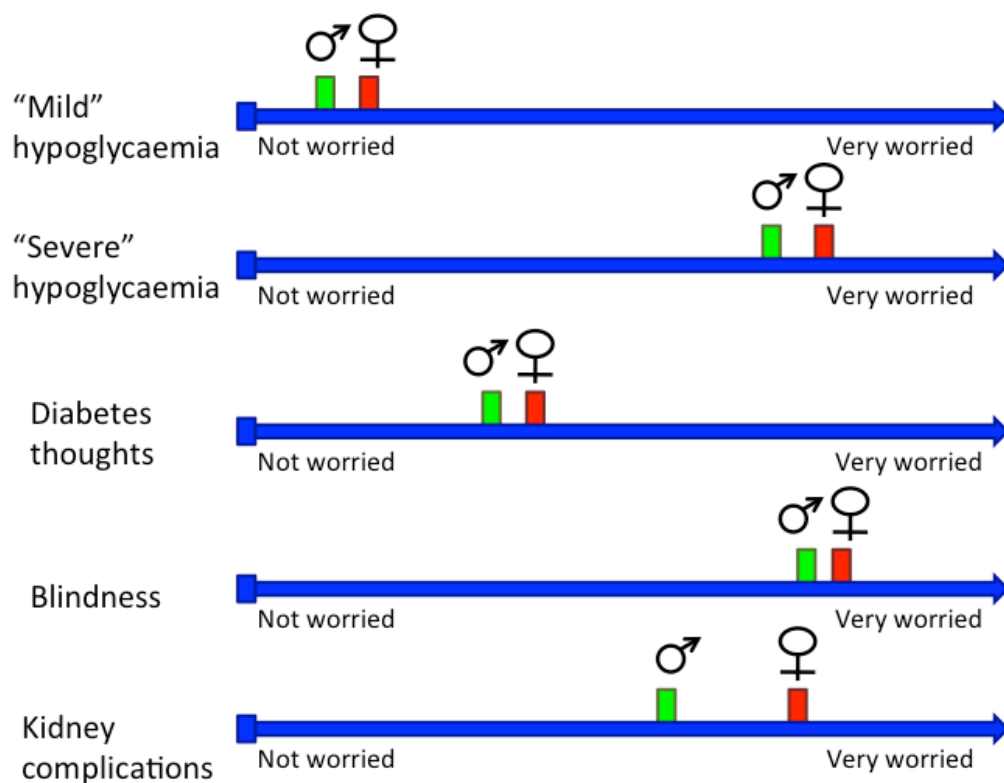


Figure 3.2: Attitudes towards different aspects of diabetes, mean values for both sexes (Pramming et al., 1991).

A large Swedish study (n=764) of people with T1DM showed that frequency of severe hypoglycaemia is the dominant factor that increases FoH, scores increased significantly if the participant had experienced one or more episode of severe hypoglycaemia in the preceding 12 months. Other significant factors included gender (women reported higher scores than men), hypoglycaemia awareness (people with impaired awareness reported higher scores) and visits to the Emergency department as a result of hypoglycaemia (scores increased after one or more visit in the previous 12 months). Participants with a higher HbA1c reported higher scores using the “aloneness” subsection of the survey that examines the fear of being alone. This may suggest that some people deliberately relax their glycaemic control to reduce the risk of hypoglycaemia when alone (Anderbro et al., 2010). A Norwegian study also reported greater FoH in women compared to men (Gjerlow et al., 2014). Despite the impact of hypoglycaemia on patient’s reported well-being; fear of hypoglycaemia scores

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have not been shown to affect clinically relevant outcomes consistently such as HbA1c (Gonder-Frederick, 2013, Wild et al., 2007).

Parents of children with T1DM report a high level of fear of hypoglycaemia (Patton et al., 2008). Parental fear of hypoglycaemia leads to poorer glycaemic control in their children with T1DM (Haugstvedt et al., 2010). Fear of hypoglycaemia and not episodes of hypoglycaemia *per se* is associated with worse quality of life for children with T1DM. Children with a greater fear of hypoglycaemia had poorer glycaemic control than those with a lower fear of hypoglycaemia (Johnson et al., 2013).

3.11 Long-term effects of hypoglycaemia on cognitive function

3.111 Effect of severe hypoglycaemia on cognitive function in adults with T1DM

While earlier case-control studies had reported that repeated severe hypoglycaemia may result in cognitive sequelae (Langan et al., 1991, Wredling et al., 1990, Lincoln et al., 1996) others did not find any association between severe recurrent hypoglycaemia and a decrement in cognitive function (Ryan et al., 1993). A history of recurrent, severe hypoglycaemia in people with T1DM for the preceding 3 years resulted in lower cognitive function test scores compared with a control group with T1DM but no history of recurrent hypoglycaemia (Wredling et al., 1990). One hundred people with T1DM were compared with 100 matched controls; verbal and performance IQ scores were modestly reduced in the people with T1DM. When a history of severe hypoglycaemia was taken into account the difference between the groups disappeared (Deary et al., 1993).

Follow up of the DCCT cohort found no association between frequency of severe hypoglycaemia and long-term cognitive dysfunction in participants allocated to the intensive treatment group despite a threefold risk of severe hypoglycaemia; the same result was found when cognitive function was re-examined a mean of 18 years after recruitment to the DCCT (Austin and

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Deary, 1999, Jacobson et al., 2007). Severe hypoglycaemia was also not associated with any decline in cognitive function in the youngest DCCT participants who were aged between 13 to 19 years at recruitment and therefore theoretically the most vulnerable (Musen et al., 2008). An accompanying editorial cautions that the DCCT cohort were healthy individuals who were all carefully selected to have a low risk of hypoglycaemia; cognitive decline would not have been expected in this cohort, even over the 18 year follow up period (Frier, 2011).

A study of adults with T1DM (n=150) failed to show a relationship between hypoglycaemia and cognitive dysfunction (Brismar et al., 2007). After 10 years of follow up, a smaller Scandinavian study compared people with T1DM who were conventionally treated (n=48) with intensive treatment (n=43). Cognitive function was unaffected by intensive treatment despite an increased number of severe hypoglycaemic episodes (Reichard et al., 1996).

3.112 Effect of severe hypoglycaemia on cognitive function in older adults with T2DM

Older age has been suggested as a potential time period during which hypoglycaemia, and in particular severe hypoglycaemia, may result in cognitive decrement. T2DM itself has also been associated with cognitive decline, particularly with regard to verbal memory (Strachan et al., 1997). This cohort of people tend to have multiple factors that may affect cognitive function (e.g. cerebrovascular disease), not just exposure to hypoglycaemia (Messier and Gagnon, 2009). Following exclusion of some of these confounding factors (i.e. duration of diabetes, vascular disease) a self-reported history of severe hypoglycaemia in a cohort of more than 1000 people with T2DM was associated with poorer cognitive ability (Aung et al., 2012). The Edinburgh type 2 diabetes study also reported that a history of previous severe hypoglycaemia either prior to recruitment or during the study was associated with impaired cognitive ability at baseline and greater cognitive decline respectively (Feinkohl et al., 2014). Cognitive function testing of a subset of the ACCORD cohort showed no difference in performance during the Digit

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Symbol Substitution test between intensive and conventional glycaemic control groups despite the increased risk of severe hypoglycaemia in the intensively treated group (Launer et al., 2011).

A history of severe hypoglycaemia has been associated with an increased risk of dementia in people with T2DM although the analysis did not adjust for several potential confounders such as subclinical cerebrovascular disease, history of alcoholism or epilepsy (Whitmer et al., 2009, Graveling and Frier, 2009). An Australian study followed a cohort of non-demented people with T2DM for 18 months, no association was found between historical hypoglycaemia and cognitive decline. Eighteen months may have been too short a follow-up period, especially as only 7.2% of the cohort reported ever experiencing severe hypoglycaemia (Bruce et al., 2009).

3.113 Effect of T1DM and severe hypoglycaemia on cognitive function in children

Biessels *et al* (2008) proposed that there are crucial periods in a person's life when the brain is most susceptible to hypoglycaemia related brain injury: early childhood (5-7 years) and older age (>60 years) (Biessels et al., 2008). During the period in between, the brain's development has slowed down or stopped and there may be a certain amount of "reserve" cognitive function. An early age of onset of T1DM is the most consistent risk factor for cognitive dysfunction in diabetes occurring at different ages (Biessels et al., 2007). A meta-analysis of 2144 children found that T1DM was associated with mildly reduced cognitive function scores in many domains compared with matched controls. Learning and memory skills were more affected in children with early onset diabetes compared with late onset (age categories unspecified) (Gaudieri et al., 2008). Early onset diabetes (<7 years) also resulted in worse cognitive function compared with diabetes onset during adolescence despite a similar duration of diabetes (Ferguson et al., 2005). A study of children aged 6-15 years with T1DM found no effect of severe hypoglycaemia on cognitive function (Wysocki et al., 2003).

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A meta-analysis of children showed that the only cognitive domain significantly affected by a history of hypoglycaemic episodes resulting in loss of consciousness or seizures was short-term verbal memory (Naguib et al., 2009). A randomised controlled trial compared intensive with conventional glycaemic control. Spatial memory performance of the intensively controlled group (n=13), with a threefold increased risk of severe hypoglycaemia, was worse than the conventional group (n=12) (Hershey et al., 1999).

Subjects with childhood onset T1DM were compared with matched controls (no difference on cognitive function testing done at baseline). After 12 years of follow up, hypoglycaemia with seizure or coma was associated with lower verbal IQ and volume reduction in thalamus (Northam et al., 2009). People with childhood onset T1DM and matched controls were followed up for 16 years. Those with early (<10 years of age) severe hypoglycaemia had poorer cognitive function although no EEG abnormalities were seen in this group (Asvold et al., 2010, Asvold et al., 2011). Figure 3.3 shows that specific cognitive domains of problem solving, verbal function and psychomotor efficiency were significantly affected by a history of early severe hypoglycaemia. Childhood onset T1DM was associated with lower verbal intelligence scores than sibling controls; exposure to severe hypoglycaemia reduced spatial intelligence and delayed recall, particularly when severe hypoglycaemia was experienced under the age of 5 (Perantie et al., 2008). Using a comprehensive battery of cognitive tests, no differences in cognitive functioning was found when children with a history of seizure or coma following hypoglycaemia were compared to matched controls (Strudwick et al., 2005).

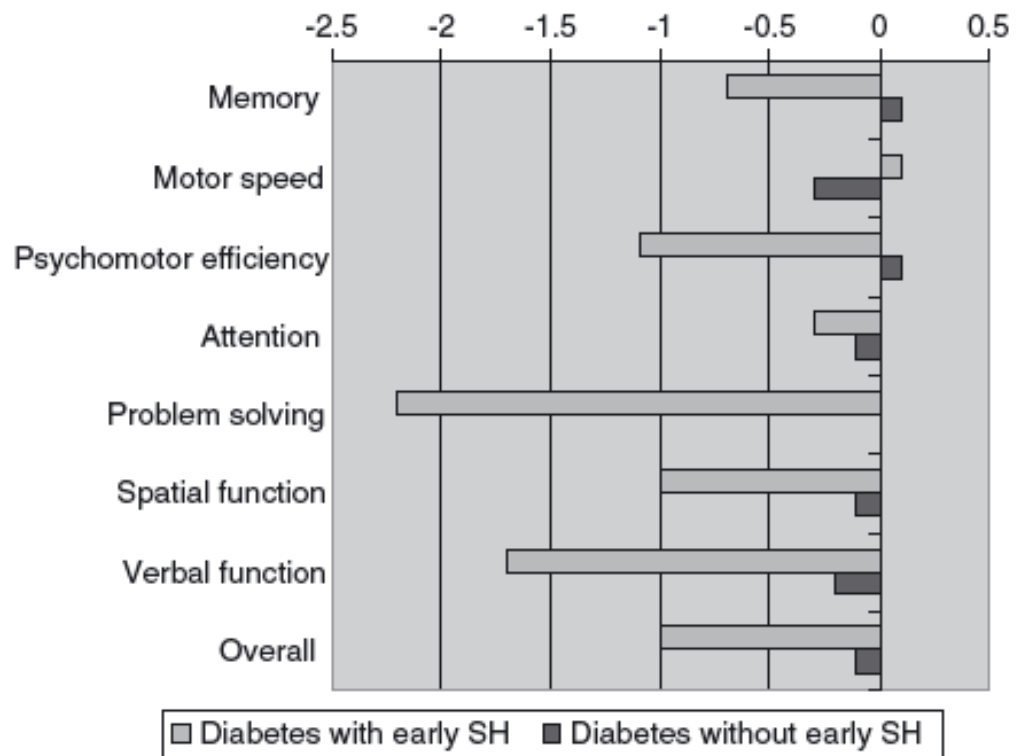


Figure 3.3: Cognitive relative scores in T1DM subjects with and without early severe hypoglycaemia. Mean cognitive relative scores (difference between diabetic subjects and matched controls, with SD controls as unit of measure) in adulthood in T1DM subjects with and without early (≤ 10 years of age). The difference in scores between T1DM subjects with and without early SH is significant for the cognitive domains problem solving (-2.2 SD; $p < 0.001$), verbal function (-1.5 SD; $p = 0.01$) and psychomotor efficiency (-1.3 SD; $p = 0.02$), and borderline significant for memory -0.8 SD; $p = 0.06$) (Asvold et al., 2010, Bjorgaas, 2012).

A meta-analysis compared studies of cognitive function in young adults with T1DM with matched controls. Compared with people without T1DM, people with T1DM experienced significant lower performance on the following cognitive domains: intelligence, speed of information processing, psychomotor efficiency, visual and sustained attention, cognitive flexibility and visual perception. Although these differences were significant the effects sizes were small to moderate (0.3-0.7). Reduced cognitive performance appeared to be

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associated with the presence of microvascular complications but not with hypoglycaemia or poor glycaemic control (Brands et al., 2005).

Children who had been admitted to paediatric intensive care and treated with an intensive insulin regimen were compared with those who had received standard glycaemic regimen. Cognitive function testing was performed a median 3.9 years after randomisation, no decrement in cognitive function was observed with some areas of improved performance such as motor coordination and cognitive flexibility (Mesotten et al., 2012).

3.12 Chapter summary

The effects of acute hypoglycaemia on general cognitive function has been recognised since the first people administered insulin experienced “insulin shocks” or hypoglycaemic episodes. Conducting tests of specific cognitive functions in an experimental setting is a complex task with many potential pitfalls. However, acute hypoglycaemia undoubtedly affects many cognitive domains with the performance of more complex tasks being preferentially affected. The disrupted cognitive functioning is of clinical relevance because of the impact on the performance of many daily tasks. Hypoglycaemia also has negative effects on mood and anxiety levels that may result in an impaired quality of life.

Most studies looking for long-term cognitive decline in young to middle-aged adults with T1DM have failed to find an association with severe hypoglycaemia. However young children or older adults may be more vulnerable to the effects of severe hypoglycaemia. Younger children with T1DM have specific defects in various cognitive domains when compared to matched controls. Whether T1DM *per se* has an impact on cognitive function or whether it is affected solely as a result of hypoglycaemia remains unclear.

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Chapter 4: Impaired awareness of hypoglycaemia

4.1 Introduction

Impaired awareness of hypoglycaemia (IAH) is an acquired complication of insulin therapy, which affects people with T1DM and insulin-treated T2DM, whereby the ability to perceive the onset of hypoglycaemia becomes diminished or absent (Graveling and Frier, 2010b). Deficiencies of the counter-regulatory hormonal responses to hypoglycaemia usually co-exist. The development of IAH and counter-regulatory failure greatly increases the risk of severe hypoglycaemia. Scoring systems have been developed that can be used in the clinical setting and assist with identification of this group of individuals at risk of severe hypoglycaemia. The mainstay of treatment of IAH is the scrupulous avoidance of hypoglycaemia.

People with T1DM are often less aware of hypoglycaemia, when blood glucose was clamped at 2.5 mmol/L, 9 out of 10 participants without diabetes were aware that they were hypoglycaemia compared to 4 out of 15 participants with T1DM (Heller et al., 1987b). More than one third of episodes of severe hypoglycaemia that occur during waking hours are not accompanied by warning symptoms (DCCT, 1991), and many people with insulin-treated diabetes develop a syndrome with a spectrum of severity in which their ability to identify the onset of hypoglycaemia becomes progressively impaired. “Impaired awareness of hypoglycaemia” (IAH) is a preferable nomenclature to the widely used “hypoglycaemia unawareness”, which suggests total loss of the symptomatic warning response that is seldom observed in clinical practice. IAH is an acquired complication of insulin treatment *per se*, in which the perception of the onset of hypoglycaemia becomes diminished or absent.

4.2 First reports of impaired awareness of hypoglycaemia

In 1922, very shortly after insulin was first used to treat diabetes, Elliot Joslin observed that hypoglycaemia could occur without warning symptoms (Joslin et al., 1922). Fredrick Banting in his 1925 Nobel Laureate lecture stated, “the

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level at which hypoglycaemic symptoms occur, is slightly higher in the diabetic with marked hyperglycaemia ... As a patient becomes accustomed to a normal blood glucose, the threshold of these reactions, becomes lower.” (Sherwin, 2008).

“Experience has shown that the severity of symptoms is not always proportional to the degree of hypoglycemia” (Maddock and Krall, 1953)

Maddock and Trimble reported a number of cases where the warning symptoms of hypoglycaemia had been lost (Maddock and Trimble, 1928). R.D. Lawrence commented that changes in the symptomatology of hypoglycaemia often occur after years of insulin treatment; after 5-10 years of treatment autonomic symptoms are sometimes lost during hypoglycaemia with the person proceeding directly to experiencing neuroglycopenic symptoms (Lawrence, 1941). A 1956 paper reported one of the first systematic studies of a cohort of such people with T1DM who had lost their warning symptoms of hypoglycaemia. A prolonged duration of diabetes with a mean duration of diabetes of 18 years in the 116 people studied. The recommended treatment was dietary modification with between meal snacks, frequent urine glucose testing and regular medical supervision (Balodimos and Foot, 1959).

“I used to have hunger, sweating, tremor, or blurring of vision; (I) knew therefore that a reaction was coming, and I had time to do something about it. Lately some (or all) reactions come on without my usual or any other warning” (Balodimos and Foot, 1959)

4.3 Impaired defences against hypoglycaemia in T1DM

In normal health, when blood glucose falls to a level that may compromise cognitive function, glucose counter-regulation is initiated (Figure 4.1). Counter-regulation has been previously discussed in Chapter 2 and is triggered when blood glucose declines below the lower end of the normal range and is preceded by suppression of endogenous insulin secretion. Hyperinsulinaemia

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frequently occurs in people with T1DM and persists in the presence of low blood glucose due exogenous insulin administration.

Glucagon and adrenaline (epinephrine) are the most important counter-regulatory hormones to acute hypoglycaemia. In people with T1DM the glucagon response to hypoglycaemia rapidly declines and is lost within five years of diagnosis (Gerich et al., 1973). The adrenomedullary secretion of adrenaline (epinephrine) becomes important when these early defensive mechanisms are compromised (de Galan et al., 2006b). In people with T1DM who are C-peptide negative, loss of endogenous insulin-secretory capacity and the glucagon response to hypoglycaemia underlie the four-fold increase in risk of severe hypoglycaemia (Mühlhauser et al., 1998).

With time, sympatho-adrenal activation becomes critical for protection of the brain from hypoglycaemia. One consequence is the generation of autonomic symptoms, the intensity of which is heightened by the secretion of catecholamines. Unfortunately, antecedent hypoglycaemia attenuates adrenaline release and moves the glycaemic threshold for its secretion to a lower blood glucose level, which both increases the risk of hypoglycaemia and reduces the intensity of symptoms generated during hypoglycaemia (Davis and Shamoon, 1991). Reduced cortisol secretion also appears to contribute to counter-regulatory failure (Davis et al., 1996).

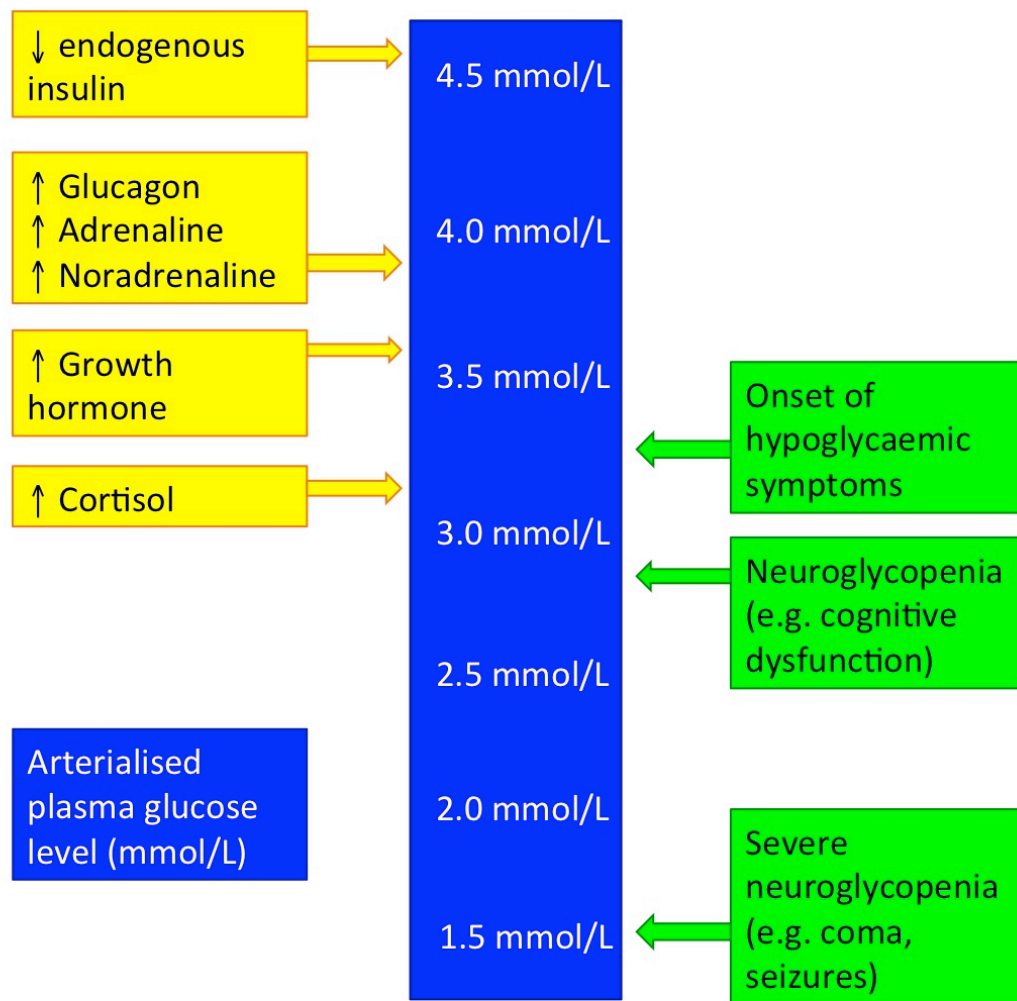


Figure 4.1: Glycaemic thresholds for counter-regulatory hormone release and clinical features of hypoglycaemia (de Galan et al., 2006b, Mitrakou et al., 1991, Schwartz et al., 1987)

Recurrent hypoglycaemia increasingly impairs the normal defences against hypoglycaemia and diminishes the ability to detect hypoglycaemia (i.e. hypoglycaemia begets hypoglycaemia). This phenomenon of progressive counter-regulatory failure and loss of awareness of symptoms of hypoglycaemia, which co-exist in T1DM (Ryder et al., 1990) has been attributed to adverse effects of exposure to recurrent hypoglycaemia on central autonomic centres, which then fail to respond effectively to a fall in blood glucose. Cryer has called this syndrome “Hypoglycaemia Associated Autonomic Failure (HAAF) and it is thought to result from a failure of

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hypoglycaemia and improved by scrupulous avoidance of hypoglycaemia, in contrast to autonomic neuropathy which, once established, is a permanent complication that progresses in severity (Cryer, 2004).

In people with IAH, adaptation of the brain occurs, shifting the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal secretion, and the onset of cognitive impairment to lower blood glucose levels, so that more profound hypoglycaemia is required to provoke these responses (Frier, 2014). It is debatable as to whether this is an adaptive or maladaptive response. Various mechanisms have been shown to cause this effect, including exposure to antecedent hypoglycaemia, recurrent hypoglycaemia and strict glycaemic control. As a consequence of the increasingly diminished (and eventually non-existent) interval between the onset of warning symptoms of hypoglycaemia and the development of significant neuroglycopenia, people with IAH have a much greater risk of developing severe hypoglycaemia (Gold et al., 1994). By contrast, people with poor glycaemic control re-set their glycaemic thresholds upwards, i.e. they mount a counter-regulatory response and experience symptoms of hypoglycaemia at higher blood glucose levels than those with good control, often within a hyperglycaemic range (Boyle et al., 1988). Thus symptomatic responses are initiated at elevated blood glucose levels, which is termed “relative hypoglycaemia” (Workgroup on Hypoglycemia, 2005). Interestingly, the glycaemic thresholds of people with T2DM who have good glycaemic control but are not treated with insulin are set at levels above those of non-diabetic individuals and people with T1DM (Segel et al., 2002, Spyer et al., 2000). This may have a protective effect against the development of severe hypoglycaemia.

4.4 Glucose sensing

This is discussed in section 2.2. It is not yet known if glucose sensors in the brain can become irreversibly damaged in adults who have suffered from longstanding IAH.

4.5 Neuroimaging studies

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The effect of hypoglycaemia on the brain can be directly visualised with neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Both imaging techniques show similar changes in regional blood flow during hypoglycaemia (Arbelaez et al., 2013). Baseline regional cerebral blood flow (measured using SPECT during euglycaemia) in the pre-frontal cortex was relatively increased in people with diabetes and particularly those with a history of severe hypoglycaemia (MacLeod et al., 1994b).

PET can be used to examine whole brain and regional changes in glucose metabolism. While animal models have indicated that antecedent hypoglycaemia increases glucose transport from blood to brain, thus allowing the brain to extract glucose more efficiently, this has not been shown in humans using PET (Segel et al., 2001). Global brain glucose content falls during acute hypoglycaemia in people with T1DM with and without IAH. However, the relative glucose metabolic rate is higher in those with normal awareness implying that increased cortical activation may be involved in awareness of hypoglycaemia (Bingham et al., 2005).

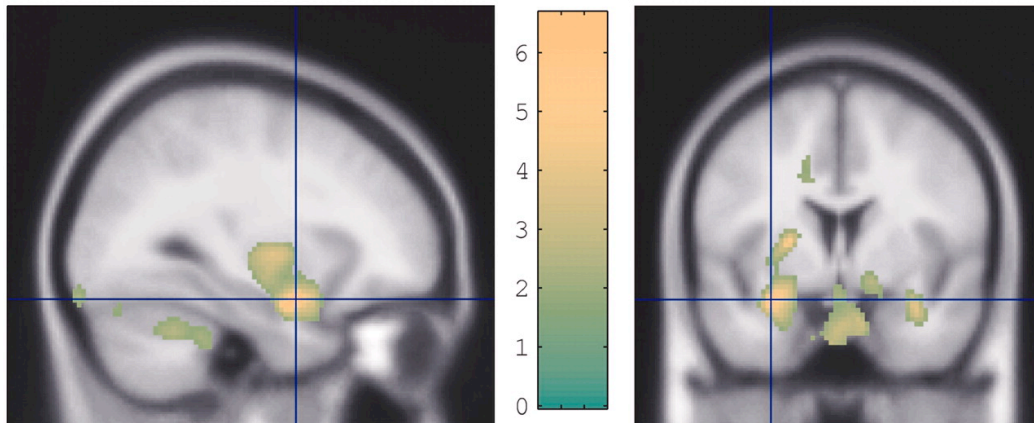
Studies of regional brain activation have identified key areas involved in glucose homeostasis and thus give insight into the pathophysiology underlying hypoglycaemia awareness. Both PET and fMRI show similar changes in regional blood flow during hypoglycaemia with increases in the thalamus, medial prefrontal cortex and globus pallidum in healthy volunteers in comparison with euglycaemia (Arbelaez et al., 2013). It is postulated that these areas might be involved in the physiological and symptomatic response to hypoglycaemia.

Antecedent hypoglycaemia was induced in healthy adults to replicate a state of counter-regulatory failure; subsequent hypoglycaemia resulted in increased activity of the dorsal midline thalamus, thought to have an inhibitory role in reducing counter-regulatory responses following antecedent hypoglycaemia (Arbelaez et al., 2008). Using functional MRI during hypoglycaemia (2.8 mmol/L), the expected increase in thalamic uptake is blunted in people with

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well-controlled T1DM in comparison to healthy adults; this may be responsible for their reduced epinephrine secretion in comparison to healthy adults (Mangia et al., 2012). Using PET, glucose uptake during hypoglycaemia by the ventromedial hypothalamus was reduced in people with IAH compared to those with normal awareness (Cranston et al., 2001).

A



B

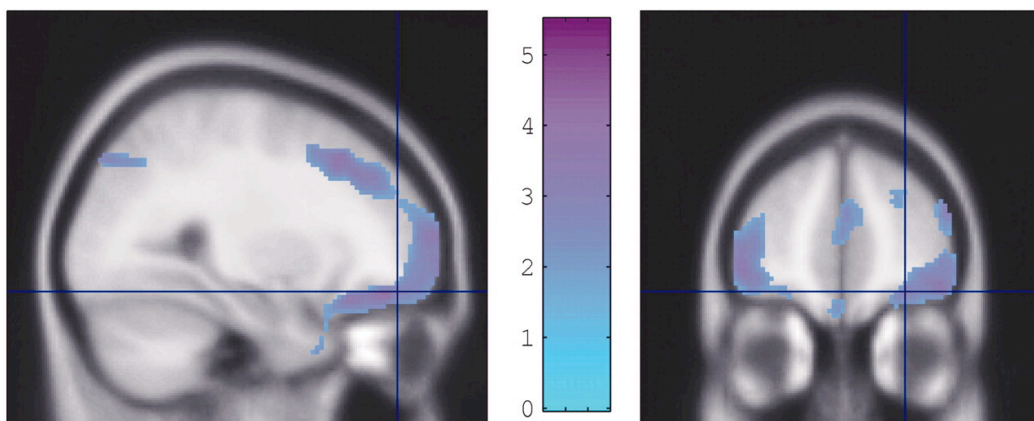


Figure 4.3: Cerebral correlates of unawareness (Dunn et al., 2007)

A: Regions where aware subjects show relatively greater uptake with hypoglycaemia than unaware subjects, showing amygdala, cerebellum, and brainstem regions.

B: Regions where aware subjects show relatively lower uptake than unaware subjects with hypoglycaemia showing right lateral orbital-frontal cortex.

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Activation of the amygdala is thought to be an unpleasant subjective experience associated with fear and anxiety. During acute hypoglycaemia, [¹⁸F]-fluorodeoxyglucose PET scanning showed greater activation in the amygdala in people with normal hypoglycaemia awareness compared to those with IAH (see Figure 5.3) (Dunn et al., 2007). These regional changes in people with IAH can be considered to be an example of “stress sensitisation”, whereby repeated exposure to a specific stress results in a reduced response. In contrast, a relative increase in activation was observed in the lateral orbitofrontal cortex during hypoglycaemia in people with IAH; activation of these areas is thought to reduce appetite and limit an appreciation of danger associated with hypoglycaemia (Figure 4.3) (Dunn et al., 2007).

4.6 Factors which modulate the counter-regulatory response and awareness of hypoglycaemia

The pathogenesis of counter-regulatory failure is likely to be multifactorial and remains unclear with a number of hypotheses having been proposed (de Galan et al., 2006b, Cryer, 2013). Even among healthy individuals without diabetes there is significant variation in the glycaemic thresholds below which a counter-regulatory response is triggered (Vea et al., 1992). People categorised as unaware experience symptoms and mount a counter-regulatory response at a lower blood glucose level than those with intact awareness; for example adrenaline secretion in those with unawareness was triggered at 2.8mmol/L compared with 3.9 mmol/L in those with intact awareness (Mokan et al., 1994).

The contribution of the adrenergic nervous system to this impaired counter-regulatory response has been assessed using the non-selective alpha-blocker phentolamine and the non-selective beta agonist propranolol during the preceding episode of hypoglycaemia. During subsequent (next day) hypoglycaemia the expected amelioration of the counter-regulatory response that was observed in the control population was not seen for adrenaline, noradrenaline and growth hormone. Cortisol, glucagon and pancreatic polypeptide concentrations were reduced as expected with no effect seen from the preceding adrenergic blockade (Ramanathan and Cryer, 2011). Prior

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infusion of adrenaline did not affect the release of counter-regulatory hormones during hypoglycaemia (de Galan et al., 2003). A cortisol infusion to produce levels of plasma cortisol typically seen during hypoglycaemia has been shown to impair counter-regulatory hormone release during subsequent hypoglycaemia (Bao et al., 2009, Davis et al., 1996).

Oral ingestion of carbohydrate prior to the induction of hypoglycaemia initially blunts the counter-regulatory response but after 90 minutes of hypoglycaemia, adrenaline and noradrenaline increased to levels above the control arm (Ertl et al., 2008) unlike an earlier study which found no difference (Heptulla et al., 2001).

4.61 Antecedent hypoglycaemia

In participants without diabetes, sustained mild hypoglycaemia of 60 minutes duration with a glucose of 3.0mmol/L has been shown to reduce symptomatic awareness despite counter-regulatory hormones remaining elevated (Kerr et al., 1989). A similar picture was seen in participants with T1DM at the end of 90 minutes of hypoglycaemia (mean glucose = 2.8mmol/L) (Kerr et al., 1991).

Antecedent hypoglycaemia has been shown in rigorously designed clamp studies to reduce the counter-regulatory response to subsequent hypoglycaemic episodes, adrenaline secretion is mostly reliably affected. This was initially shown in healthy volunteers but has also been demonstrated in those with T1DM and T2DM (Adler et al., 2009, Heller and Cryer, 1991, Dagogo-Jack et al., 1993, Davis and Shamoan, 1991). The degree of antecedent hypoglycaemia affects which counter-regulatory hormones are affected and to what degree (Amiel, 2009). Antecedent hypoglycaemia has also been shown to reduce number of symptomatic episodes of hypoglycaemia following the experimental period suggesting a reduction in hypoglycaemia awareness (Ovalle et al., 1998).

Duration of antecedent hypoglycaemia was examined with two episodes of antecedent hypoglycaemia lasting 5 minutes each compared with two episodes

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lasting 30 minutes or 120 minutes. There were no significant differences of the counter-regulatory response to subsequent hypoglycaemia with the differing duration of antecedent hypoglycaemia although hypoglycaemic symptoms were only significantly blunted by the 30 minute or 120 minute duration of antecedent hypoglycaemia (Davis et al., 2000b).

George *et al* (1995) purportedly examined whether the effect of antecedent hypoglycaemia is prolonged comparing counter-regulatory responses during hypoglycaemia 2 days after the initial episode compared with 7 days after. Due attention to the study design is beneficial; the (30 minute) episode of hypoglycaemia after 2 days may have affected the counter-regulatory responses during hypoglycaemia after 7 days and was thus acknowledged as a potential confounder (George et al., 1995).

While antecedent hypoglycaemia is known to attenuate the counter-regulatory response, antecedent hyperglycaemia does not have the same opposite effect as might be expected (Fanelli et al., 1995).

4.62 Intensive glycaemic control

Intensive glycaemic control (mean HbA1c 8.1-8.3%) considerably blunts the counter-regulatory response to hypoglycaemia compared to those measured during periods of poorer glycaemic control (mean HbA1c 11.2-14.6%) (Jones et al., 1997, Simonson et al., 1985).

4.63 Type and route of insulin administration

Claims in the 1980s that human insulin can cause impaired awareness of hypoglycaemia in contrast to animal insulins (Berger et al., 1989) were not substantiated by extensive research, and a subsequent meta-analysis and Cochrane review have shown no difference in the frequencies of severe hypoglycaemia or in IAH between the use of human and animal insulins (Airey et al., 2000, Richter and Neises, 2005).

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Peripheral versus portal administration of insulin has differing effects on the release of various counter-regulatory hormones. Adrenaline and noradrenaline are unaffected, whereas glucagon and growth hormone undergo a greater increment when insulin is infused peripherally rather than via pancreatic insulin secretion (portal) using intravenous tolbutamide. It is probably significant that despite similar peripheral glucose concentrations, peripheral insulin concentrations were approximately 50% greater due to the first pass hepatic extraction of portal insulin (Lewis et al., 1999).

4.64 Autonomic neuropathy

While classical autonomic neuropathy is not primarily responsible for the reduction in counter-regulatory responses during hypoglycaemia, its presence does diminish counter-regulatory secretion in otherwise similarly matched people with T1DM (Meyer et al., 1998).

4.65 Age

Age has been suggested as a potential modifier of awareness of hypoglycaemia. Men without diabetes aged 65-80 had lower symptom scores with hypoglycaemia than those aged 24-49 years (Brierley et al., 1995). Men with T1DM aged 60-70 were less likely to be aware of hypoglycaemia than those aged 22-26 during a glucose clamp study (Matyka et al., 1997).

4.66 Gender

A reduction in the amplitude of counter-regulatory hormonal secretion is seen in women in comparison with men (Fanelli et al., 1994, Davis et al., 2000c). Post-menopausal women on HRT were compared to those not taking HRT with a male control group. Counter-regulatory responses were significantly diminished in the group taking HRT compared with both men and those not taking HRT. The counter regulatory responses of the male group and women not taking HRT were broadly similar with only a difference in glucagon secretion. This would suggest that oestrogen is the hormone responsible for this sexual dimorphism (Sandoval et al., 2003). Oestrogen is also known to

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antagonise the effects of growth hormone; women on oral contraceptives (OCP) have higher growth hormone levels than those not taking OCPs (Rickenlund et al., 2010). During hypoglycaemia in healthy women, oral contraceptive use resulted in significant elevations in growth hormone that may help improve awareness of hypoglycaemia (Friedrich et al., 2012).

4.67 Posture

Posture affects appreciation of hypoglycaemia. Standing increases the early awareness of hypoglycaemia with a greater increase in symptom scores and counter regulatory hormones. During prolonged hypoglycaemia, the symptom score difference was lost although counter regulatory hormones remained elevated (Robinson et al., 1994).

4.68 Type 2 diabetes

Type 2 diabetes is a heterogeneous disease state ranging from diet controlled T2DM to insulin requiring T2DM of long duration. Participants on oral hypoglycaemic therapy with well controlled T2DM of mean 46 months disease duration have similar counter-regulatory responses to healthy volunteers (Heller et al., 1987a). A direct comparison of those with T2DM on oral hypoglycaemic therapy compared with T1DM of similar disease duration (mean 8-9 years) showed an intact glucagon response for those with T2DM. Counter-regulatory hormones were released in greater quantity and at a higher glucose threshold in T2DM than those with T1DM (Levy et al., 1998). Six months of intensive glycaemic control resulted in a mean HbA1c 6.7% compared with a baseline mean HbA1c of 10.2%. Intensive glycaemic control resulted in a general reduction in counter-regulatory hormone release during hypoglycaemia, both with and without preceding hypoglycaemia (Davis et al., 2009).

4.7 Definition and prevalence of IAH

The lack of an acceptable clinical definition of IAH has hindered accurate ascertainment of the prevalence of IAH and research into this condition.

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“Awareness” of hypoglycaemia and its progressive impairment represent a continuum ranging from normal perception of the onset of hypoglycaemia to complete inability to detect its onset (Frier, 2014). For the purposes of developing a clinical scoring system, awareness of hypoglycaemia was arbitrarily divided into normal, “partial” and “absent” awareness, where “partial” represented diminution of the ability to perceive the onset of hypoglycaemia, but without total absence of a symptomatic response (Gold et al., 1994, Clarke et al., 1995). Partial and absent awareness of hypoglycaemia combined was present in 25% of a group of 302 people with T1DM (Hepburn et al., 1990), which was consistent with other surveys in which the syndrome was not precisely defined (Gerich et al., 1991) and more recently the syndrome of IAH was identified in 19.5% of a randomly selected cohort of 518 people with T1DM attending a secondary care diabetes clinic (Geddes et al., 2008). Using the Gold questionnaire the prevalence of IAH was found to be similar at 17% of a Norwegian cohort of people with T1DM (median diabetes duration 21 years) (Olsen et al., 2014).

IAH is less common in people with insulin-treated T2DM with an estimated incidence of 8-10% (Henderson et al., 2003, Schopman et al., 2010). The extent to which IAH affects people treated with insulin secretagogues such as sulfonylurea therapy is not known. Although IAH affects a smaller proportion of people with insulin-treated T2DM, in view of the number of people now affected by T2DM on a global basis, this clinical problem will have a greater impact than is currently appreciated.

4.8 Risk factors for IAH

Factors that influence the awareness of hypoglycaemia are shown in table 4.1 although this is not an exhaustive list. Many episodes of severe hypoglycaemia are under-reported by people with IAH. Furthermore, if blood glucose monitoring is infrequent, many episodes of asymptomatic (or biochemical) hypoglycaemia are not detected. Major risk factors that are associated with the development of IAH in T1DM include increasing age and duration of diabetes and strict glycaemic control (Geddes et al., 2008, Pedersen-Bjergaard et al.,

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2004). The prevalence of IAH increases from 3% in those with a diabetes duration of 2-9 years to 28% for those with a diabetes duration ≥ 30 years (Olsen et al., 2014). An early insulin pump study showed an impressive reduction in HbA1c from a mean of 11.2% to 8.1% with 4-8 months of insulin pump therapy; however a significant reduction in counter-regulatory hormone release was also noted along with an increased frequency of hypoglycaemia (Simonson et al., 1985).

Table 4.1: Factors influencing awareness of hypoglycaemia (Frier, 2014)	
Internal	External
Physiological <ul style="list-style-type: none"> • Recent glycaemic control • Degree of neuroglycopenia • Symptom intensity/sensitivity 	Drugs <ul style="list-style-type: none"> • Beta-blockers (non-selective) • Hypnotics, tranquillisers • Alcohol
Psychological <ul style="list-style-type: none"> • Focused attention • Congruence; denial • Competing explanations 	Environmental <ul style="list-style-type: none"> • Posture • Distraction
Education <ul style="list-style-type: none"> • Knowledge • Symptom belief 	

4.81 Behavioural factors

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People with T1DM who have IAH are less likely to adhere to therapeutic decisions (e.g. following a suggested management plan following a diabetes clinic consultation) (Smith et al., 2009). Graveling and Frier highlighted two earlier studies that are consistent with this observation (Graveling and Frier, 2010a). In a 12-month prospective study of the incidence of severe hypoglycaemia in 60 people with T1DM (29 with IAH), people with IAH worried more about hypoglycaemia than those with normal awareness, but failed to modify their behaviour to avoid hypoglycaemia despite recording a significantly greater fear of hypoglycaemia on the worry subscale of the *Hypoglycaemia Fear Survey* (section 3.10 discusses fear of hypoglycaemia) (Cox et al., 1987, Gold et al., 1994).

A larger study of 305 people with T1DM, 111 of whom had IAH, found that increased worry of hypoglycaemia was exhibited by the people with IAH, although again they made no attempt to modify their behaviour to either prevent, avoid or correct hypoglycaemia with any greater frequency or vigilance than the people who had normal awareness (Hepburn et al., 1994). Qualitative research using structured interview in 17 people with IAH identified that 13 of the group were not particularly concerned regarding their lack of awareness (Rogers et al., 2012). Three themes emerged:

- 1) Normalising hypoglycaemia unawareness: IAH was not viewed as a problem, rather as a normal part of having diabetes
- 2) Underestimating the effect of hypoglycaemia on activities of daily living: Some participants felt they could function normally with a blood glucose <3.0 mmol/L
- 3) Avoiding the “sick role”: Participants felt treating hypoglycaemia in the absence of symptoms was unnecessary and wanted to “get on with life”

It is unclear whether people who develop IAH have a particular personality type, or whether their behaviour and approach to self-management are influenced by exposure to recurrent severe hypoglycaemia. The role of personality on the behavioural responses to hypoglycaemia merits further

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investigation, and people with IAH may require psychological counselling to help them modify management of their diabetes.

4.82 Genetic factors

Genetic predisposition to hypoglycaemia unawareness is now being examined. The Gly16 variant of the beta adrenoceptor was thought to result in hypoglycaemia unawareness through chronic stimulation of the beta-adrenoceptor resulting in desensitisation. In healthy adults antecedent hypoglycaemia did not affect beta-adrenoceptor sensitivity in homozygotes for Gly16 but increased it in homozygotes for arginine 16 homozygosity (Schouwenberg et al., 2011). Hypoglycaemia unawareness (determined using the Clarke method) is increased 3.4 fold in those with T1DM who are homozygotes for Gly16 (Schouwenberg et al., 2008).

4.83 Medications

Any medication that affects the counter-regulatory response to hypoglycaemia could potentially affect hypoglycaemia awareness. Theoretically beta-blockers should reduce counter-regulation and diminish the intensity of symptoms that are adrenergically-mediated by suppressing adrenoceptor responses. In effect, selective beta-blockers do not appear to have any significant clinical effect. Glucose clamp experiments showed that the threshold for autonomic symptoms was shifted to a lower blood glucose level while neuroglycopenic symptoms and cognitive function were unaffected (Hirsch et al., 1991). During moderate hypoglycaemia, both selective and non-selective beta-blockers failed to modify awareness or symptom intensity during hypoglycaemia (Kerr et al., 1990b). Beta-blockers have not been shown to increase the risk of severe hypoglycaemia although one study reported that usage of non-selective beta-blockers was associated with an increased risk of severe hypoglycaemia (ter Braak et al., 2000, Morris et al., 1997, Thamer et al., 1999). In summary, beta-blockers may modify symptomatology (and in particular increase diaphoresis) but do not appear to increase the risk of severe hypoglycaemia (Sawicki and Siebenhofer, 2001).

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Despite some case reports suggesting a reduction in symptom intensity during hypoglycaemia, a glucose clamp study, in which non-depressed, non-diabetic subjects were given fluoxetine, demonstrated that counter-regulatory hormone release was increased, but with no concurrent change in symptom scores (Briscoe et al., 2008).

4.9 Clinical assessment of IAH

Glucose clamp studies have been used to determine awareness of hypoglycaemia (Mokan et al., 1994) and to demonstrate the hierarchy of responses that occur as blood glucose declines. Autonomic symptoms occur before neuroglycopenic symptoms, with a difference of around 0.5 mmol/L between the thresholds at which they are generated (Schwartz et al., 1987, Mitrakou et al., 1991). However, this artificial and controlled experimental setting bears little relationship to everyday life with its myriad distractions, and this small threshold difference is unlikely to be detected by affected individuals (Hepburn et al., 1991a, Cox et al., 1993). The most useful method of identifying impaired awareness of hypoglycaemia and its importance to the individual is to take a careful clinical history. People with T1DM who state that they have IAH are generally correct (Clarke et al., 1995).

A structured questionnaire of hypoglycaemia experience has been developed to confirm the clinical history (Clarke et al., 1995), while a simpler method employs a single question and asks the person with diabetes to score their awareness on a 7 point Likert scale, where a low score represents normal awareness and a high score designates loss of awareness (Gold et al., 1994). To be utilised effectively the participant must have experienced hypoglycaemia on at least one occasion in the preceding year, and for reasons explained below, the answers must be based on experience of hypoglycaemia that occurs during waking hours. These two questionnaires display good concordance in the adult population (Geddes et al., 2007). A third method from Denmark (Pedersen-Bjergaard et al., 2001), which has attempted to relate symptomatic awareness to subjective experience generally over-estimates the frequency of IAH, with almost two thirds of people with T1DM being described as having this

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problem, which is not consistent with clinical experience (Geddes et al., 2007). A revised, trichotomised version of this method that subdivided the participants into three groups: “aware”, “intermediate” and “impaired”, improved concordance with the two established methods (Høi-Hansen et al., 2009), but the terminology used in the Danish method is open to misinterpretation. Use of a non-validated assessment of hypoglycaemia awareness failed to show any of the expected differences (i.e. tighter glycaemic control, longer duration of diabetes) between the aware and non-aware groups (Berlin et al., 2005).

In both the Clarke and Gold methods a degree of uncertainty exists regarding assessment in the middle range, equivalent to a score of 3 in both scales. It is unclear if people with this score have definite IAH, and whether they represent people with partial loss of awareness who have yet to progress to expression of the full-blown syndrome. Longitudinal cohort studies would help determine the natural history of this condition.

The semantics of IAH present difficulties and translation of the Clarke and Gold methods into languages other than English may introduce anomalies. The method of Clarke et al (1995) has been validated by a Dutch study that also utilised prospective blood glucose monitoring and glucose clamps to assess hypoglycaemia awareness (Janssen et al., 2000).

IAH is associated with a 2 to 6 fold higher frequency of asymptomatic biochemical hypoglycaemia (capillary blood glucose < 3.5 mmol/L) (Gold et al., 1994, Geddes et al., 2008, Schopman et al., 2011). Continuous glucose monitoring (CGM) has demonstrated that much hypoglycaemia remains undetected and has suggested that asymptomatic biochemical events are fourfold higher in people with IAH compared to those with normal awareness (Kubiak et al., 2004, Giménez et al., 2009). However, despite an increased risk of severe hypoglycaemia and evidence of more hypoglycaemia during prospective self-monitoring of capillary blood glucose, retrospective blood glucose analysis of CGM records for up to 72 hours of monitoring failed to identify those with IAH, who had a similar frequency, duration and severity of biochemical hypoglycaemia as those with normal awareness. At the time of

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this particular study the technology was not sufficiently sensitive to reliably identify the presence of this syndrome (Choudhary et al., 2010), but increasingly sophisticated CGM technology may improve detection by this approach.

4.10 Morbidity and mortality associated with IAH

Section 2.4 discusses the morbidity and mortality associated with hypoglycaemia. Severe hypoglycaemia may result in many serious forms of morbidity including seizure, coma, fractures and joint dislocation and cardiac arrhythmias, and is occasionally fatal. However, although these problems are more frequent in people with IAH the frequencies of these morbidities associated with severe hypoglycaemia have not been formally estimated. People who have impaired awareness of hypoglycaemia have a much greater risk of severe hypoglycaemia, up to six fold (Gold et al., 1994, Choudhary et al., 2010). A history of hypoglycaemia unawareness was reported in more than half (51%) of people who had suffered a hypoglycaemic coma in the past year compared with 21% of those with no history of severe hypoglycaemia (ter Braak et al., 2000).

The strict glycaemic control required during the management of T1DM during pregnancy and the increased frequency of hypoglycaemia may result in the development of IAH. Pregnant women with diabetes are subject to hypoglycaemia-induced morbidity, particularly in the first trimester, but there is no evidence that this harms the foetus (Gold and Pearson, 2007).

Preclinical markers of atherosclerosis have been shown to be present to a greater extent in people with T1DM and IAH compared to those with normal awareness. As well as the expected higher incidence of hypoglycaemia subjects with IAH had significantly greater carotid and femoral intima-media thickness and reduced flow-mediated brachial dilatation (Gimenez et al., 2011).

4.11 Effect of alcohol, sleep, exercise and distraction on awareness of hypoglycaemia

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Alcohol is an important risk factor for hypoglycaemia (Potter et al., 1982). The clinical features of hypoglycaemia can be mistaken for those of alcohol intoxication which may delay appropriate treatment of the hypoglycaemic episode. The risk of hypoglycaemia also extends into the next day following alcohol ingestion the evening before (Richardson et al., 2005b). Despite increased counter-regulatory responses in those who had consumed alcohol compared with those who had not, during experimental hypoglycaemia, those who had consumed alcohol were less likely to recognise that they were hypoglycaemic (2 out of 15 versus 11 out of 15 respectively) (Kerr et al., 1990a).

Exercise is a recognised risk factor for hypoglycaemia (see chapter 1.61). Antecedent exercise blunts the counter-regulatory response to subsequent hypoglycaemia in both healthy adults and those with T1DM (Galassetti et al., 2001a, Galassetti et al., 2003). Counter-regulatory responses to exercise following antecedent hypoglycaemia are also blunted which may mask any subsequent hypoglycaemia occurring during the exercise period (Davis et al., 2000a). Therefore both exercise and hypoglycaemia have similar blunting effects on counter-regulatory hormone release (Sandoval et al., 2006).

Differing intensities of antecedent exercise have similar effects on counter-regulatory hormone release to subsequent hypoglycaemia although gender specific differences are observed with greater blunting of glucagon, adrenaline and noradrenaline release in men (Sandoval et al., 2004, Galassetti et al., 2001b). In participants with T1DM, clamping blood glucose levels at 3.9, 3.3 or 2.8 mmol/L induced progressively greater blunting of counter-regulatory responses with each decrement in blood glucose level (Galassetti et al., 2006).

Sleep is a physiological state where warning symptoms of hypoglycaemia are usually absent and presents a particular problem to people with T1DM as many severe hypoglycaemic episodes occur during sleep (DCCT, 1991, Jauch-Chara and Schultes, 2010). Symptomatic responses to hypoglycaemia are diminished in the supine posture (Hirsch et al., 1991) and the plasma adrenaline response is also lower when lying down (Robinson et al., 1994). Hypoglycaemia in

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healthy adults during sleep decreases the glucose level below which a counter-regulatory response is triggered compared to when they are awake (Gais et al., 2003). When hypoglycaemia occurs during sleep in people with T1DM counter-regulatory responses, particularly the release of catecholamines, are markedly attenuated compared with responses when awake (Banarer and Cryer, 2003, Jones et al., 1998). Adults with T1DM experienced less disruption to their quality of sleep during hypoglycaemia, spending 77% of the time asleep in comparison to 26% in non-diabetic participants (Banarer and Cryer, 2003). During hypoglycaemia only 1 person out of 16 with T1DM awoke during hypoglycaemia in comparison to 10 out of 16 of those without diabetes (Schultes et al., 2007). Unrecognised nocturnal hypoglycaemia presents a possible explanation why people with T1DM develop IAH, by modifying glycaemic thresholds to subsequent hypoglycaemia (Veneman et al., 1993).

Driving simulator studies have shown that people with T1DM whose symptomatic awareness is not impaired are often unaware of the onset of cognitive dysfunction while modest hypoglycaemia is being induced and fail to take corrective action (Cox et al., 2000). Participants failed to recognise both deterioration in their driving performance and their current hypoglycaemic status, this may be partly attributable to distraction. People who are distracted by a stressful event (i.e. preparing and giving a speech) report lower symptom intensity scores during acute hypoglycaemia despite greater counter-regulatory hormonal release (Pohl et al., 1998).

4.12 Effect of IAH on cognitive function

The effect of hypoglycaemia on cognitive function is discussed in chapter 3. People with IAH often state that they do not experience any cognitive impairment during hypoglycaemia and are capable of carrying out the usual activities of daily living even though they may be exposed to frequent asymptomatic hypoglycaemia. It is sometimes difficult to convince some people with IAH both of the scale of the problem and the imperative to avoid hypoglycaemia wherever possible, especially when consultations with

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specialists tend to focus on the necessity of attaining good glycaemic control (Rogers et al., 2012). However, most people with this syndrome are fully cognisant of the dangers that it imposes, and the threat to retaining their driving licence and some forms of employment.

The evidence for the effect of acute hypoglycaemia on cognitive function is conflicting. The glycaemic threshold for cognitive dysfunction is re-set at a lower blood glucose level, in the same way as those for generation of symptoms and the stimulation of counter-regulatory hormonal secretion (Hepburn et al., 1991b, Mookan et al., 1994). Zammitt *et al* (2008) reported that cognitive function is less affected during moderate hypoglycaemia and recovery is quicker in people with IAH compared to people with normal awareness and T1DM (Zammitt et al., 2008). Other studies have also demonstrated that cognitive dysfunction occurs at lower blood glucose levels in those with IAH compared to those with normal awareness or people without diabetes (Fanelli et al., 1993, Mookan et al., 1994). In contrast, people with IAH have been shown to perform less well on a limited number of cognitive function tests applied during both euglycaemia and hypoglycaemia (Hepburn et al., 1991b). More profound cognitive dysfunction during acute hypoglycaemia was observed in those with IAH compared to those with normal awareness (Gold et al., 1995).

The long-term effects of exposure to repeated episodes of hypoglycaemia are discussed in chapter 3.11. Exposure of the brain to repeated episodes of hypoglycaemia over many years in people with T1DM had no apparent effect on long-term cognitive function in the DCCT/EDIC study (Jacobson et al., 2007). People with T1DM and a history of severe hypoglycaemia had greater cognitive impairment than those with no history of severe hypoglycaemia (MacLeod et al., 1994a). Few studies have examined the long-term effects on cognitive function in people who have developed impaired awareness of hypoglycaemia, which is associated with a very much high frequency of severe hypoglycaemia (Gold et al., 1994, Geddes et al., 2008). Animal studies have shown that antecedent moderate hypoglycaemia can protect the brain against

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subsequent severe hypoglycaemia with evidence of less neuronal damage (Puente et al., 2010). While people with IAH may develop a lesser degree of cognitive impairment during mild acute hypoglycaemia, because profound neuroglycopenia is a more common occurrence, it seems likely that this will be detrimental to cognitive function in the long term.

4.13 Management of IAH

The mainstay of treatment of IAH is the complete avoidance of hypoglycaemia, which is of course very difficult to achieve. Reducing the frequency of hypoglycaemia can be attempted by various measures as shown in table 4.2. Hypoglycaemia awareness can be restored by scrupulous avoidance of hypoglycaemia, although this may be at the cost of jeopardising glycaemic control (Cranston et al., 1994, Fritsche et al., 2001). An Italian study demonstrated an improvement in counter-regulatory response after six months of strict avoidance of hypoglycaemia reduced the frequency of hypoglycaemia from 20 episodes to 2 episodes per participant, per month (Fanelli et al., 1997). Hypoglycaemia avoidance can lead to a significant improvement in hypoglycaemia symptom scores during exposure to subsequent hypoglycaemia (Fritsche et al., 2001).

Table 4.2: Treatment strategies for people with IAH (Frier, 2007)

- Frequent blood glucose monitoring (including nocturnal measurements)
- Avoid blood glucose values < 4.0mmol/L
- Revise blood glucose targets upwards (e.g. pre-prandial target 6.0-12.0 mmol/L & bedtime > 8.0 mmol/L)
- Avoid HbA1c being within non-diabetic range
- Use predominantly short-acting insulins (basal bolus regimen; CSII; insulin analogues)

- Regular snacks between meals and at bedtime, containing unrefined carbohydrate
- Appropriate additional carbohydrate consumption and/or insulin dose adjustment before exercise
- Learn to identify subtle neuroglycopenic cues to low blood glucose

4.131 Hypoglycaemia avoidance programmes

Long-term effectiveness of these hypoglycaemia avoidance programmes was demonstrated in a small cohort (n=4) three years after a period of hypoglycaemia avoidance for three months. During hypoglycaemia, the symptom scores remained higher than baseline but less than those achieved immediately after the period of hypoglycaemia avoidance (Dagogo-Jack et al., 1999). Hypoglycaemia avoidance programmes are labour intensive for both patient and clinician as they tend to require frequent monitoring of blood glucose including measurements at night; the frequent insulin dose adjustments may take months to implement (Heller, 2008). The HYPOcompass study is described in more detail in section 4.132, the education programme reinforced 4 key points:

- Never delay hypoglycaemia treatment
- Recognise personalised times of increase risk
- Detect subtle symptoms
- Confirm low glucose levels through regular self monitoring; particularly for nocturnal hypoglycaemia

Despite the improvement in symptom scores, deficient counter-regulatory hormonal responses to subsequent hypoglycaemia are relatively unaffected (Dagogo-Jack et al., 1994, Fritsche et al., 2001) although a more recent study

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reported increased adrenaline secretion to hypoglycaemia following a six month intervention study aimed at hypoglycaemia avoidance (Leelarathna et al., 2013). This illustrates a divergence between continuing subnormal counter-regulatory response and an improvement in symptomatic responses, which suggests that other factors are probably important in promoting the symptomatic recovery.

4.132 CSII or CGM as adjuncts in the management of IAH

The recent HYPOcompass study was a multifactorial randomised controlled trial comparing multiple daily injection therapy with CSII and conventional SMBG with real time CGM in people with T1DM and IAH. No reduction in hypoglycaemia awareness was seen when comparing CSII with multiple daily injection therapy or real time CGM with conventional SMBG (Little et al., 2014).

Substitution of nocturnal continuous subcutaneous insulin infusion (CSII) for isophane (NPH) insulin at bedtime resulted in a lower frequency of hypoglycaemia. Warning symptoms and counter-regulatory responses were improved during subsequent acute hypoglycaemia (Kanc et al., 1998). CSII was used for 24 months in a cohort in which 95% had established IAH and had experienced two or more episodes of severe hypoglycaemia in the preceding two years. The participants reported fewer episodes of severe hypoglycaemia, an improved quality of life, unchanged glycaemic control and an improved symptomatic response to experimentally-induced hypoglycaemia (Giménez et al., 2010).

Real time CGM has been trialled as a “glucose alert” system. Adolescents with IAH were randomised to CGM or usual care for 4 weeks, although rates of hypoglycaemia were not reported, the CGM group exhibited an increased counter-regulatory response to hypoglycaemia at the end of the study period (Ly et al., 2011).

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Over six months an Australian study of people with T1DM and IAH (assessed using the Clarke method) compared standard CSII with CSII in combination with CGM the latter utilising an automated low glucose suspend feature. The combination treatment was shown to reduce hypoglycaemia requiring third party assistance (9.5 events versus 34.2 events per 100 patient months in the intervention group and control group respectively) and hypoglycaemia resulting in coma or seizure (0 over six months compared with 6 events over the same time period) (Ly et al., 2013). The intervention group therefore received two interventions compared with the control group, i.e. CGM and low glucose suspend. This study demonstrated that CGM with a low glucose suspend feature can reduce hypoglycaemia in targeted patient populations.

4.133 Diabetes treatment regimens

One potential advantage of long-acting insulin analogues is their association with a lower rate of nocturnal hypoglycaemia (Horvath et al., 2007). Hypoglycaemia induced by insulin detemir generated higher symptom scores when compared with human insulin although the difference in total symptom scores only just achieved significance ($p=0.048$) and the study was not blinded to insulin type (Tschritter et al., 2009).

Administration of bolus doses of glucagon at times of impending hypoglycaemia lowered the frequency of hypoglycaemia (Castle et al., 2010). Islet cell transplantation resulted in a decline in prevalence of IAH from 87% before transplantation to 13% post-transplantation; the blood glucose threshold that was required to trigger symptoms of hypoglycaemia increased from 2.3 mmol/L to 3.2 mmol/L (Leitão et al., 2008).

4.134 Other medications

Although it has been suggested that people with IAH may have reduced sensitivity to beta agonists, one study has shown that beta-adrenoceptor sensitivity is preserved (De Galan et al., 2006a). Beta agonists (e.g. terbutaline) have been shown to significantly reduce nocturnal hypoglycaemia

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at the cost of inducing morning hyperglycaemia (Raju et al., 2006, Cooperberg et al., 2008). Beta agonists have therefore been suggested as possible therapeutic options (De Galan et al., 2006c).

Caffeine has been shown to augment symptom intensity and improve counter-regulatory responses (Kerr et al., 1993). A double-blind, placebo controlled study using CGM showed that caffeine reduces the total duration of nocturnal hypoglycaemia; the 250mg of caffeine used is equivalent to the mean daily caffeine intake in the UK (Richardson et al., 2005a). Functional MRI shows 250mg of caffeine can restore regional brain activation normally lost during acute hypoglycaemia (Rosenthal et al., 2007). However, the daily doses required may not make this a practical proposition in treating people with IAH.

Infusion of the opioid antagonist (naloxone) during antecedent hypoglycaemia has been shown to restore counter-regulatory responses to subsequent hypoglycaemia to normal levels in healthy adults (Leu et al., 2009, Vele et al., 2011). Naloxone infusion also prevents the blunting of counter-regulatory responses to subsequent hypoglycaemia seen with antecedent exercise (Milman et al., 2012).

4.14 Chapter Summary

Impaired awareness of hypoglycaemia is an acquired syndrome associated with the use of insulin and exposure to hypoglycaemia that is common in people with T1DM and is observed less frequently in insulin-treated T2DM. It should be defined by the loss of ability to perceive the onset of hypoglycaemia, which is usually manifested by a reduced intensity and number of symptoms and a change in symptom profile. Asymptomatic biochemical hypoglycaemia occurs more frequently and people with established IAH have a much higher risk of developing severe hypoglycaemia.

In those affected, cognitive dysfunction is less pronounced during acute hypoglycaemia and recovery is more rapid. However, the glycaemic thresholds for the generation of symptoms, counter-regulatory hormonal

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secretion and cognitive impairment are re-set at lower blood glucose levels as a result of cerebral adaptation, but this allows little opportunity for correcting hypoglycaemia when blood glucose falls to dangerously low levels, and neuroglycopenia rapidly supervenes which prevents appropriate self-treatment.

Exposure to antecedent hypoglycaemia, especially repeated episodes, is an important factor in the pathogenesis of IAH. Neuroimaging has allowed identification of key areas of the brain that are involved in maintaining glucose homeostasis and responding to hypoglycaemia. Two methods are currently available for the assessment of awareness of hypoglycaemia in adults, which can be used to identify people with impaired awareness.

As antecedent hypoglycaemia appears to have an important role in the pathogenesis of IAH, scrupulous avoidance of hypoglycaemia appears to be crucial in maintaining defences against the development or progression of IAH.

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Chapter 5 Treatment and prevention of hypoglycaemia

5.1 Acute treatment of hypoglycaemia

The treatment of hypoglycaemia requires ingestion of quick-acting carbohydrate to restore euglycaemia. The quick-acting carbohydrate should be followed up longer-acting carbohydrate either in the form of a snack or a meal if due (Walden et al., 2013). Adherence to treatment guidelines is often poor with only 35-40% of people adhering to these treatment recommendations (Sommerfield et al., 2003, Banck-Petersen et al., 2007). Correct initial treatment of hypoglycaemia (i.e. ingestion of an appropriate amount of fast acting carbohydrate) was only reported by 50% with 37% over-treating and 13% under-treating; women had better compliance than men (Banck-Petersen et al., 2007).

5.11 Evidence for oral treatment options

There is limited evidence regarding the quantity of quick-acting carbohydrate required to successfully treat an episode of hypoglycaemia. The initial quantities chosen were the result of expert consensus subsequently backed up with glucose clamp studies (Brodows et al., 1984, Slama et al., 1990). Vindedzis *et al* (2012) compared 15g versus 20g and found that 32-63% of episodes resolved after one treatment with 15g carbohydrate compared with 55-89% of episodes with 20g carbohydrate (Vindedzis et al., 2012). Larsen *et al* (2006) used continuous glucose monitoring (CGM) to monitor 125 adults with T1DM over 6 days; they defined adequate treatment as ingesting 10-20g of quick-acting carbohydrate (Larsen et al., 2006). They reported that 30% of hypoglycaemic episodes were under-treated and 38% were over-treated. Participants that were under-treated had a 57% chance of remaining hypoglycaemic at the repeat test, this compares with 30% for those adequately treated and 26% for those over treated. This reinforces the suggestion that treatment of hypoglycaemia with less than 10g of quick-acting carbohydrate is likely to be inadequate.

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Chocolate is no longer recommended for the treatment of hypoglycaemia. Chocolate contains quick-acting carbohydrate and fat, the addition of fat has been shown to slow the absorption of quick-acting carbohydrate (Cedermark et al., 1993, Shively et al., 1986). Given a choice of a range of foods, people are more likely to choose high fat rather than high carbohydrate foods (e.g. muffins) after hypoglycaemia with a significant increase in caloric intake in comparison with placebo (Dewan et al., 2004). Sugar or sucrose is also less commonly recommended as it takes longer to affect blood glucose levels than glucose (Georgakopoulos et al., 1990). Orange juice (which contains fructose) remains a popular treatment for hypoglycaemia. The results of two studies using a modified glucose clamp technique have suggested that orange juice may not be the most effective treatment in adults with T1DM; almost double the amount of orange juice was required to produce a similar increment compared with glucose tablets (Slama et al., 1990, Brodows et al., 1984). The total sugar content of any fruit juice varies according to the ripeness of the fruit, the season it is picked and the addition of any sugar when packaged (Slama et al., 1990). A more recent study showed that fructose (in the form of a fruit bar) was less effective than sucrose in successfully treating hypoglycaemia in children with T1DM. The fibre in the bar may have slowed down the absorption of the fructose, reducing its efficacy as a treatment for hypoglycaemia (Husband et al., 2010). By contrast, a recent “real-world” study of children with T1DM attending a diabetes camp found orange juice to be as effective as other treatments (McTavish and Wiltshire, 2011).

Several studies have examined the time interval between treatment and re-testing to confirm resolution of hypoglycaemia. All are supportive of a minimum interval of at least 10 minutes before retesting to ensure resolution of hypoglycaemia (McTavish and Wiltshire, 2011). Slama et al (1990) concluded that repeating carbohydrate intake every 5-10 minutes would not allow adequate time for the treatment to take effect thus leading to over treatment (Slama et al., 1990). Vindedzis et al (2012) reported when hypoglycaemia was treated with 20g of carbohydrate that 55% were adequately treated after a

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5 minute wait, compared with 89% after a 10 minute wait (Vindedzis et al., 2012).

5.12 Evidence for parenteral treatment options

Intramuscular glucagon and intravenous dextrose in varying concentrations are the main treatment options. A randomised trial of people attending the Emergency department with hypoglycaemia found glucagon almost as effective as intravenous dextrose with no difference in adverse events (e.g. vomiting) although recovery of blood glucose levels was slower with glucagon (Collier et al., 1987, Patrick et al., 1990). Faster recovery of blood glucose levels using intravenous dextrose compared with intramuscular glucagon were shown in two subsequent studies into the pre-hospital treatment of hypoglycaemia (Howell and Guly, 1997, Carstens and Sprehn, 1998). Repeated administration of glucagon is not advised, only 1% of people responded to a second injection of glucagon who had not responded to the first injection (MacCuish et al., 1970). Glucagon may be less effective in those people with depleted glycogen reserves such as those with impaired hepatic function (i.e. people with an excessive alcohol consumption). In summary glucagon is effective and can be a useful treatment option, especially out with the hospital setting. However, the slower recovery and higher treatment failure rate makes intravenous dextrose the preferred option.

The increment in blood glucose after administration of 50% glucose varies widely between individuals with hypoglycaemia. The mean increment in participants with diabetes was 9.8 mmol/L with a large standard deviation of 4.4mmol/L (Adler, 1986). There is a paucity of evidence comparing 10% or 20% dextrose with 50% dextrose. Moore and Wollard (2005) administered 5g aliquots of either 10% or 50% glucose at 1-minute intervals to people with hypoglycaemia until recovery of consciousness level had occurred. Participants were selected on the basis of confusion or impaired consciousness level sufficient to make treatment with oral carbohydrate inadvisable. Using 10% dextrose resulted in lower post treatment glucose levels (6.2 versus 9.4 mmol/L) (Moore and Woollard, 2005).

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The risk of extravasation injury with any hypertonic solution may make 10% dextrose safer than 50% dextrose (Wood, 2007). Dextrose 10% preparations are considerably less hypertonic than the 50% preparation and therefore less destructive to the venous endothelium (Nolan, 2005). A Japanese study using rabbit ears found that increasing the duration of infusion decreased the tolerance of peripheral veins to solutions of increased osmolality (Kuwahara et al., 1998). Ten percent glucose has an osmolality of 506mOsm/L compared with 2522mOsm/L for 50% dextrose (Nehme and Cudini, 2009). For these reasons 10% or 20% dextrose solutions are preferred (Walden et al., 2013).

5.2 Behavioural strategies to reduce hypoglycaemia risk

People with diabetes may utilise strategies such as eating extra snacks or avoiding exercise to avoid hypoglycaemia that while undoubtedly effective in the short term, are not ideal behaviours as part as a long term treatment strategy (Bohme et al., 2013). A low GI snack following evening exercise (compared with an isocaloric high GI snack) has been shown to reduce the risk of early nocturnal hypoglycaemia but not late nocturnal hypoglycaemia (Campbell et al., 2014).

In Germany an intensive insulin regimen combined with a structured teaching programme improved glycaemic control without causing a higher rate of severe hypoglycaemia; this involved a 5-day course of inpatient tuition that is not feasible in most countries (Muhlhauser et al., 1987). Long-term follow up of over 9000 adults showed an improved HbA1c (7.3% vs. 8.1%) and a lower incidence of severe hypoglycaemia (Samann et al., 2005). From this earlier work more focussed programmes evolved which concentrated on hypoglycaemia anticipation, awareness and treatment. Blood glucose awareness training reduced both severe hypoglycaemia and fear of hypoglycaemia (Schachinger et al., 2005). Use of a similar programme in people with a history of severe hypoglycaemia lowered the incidence of severe hypoglycaemia without compromising glycaemic control (Cox et al., 2004). A different training programme for the recognition and management of hypoglycaemia demonstrated a reduction in mild hypoglycaemia with

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improved hypoglycaemia awareness (assessed using the Clarke method) although in comparison to the control group, who received more generalised structured education, there was no reduction in severe hypoglycaemia (Hermanns et al., 2007). Extended follow up at 31 months showed a significant reduction in severe hypoglycaemia (Hermanns et al., 2010).

In the UK, more generalised structured education programmes such as DAFNE (Dose Adjustment for Normal Eating) may be beneficial in reducing hypoglycaemia. Although no reduction in severe hypoglycaemia was reported by the original RCT, a later study showed that severe hypoglycaemia was reduced from 15 events per year to 6 per year in the 124 participants analysed (Keen et al., 2012, Dafne Study Group, 2002). While effective, these programmes are resource and time intensive.

Some of the less helpful behavioural modifications exhibited by people with IAH have been previously discussed in section 4.81. A recent Norwegian study reported the expected association between longer duration of diabetes and lower intensity of autonomic symptoms. The novel finding was that people with IAH experienced a lower intensity of autonomic but not neuroglycopenic symptoms (Olsen et al., 2014). People with IAH may selectively pay greater attention to neuroglycopenic symptoms to herald the onset of hypoglycaemia, perhaps as a defence mechanism against their reduced autonomic symptom intensity.

5.3 Alternative type or delivery of insulin to reduce risk of hypoglycaemia

Various strategies can be employed to reduce the incidence of nocturnal hypoglycaemia, including bedtime snacks and adjustment of insulin regimens.

5.31 Human insulin

The introduction of human insulin led to claims that human insulin diminished the symptomatic responses to hypoglycaemia although the methodology was subsequently criticised (Teuscher and Berger, 1987, Hepburn and Frier, 1989).

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A systematic review of 52 randomised controlled trials (RCT) found no evidence that treatment with human insulin affected the frequency, severity or symptoms of hypoglycaemia (Airey et al., 2000). A subsequent Cochrane review also concluded that there was no increased risk of hypoglycaemia with human insulin (Richter and Neises, 2005).

5.32 Analogue insulin

A comparison of human insulin with analogue insulin concluded that they result in the same counter-regulatory and symptomatic response to hypoglycaemia (Frier et al., 2000). Insulin analogues have proved useful in limiting risk of nocturnal hypoglycaemia (Vardi et al., 2008). Direct comparisons between insulin analogues are limited. The BEGIN study compared degludec with glargine and found no difference in overall rates of hypoglycaemia but a reduction in nocturnal hypoglycaemia (Heller et al., 2012). A meta-analysis of the phase 3 trials comparing degludec with glargine also found a reduction in nocturnal hypoglycaemia (Ratner et al., 2013).

A Cochrane review of short acting insulin analogues compared with short acting human insulin found comparable rates of overall hypoglycaemia (Siebenhofer et al., 2009).

5.33 Continuous subcutaneous insulin infusion

Continuous subcutaneous insulin infusion (CSII or “insulin pump”) therapy aims to replicate more closely the normal physiology of insulin secretion compared with that achieved using multiple insulin injections (Pickup, 2012). A meta-analysis reported a significant reduction in severe hypoglycaemia compared with multiple daily injections (rate ratio 4.19, 95% confidence interval 2.86-6.13) (Pickup and Sutton, 2008). A reduction in severe hypoglycaemia for CSII in comparison to basal bolus insulin regimen was also reported by the most recent Cochrane review (Misso et al., 2010). Nocturnal CSII use has been shown to reduce the frequency of nocturnal hypoglycaemia compared to bedtime NPH insulin (Kanc et al., 1998).

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According to the NICE guidelines one of the main criteria for CSII is that attempts to achieve target HbA1c levels (<8.5%) with multiple daily injections (i.e. basal bolus insulin regimen) have resulted in disabling hypoglycaemia. Disabling hypoglycaemia is defined as the repeated and unpredictable occurrence of hypoglycaemia that results in persistent anxiety about recurrence and is associated with a significant adverse effect on quality of life (NICE, 2008).

5.34 Islet transplant

Islet cell transplant has been shown to improve adrenaline secretion and normalise glucagon secretion and hypoglycaemia symptom recognition during hypoglycaemia (Kendall et al., 1997).

5.4 Blood glucose monitoring to reduce hypoglycaemia

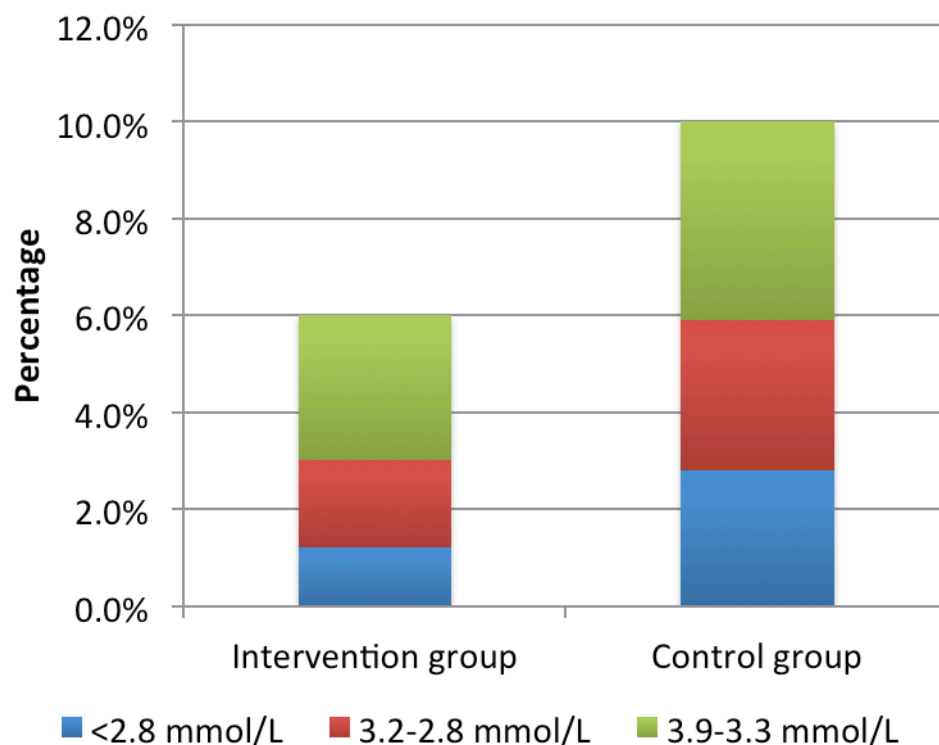
Cox *et al* (2007) developed an algorithm that analyses SMBG (self monitoring of blood glucose) data. If five SMBG readings were available in the 24 hours before an episode the algorithm predicted 63% of episodes of severe hypoglycaemia for people with T1DM and 75% of episodes for people with T2DM; this fell to 58% in T1DM and 60% of T2DM if only 3 SMBG readings were available (Cox et al., 2007).

Using predictive algorithms, CGM systems can provide warning of impending hypoglycaemia and have been shown to reduce nocturnal hypoglycaemia by 84% in adolescents and adults (Buckingham et al., 2010, Dassau et al., 2010). The pros and cons of CGM are discussed in a recent review article, however a Cochrane review of continuous glucose monitoring (CGM) showed no difference in the risk of severe hypoglycaemia between CGM and intermittent self-monitoring of capillary glucose (Langendam et al., 2012, Hermanides et al., 2011). A more recent retrospective audit of people with unawareness of hypoglycaemia who received CGM for at least 1 year showed a significant reduction in nocturnal hypoglycaemia (Choudhary et al., 2013).

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The combination of an insulin pump (CSII) and CGM has long been suggested as a possible treatment option for people with T1DM. Manual closed loop delivery has been shown to reduce nocturnal hypoglycaemia and more recently automated closed loop delivery has also been shown to reduce nocturnal hypoglycaemia (Hovorka et al., 2010, Phillip et al., 2013, Choudhary et al., 2011). An automated pump suspend feature stops the delivery of insulin when the linked CGM device detects blood glucose levels in the hypoglycaemic range. Nocturnal hypoglycaemia is more likely to be affected by this feature than daytime hypoglycaemia as low glucose suspend only stops basal infusion and cannot reverse the effects of a recent bolus such as that given preceding meals.

CGM that utilises an automated low glucose suspend feature was compared with standard CGM in people with T1DM on CSII with no history of severe hypoglycaemia in the preceding 6 months (Figure 5.1) (Bergenstal et al., 2013). A reduced frequency of nocturnal hypoglycaemia was observed (31.8% reduction) while glycaemic control remained unchanged.



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Figure 5.1: Percentage of nocturnal CGM readings <3.9mmol/L in people with and without a glucose suspend function on their insulin pumps (Bergenstal et al., 2013). Reproduced with permission from New England Journal of Medicine, Copyright Massachusetts Medical Society.

5.5 Adjunctive treatment to reduce the risk of hypoglycaemia

Glucagon administration during times of impending hypoglycaemia in people with both CGM and CSII has been shown to reduce the frequency of hypoglycaemia (Castle et al., 2010).

A number of medications have been shown to reduce hypoglycaemia such as terbutaline or caffeine (Cooperberg et al., 2008, Debrah et al., 1996, Richardson et al., 2005). Terbutaline has been shown to reduce the risk of nocturnal hypoglycaemia at the expense of morning hyperglycaemia (Raju et al., 2006). Heller (2008) provides a fairly recent review of the various available treatments that have been considered (Heller, 2008).

The realisation that the brain can utilise alternative fuels for cerebral metabolism, especially during hypoglycaemia has led to the idea that an infusion of one of these fuels might have a protective effect. A lipid infusion containing soybean oil, egg phospholipid and glycerol resulted in reduced counter-regulatory hormonal response but had no effect on cognitive function (Evans et al., 1998).

5.6 Chapter summary

Oral glucose ingestion is the cornerstone of treatment of mild hypoglycaemia. Optimal treatment requires careful attention to the type and amount of carbohydrate consumed and some commonly used treatments are less effective than others (i.e. chocolate). Rechecking blood glucose levels to ensure resolution of hypoglycaemia is also important along with due attention to identifying the cause and preventing a recurrence. Parenteral treatments of hypoglycaemia are usually effective although care must be taken with hypertonic 50% glucose solutions.

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Behavioural modification programmes can provide sustained reductions in the incidence of hypoglycaemia but are often resource and time intensive for both the patient and healthcare professionals. Different insulin types and delivery devices have also shown some benefit and are likely to show further benefits with improved technology (i.e. CSII combined with CGM and low glucose suspend).

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Chapter 6: Acute hypoglycaemia and executive cognitive functioning in adults with and without diabetes

6.1 Introduction

The human brain is dependent on glucose as its energy source; acute hypoglycaemia results in neuroglycopenia with subsequent cognitive impairment. Individuals with T1DM are exposed to an average of two episodes of self-treated hypoglycaemia per week (Pedersen-Bjergaard et al., 2004). The effect of hypoglycaemia on cognitive function has been previously discussed in chapter 3 and the next paragraph provides a brief summary.

In general, performance on complex cognitive tasks deteriorates when blood glucose declines below 3.0 mmol/L (Mitrakou et al., 1991, Maran et al., 1995). Previous studies have demonstrated that, for complex tasks, accuracy is often preserved at the expense of speed (Warren and Frier, 2005). The impairment of cognitive function is reversible, although full recovery requires between 20 to 75 minutes after the restoration of euglycaemia (Evans et al., 2000, Zammitt et al., 2008). Acute hypoglycaemia has been shown to impair various cognitive domains including memory, attention, information processing, psychomotor function, and spatial ability (Sommerfield et al., 2003a, Warren et al., 2007, Wright et al., 2009, Geddes et al., 2008). However, the effect of hypoglycaemia on executive cognitive function, which is important for everyday functioning, has received little systematic study.

Despite many attempts, executive function lacks an accepted universal definition. Executive function is an umbrella term that incorporates a number of complex, interdependent cognitive processes that allow an individual to plan, initiate, sequence, monitor and inhibit complex behaviour (American Psychiatric Association, 1994, Lezak et al., 2004, Goldstein and Naglieri, 2014). Executive functions have also been defined as mental functions associated with the ability to engage in purposeful, organised, self-regulated and goal-directed behaviour (McCloskey et al., 2008). Phineas Gage, a railway foreman, was one of the most famous sufferers of impaired executive function after he suffered an accident in 1848 when an iron rod pierced his frontal lobe. After a period of recovery his personality

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was altered; he had become disinhibited with a loss of social inhibition (Harlow, 1948, Ratiu et al., 2004).

Executive function allows a person to organise thoughts, prioritise tasks, manage time efficiently and make decisions. It is therefore vital for the performance of many everyday activities such as composing a shopping list. In children with diabetes, inadequate executive functioning has been linked to poorer adherence to treatment (McNally et al., 2010, Bagner et al., 2007); a subsequent study reported only reported this association for boys and not for girls (Graziano et al., 2011).

Executive functioning is demonstrated by a number of cognitive processes that are moderately correlated with each other but clearly separable (Miyake et al., 2000). Response “inhibition” is a classic example that refers to the deliberate suppression of an automatic response. Cognitive flexibility or “shifting” which requires the transfer of attention between different tasks or instruction sets and “updating” refers to a process by which incoming information is monitored for relevance to an active task (Rucker et al., 2012, Miyake et al., 2000). Updating, inhibition, shifting and a fourth factor, word fluency have been identified using factor analysis as four sub-groups of executive function in studies of cognitive ageing (Fisk and Sharp, 2004).

Executive function is not localised to one particular area of the brain (Miller, 1984), although evidence from neuroimaging studies suggests that the frontal lobes of the brain (and their connections to other regions) are closely associated with this cognitive domain (Elliott, 2003). Frontal cortex lesions are known to result in poorer executive functioning (Goel and Grafman, 1995), although the relationship is complex as there is limited correlation between severity and location of frontal lobe lesions and functional outcome (Keifer and Tranel, 2013).

Several studies have utilised various measures of executive function and shown areas of worse performance in people with T2DM compared to participants without diabetes (Lowe et al., 1994, Grodstein et al., 2001, Hewer et al., 2003), poorer glycaemic control was also associated with worse executive function (de Wet et al., 2007). People with T2DM scored lower in the inhibition measure with no

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differences in the other cognitive domains compared to control subjects (Bottiroli et al., 2014).

Many of the commonly used marker tests used during “clamp” studies examine some aspect of executive function and performance is impaired during hypoglycaemia in participants with T1DM (Draeos et al., 1995). The present study examined the effects of acute hypoglycaemia on executive function in adult humans with and without T1DM, using a well-validated test battery (Delis et al., 2001, Homack et al., 2005, Wechsler, 1981). Performance was examined, in a counterbalanced design, under euglycaemic and hypoglycaemic conditions.

6.2 Research design and methods

6.21 Participants

Sixteen adults with T1DM and 16 adults without diabetes were studied. Baseline demographics are shown in table 6.1 (see below). The groups were matched for age and body mass index. Participants with diabetes were recruited from the diabetes clinic at the Royal Infirmary of Edinburgh and had no history of macrovascular or microvascular disease. Digital retinal screening was used to exclude diabetic eye disease, peripheral neuropathy was excluded using clinical examination and nephropathy was excluded by the absence of microalbuminuria. Participants without diabetes were recruited by e-mail and paper advertisements within the local hospital and university. None of the participants had a history of seizures, head injury, psychiatric disorder, or alcohol or drug abuse. Participants were on no medication other than insulin or the oral contraceptive pill. Other exclusion criteria included impaired awareness of hypoglycaemia (Gold et al., 1994), colour blindness, pregnancy, a co-existing systemic disease or malignancy.

HbA1c was measured by high performance liquid chromatography (non-diabetic reference range 5.0-6.05% (31-43 mmol/mol); Bio-Rad Laboratories, Munich, Germany) and was Diabetes Control and Complications Trial-aligned. All participants gave written consent before participating in the study, which had been approved by the local medical ethics advisory committee.

Table 6.1: Baseline demographic characteristics of participants			
	Participants without diabetes	Participants with diabetes	<i>p</i> value
n	16	16	n/a
Age (years)	29.0 (26.0-31.4)	29.9 (25.3-35.5)	0.83 (t-test)
BMI (kg/m ²)	24.2±2.9	25.5±2.6	0.22 (t-test)
Male/female	7/9	10/6	0.48 (Fisher's exact test)
Duration of diabetes (years)	n/a	9.2 (4.5-11.9)	n/a
HbA1c (% (mmol/mol))	n/a	7.7±0.9 (61±9.8)	n/a
CSII (insulin pump) n (%)	n/a	3 (18.8%)	n/a
Data are median (interquartile range) and means ± SD unless otherwise indicated			
CSII = Continuous Subcutaneous Insulin Infusion			

6.22 Study procedure

Experimental sessions were performed in the Wellcome Trust Clinical Research Facility at the Royal Infirmary of Edinburgh. Participants attended for two experimental sessions at least two weeks apart. Participants with T1DM were required to monitor their blood glucose frequently for the 48 hours preceding each experimental session, which was postponed if they had recorded a blood glucose

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level $<3.5\text{mmol/L}$ or had experienced symptoms suggestive of hypoglycaemia. Sessions commenced at 08:00h and all participants fasted overnight. Participants with T1DM omitted their morning fast-acting insulin or switched off their insulin pump.

During each session a modified hyperinsulinaemic glucose clamp was performed (DeFronzo et al., 1979). To arterialise any blood samples, the non-dominant arm was wrapped in a warmed blanket with a retrograde intravenous cannula inserted into the forearm (Gallen and Macdonald, 1990). By raising the temperature of the sampling vein, “arterialised” blood samples were obtained for analysis of blood glucose concentrations. Even under hypoglycaemic conditions the difference in glucose concentrations between arterialised and arterial blood is clinically insignificant (0.1mmol/L) (Liu et al., 1992). Arterialised venous blood has therefore been shown to be satisfactory surrogate of arterial glucose estimation (Wahab et al., 1992).

An additional cannula was inserted into the non-dominant antecubital fossa to infuse insulin (Human Actrapid, Novo Nordisk Pharmaceuticals, Crawley, UK) and 20% dextrose. Both intravenous cannulae had to be sited in the non-dominant arm of the participant to leave their dominant arm free to perform the various cognitive tasks. To minimise the possibility of cross contamination the infusion cannula was placed in the antecubital fossa with the antegrade cannula used for sampling sited upstream in the dorsum of the hand.

Insulin was infused at a constant rate of 1.5mUnit/kg/min using a Gemini PCI pump (Alaris Medical Systems, San Diego, California). Blood samples were taken at 5-minute intervals and analysed using a glucose oxidase method (2300 Stat, YSI, Yellow Springs, OH). The YSI blood glucose analyser is used by many clinical laboratories and avoids the problems of inaccuracy using handheld measurements of capillary blood glucose, particularly when sampling blood glucose concentrations $<4\text{mmol/L}$ (Graveling, 2010). The dextrose infusion rate was adjusted based on the prevailing blood glucose concentration to maintain the arterialised blood glucose concentration within the target range.

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Two experimental conditions (hypoglycaemia and euglycaemia) were studied in a single blind, random counterbalanced order. Figure 6.1 shows the order of each experimental session. Initially arterialised blood glucose was maintained at 4.5 mmol/L for 30 minutes, it was then either maintained at 4.5 mmol/L throughout (the euglycaemia condition), or lowered over 20 minutes to 2.5 mmol/L (the hypoglycaemia condition). The experimental condition lasted for 60 minutes, after which euglycaemia was restored. Participants consumed a meal on completion of the study.

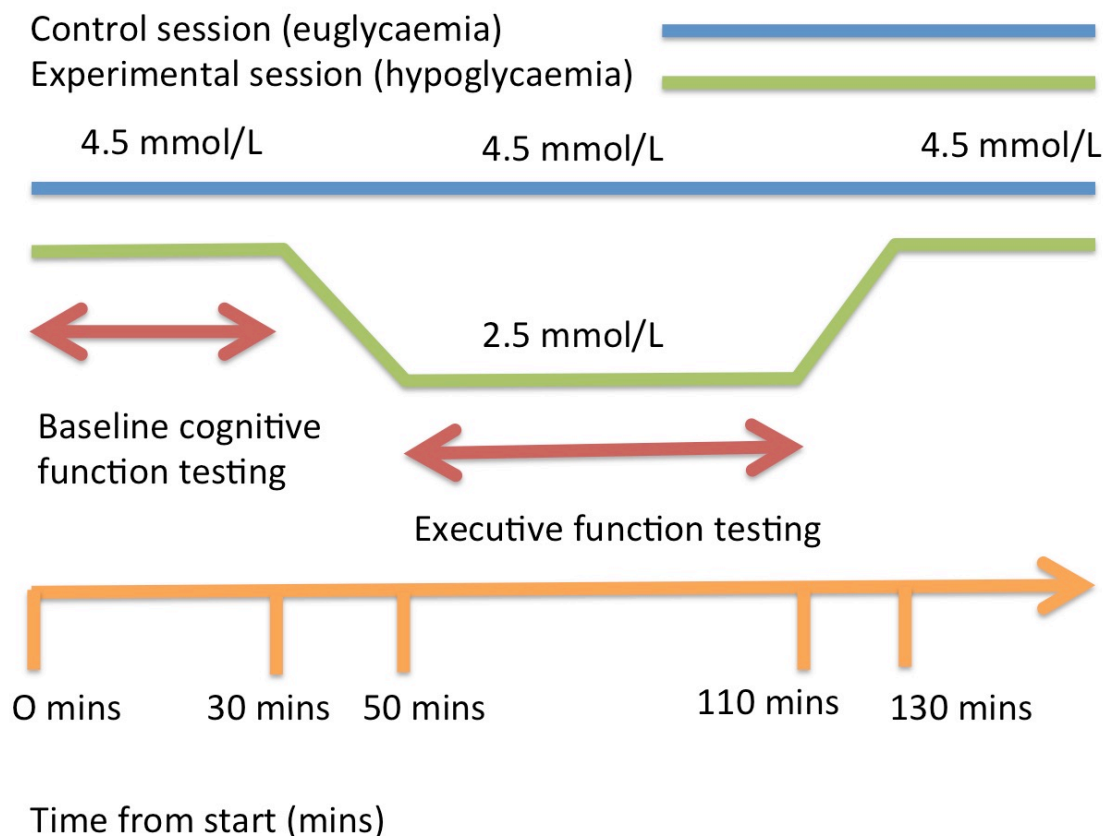


Figure 6.1: Experimental session outline

6.23 Hypoglycaemia scores

Participants scored their symptoms at baseline and during the experimental period using a subjective, validated questionnaire, the *Edinburgh Hypoglycaemia Symptom Scale*. This measures the intensity of commonly experienced hypoglycaemic symptoms graded on a 7 point Likert scale (1 = not present, 7= very intense); these

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symptoms have been grouped previously into autonomic, neuroglycopenic and malaise sub-groupings (Deary et al., 1993, Likert, 1932, Carifio and Perla, 2007). Mean scores are not significantly affected whether using 5 or 7 data points are used although the mean score is slightly higher with 10 point scales (Dawes, 2008).

6.24 Baseline intelligence and educational achievement

The National Adult Reading Test (NART) tests the pronunciation of 50 phonologically irregular English words and is widely used as an estimate of peak intellectual ability (Deary et al., 2004, Crawford et al., 2001). Educational achievement was determined by whether a participant had secondary school, degree or doctoral level qualifications.

6.25 Cognitive function tests

Tests of executive function were performed during both experimental conditions. All tests were from the Delis-Kaplan Executive Function (D-KEFS) test suite and are described below. The D-KEFS is a well validated series of tests which comprehensively assess the domain of executive functions and is suitable for adults with a range of ability levels (Delis et al., 2001, Homack et al., 2005, Delis et al., 2004, Goldstein and Naglieri, 2014). The D-KEFS increases processing demands by using more complex versions of common cognitive tests (i.e. using a *trail making B* test which covers two pages of A4 rather than one) to avoid a ceiling effect encountered by previous studies examining different aspects of cognitive function (Swanson, 2005).

Practice effect was controlled for by counterbalancing the order of the experimental conditions (euglycaemia before hypoglycaemia and *vice versa*) and counterbalancing the parallel forms of the tests (battery A before battery B and *vice versa*) using a Latin Square (Davidson et al., 2003). This study design was chosen to minimize many of the previous criticisms of cognitive function testing during hypoglycaemia (Heller and Macdonald, 1996). Order effects were sought, although from prior experience in cognitive testing in hypoglycaemic clamp studies, none are usually found.

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The *Digit Symbol Substitution Test* (DSST) (from the Wechsler Adult Intelligence Scale III-UK) and *Trail Making B* (from the Delis-Kaplan Executive Function System) tests were used as ‘marker’ cognitive tests that are reliably affected by moderate hypoglycaemia (Wechsler, 1981, Reitan, 1958). The DSST is a test of coding performed at speed, and for each mistake five points were subtracted from the score achieved to give an overall score. *Trail Making B*, also a test of executive function, tests a wide range of cognitive processes including complex attention, visual scanning, psychomotor speed and mental flexibility (Salthouse, 2011). The test is a modification of the classic test originally developed by Partington (Brown and Partington, 1942) and requires the participant to switch back and forth between connecting numbers and letters in sequence (e.g. 1-A-2-B-3-C); it covers two pages which increases spatial scanning demands. Time taken (in seconds) was subtracted from 200; for each mistake five additional points were subtracted to give a total score.

6.26 Executive function tests

Verbal fluency (category switching): This test requires both rapid retrieval from semantic knowledge and cognitive flexibility to allow switching between categories. Participants were required to generate words, alternating between two different semantic categories (e.g. fruit and furniture). The outcome variable was the total score with one point awarded for each correct pair named during the time limit.

Sorting test: Based on the Wisconsin Card Sorting Test (Berg, 1948), this test is designed for isolating and measuring multiple components of concept-formation and problem-solving abilities. Each participant was shown two groups of three cards each and was then required to state how the two groups were sorted (e.g. one card set shows singular words and the other displays plural words). Outcome variables were the total score, with four points awarded for each correct description, and time taken.

Twenty questions test: The participant is presented with a stimulus page depicting pictures of 30 common objects (e.g. banana, airplane or bowl). The participant must ask the fewest number of yes/no questions possible in order to identify the unknown target object. The ideal response would eliminate half of the remaining objects. This

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test assesses the participant's ability to perceive the various subcategories (e.g. land-based objects and those that fly). By incorporating feedback from previous answers, participants can formulate a yes/no question to eliminate the maximum number of objects. One point was awarded for each correctly phrased question with a lower score denoting better performance. Participants performed this test twice, outcome variables included combined score and total time taken. Analysis of the quality of responses was then made in a quantitative manner to give the third outcome variable. Subjects scored five points for an answer which eliminated half of the remaining objects, four points for a response that eliminated ± 1 of half the remaining objects, three points for ± 2 , two points for ± 3 , 1 point for ± 4 and 0 points for ± 5 . So if there were 8 remaining objects and a response eliminated 3 objects then that question would score 4 points for that response. This score was then divided by the number of questions taken to determine the correct object; this gave the third outcome variable.

Tower test: Edouard Lucas is credited with devising the "Tower of Hanoi" in 1883. The *tower test* is derived from this and assesses several key executive functions including spatial planning and maintaining an instructional set (Goel and Grafman, 1995). Participants must build the designated tower in the fewest number of moves possible by moving differently sized disks across three pegs. Four towers of increasing difficulty were constructed during each experimental session; to avoid a practice effect a parallel version of equivalent difficulty was created by shifting each piece to the right. One point was awarded for each move taken; therefore a lower score denoted better performance. Outcome variables were the combined score for all four towers and the total time taken.

Colour-Word Interference Test (Stroop): Based on the classic Stroop procedure, these four tests assess the participant's ability to inhibit an overlearned verbal response (i.e. name the ink colour of the word instead of reading the printed word) (Stroop, 1935). The first two (baseline) tasks require the participant to name blocks of colour (*Stroop 1*) and read colour words printed in black ink (*Stroop 2*). The third task prints colour words in a different colour (*Stroop 3*), e.g. the word "red" printed in blue ink (inhibiting). The fourth task involves asking the participant to switch back and forth between naming ink colours and inhibiting (*Stroop 4*), this tests both

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inhibition and cognitive flexibility. Time required for completion became the score for that task; four seconds were added for an uncorrected error and two seconds for a corrected error. Five combined task scores were calculated (Table 6.2).

Stroop A is the sum of all four tasks and *Stroop B* is the sum of the first two tasks and an indication of performance in key lower level skills (i.e. reading and naming). *Stroop C* and *Stroop D* demonstrate any effect on executive functioning while attenuating the impact of any deficit in more basic cognitive functioning (i.e. reading printed words). The “Stroop Interference Effect” (*Stroop C*) indicates the increase in time taken to perform the task requiring an inhibited response compared with simply reading or naming the ink colour (Van der Elst et al., 2006). *Stroop E* demonstrates the additional time required to switch between tasks (cognitive flexibility) while attenuating the effect of inhibition. Many of the Stroop tests rely on colour discrimination, this has been shown previously to be unaffected by moderate hypoglycaemia although may become impaired with more profound hypoglycaemia (Hardy et al., 1995, Harrad et al., 1985).

6.27 Statistical Analysis

A general linear model (repeated measures ANOVA) was used. Glycaemic condition (euglycaemia or hypoglycaemia) was the within-participant factor (repeated measure). Order of session (euglycaemia followed by hypoglycaemia or vice-versa), order of test battery (test battery A followed by battery B or vice versa) and diabetes status (participants with or without diabetes) were between-participants' factors with the NART score as a covariate. Effect sizes were calculated using Cohen's *d* to assess the extent of any cognitive decrement caused by hypoglycaemia ($d=0.2$ small, $d=0.5$ medium, $d=0.8$ large) (Cohen, 1988). All analyses were performed using Microsoft Excel 2010 (Redmond, Washington, USA) and SPSS version 18.0 (SPSS, Chicago, USA) both for Windows. Unless otherwise stated, data are expressed as mean \pm SD and $p<0.05$ was considered to be significant.

6.3 Results

6.31 Blood glucose

Target blood glucose levels were achieved for both the hypoglycaemic (2.45 ± 0.11 mmol/L) and euglycaemic (4.54 ± 0.09 mmol/L) conditions; glucose levels were similar in participants with or without diabetes ($p=0.23$ and $p=0.11$ respectively, t-test).

6.32 Symptom scores

Autonomic symptom scores increased from 10.6 ± 4.1 during euglycaemia to 22.6 ± 9.3 during hypoglycaemia ($p < 0.001$, Cohen's d 1.68). Neuroglycopenic symptom scores increased from 10.8 ± 5.5 to 19.6 ± 8.7 ($p < 0.001$, Cohen's d 1.22). Malaise symptom scores increased from 2.5 ± 1.3 to 3.4 ± 1.8 ($p=0.004$, Cohen's d 0.63).

6.33 Educational achievement and baseline intelligence

Nine (56.3%) healthy volunteers had doctorate level qualifications compared with four (25.0%) participants with diabetes ($p=0.20$, Pearson Chi Square). Mean NART scores were significantly lower in participants with diabetes than those without (36.3 ± 3.8 and 40.5 ± 5.4 respectively, $p < 0.02$, t-test). As expected, National Adult Reading Test (NART) scores (taken at baseline) did not differ significantly between the two experimental sessions ($p=0.18$, t-test).

6.34 General cognitive function tests

Performance during hypoglycaemia was significantly impaired in both the *trail making* and DSST (see Figure 6.2) ($p < 0.001$ for both, Cohen's d 1.16 for *trail making* and 0.84 for DSST). No significant difference on these tests was observed between people with, and without, diabetes (*trail making* $p=0.67$ and DSST $p=0.11$).

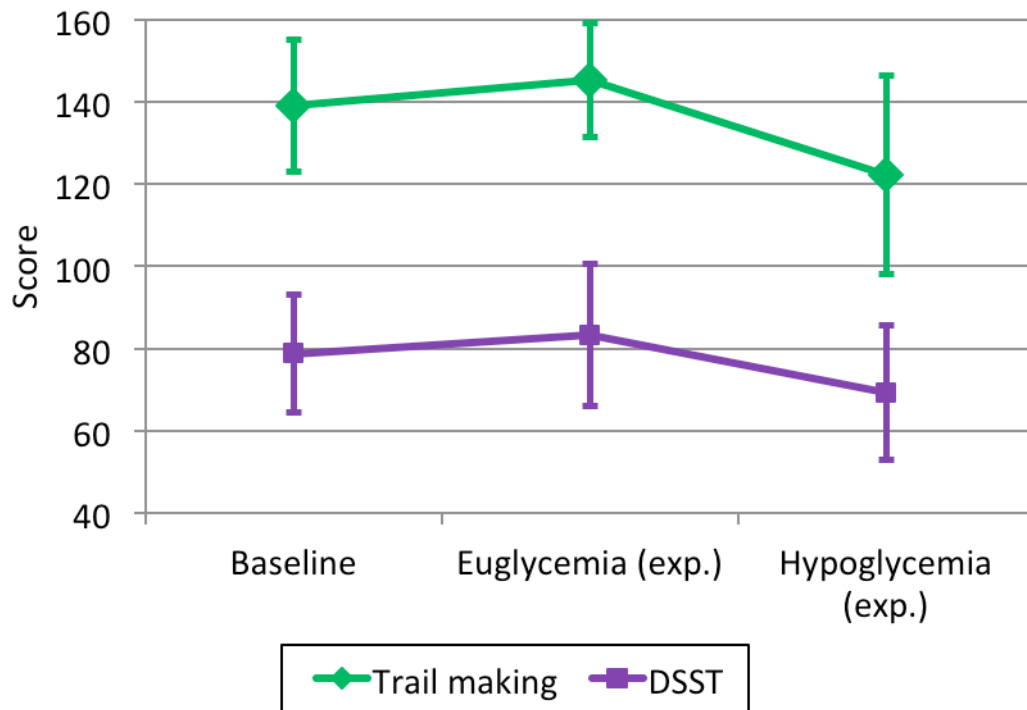


Figure 6.2: General (“marker”) cognitive test scores

6.35 Executive function tests

No significant effects were found for order of session (hypoglycaemia followed by euglycaemia or *vice versa*). The only significant effects for diabetes status were for the *Stroop A* ($p < 0.05$), *Stroop B* ($p < 0.05$) and *verbal fluency* ($p < 0.03$) tasks; performance during both euglycaemia and hypoglycaemia of participants with diabetes was worse than those without diabetes.

Performance during hypoglycaemia was significantly impaired on every measure of executive function examined other than *Stroop E*, both in terms of scores achieved and time taken (Tables 6.2 & 6.3). Hypoglycaemia significantly prolonged the time to completion in all of the tests where time was not fixed. The high Cohen’s d values (> 0.8) indicate that hypoglycaemia induced decrements with large effect sizes (see table 6.2 & 6.3 for Cohen’s d values).

Table 6.2: Stroop test results*

Name	Calculation (see below for description of Stroop 1 to 4)	Euglycae mia time (seconds)	Hypoglyca emia time (seconds)	Eu- vs. hypo- glycaemia		Diabetes status (Diabetes versus non- diabetes) (<i>p</i> value)
				<i>p</i> value	Cohen 's <i>d</i>	
Stroop A	All 4 scores combined	148.4±29. 9	198.1±47.8	<0.00 1	1.25	0.047
Stroop B	Mean of Stroop 1 & 2	24.0±4.1	31.8±7.3	<0.00 1	1.32	0.045
Stroop C	Stroop 3 – Stroop B	22.0±9.7	29.3±14.3	0.003	0.60	0.66
Stroop D	Stroop 4 – Stroop B	31.8±11.5	42.8±19.2	<0.00 1	0.69	0.09
Stroop E	Stroop 4 – Stroop 3	9.8±10.0	13.5±19.8	0.22	0.24	0.18

*Data are mean±SD. Significance level was $p < 0.05$; Cohen's *d* was calculated as an estimate of effect size.*

Stroop 1: naming blocks of colour; Stroop 2: reading words; Stroop 3: naming ink colour of words (e.g. "blue" printed in red ink); Stroop 4: alternating between naming ink colour of words and reading the printed word.

**Stroop is scored using seconds to complete, a lowers score denotes better performance*

Table 6.3: Executive function test scores and times									
Executive Function test	Euglycaemia score	Hypoglycaemia score	Eu- vs. hypo-glycaemia*		Euglycaemia time (seconds)	Hypoglycaemia time (seconds)	Eu- vs. hypo-glycaemia		
			<i>p</i> value	Cohen's <i>d</i>			<i>p</i> value	Cohen's <i>d</i>	
Verbal fluency	8.7±2.0	6.3±2.0	<0.001	1.21	Time taken is a constant				
Sorting test	24.4±4.7	19.5±4.9	<0.001	1.02	199.9±5 1.5	262.0±8 9.4	<0.001	0.85	
Twenty questions**	11.8±2.5	13.8±3.8	0.001	0.62	66.2±31. 0	113.1±6 3.2	<0.001	0.94	
Tower Test (combined)**	94.1±18.0	114.6±23.8	<0.001	0.97	277.3±95.9	351.9±84.5	<0.001	-0.83	
Data are mean±SD. Significance level was $p<0.05$; Cohen's <i>d</i> was calculated as an estimate of effect size.									
*main effect of glycaemic condition									
**lower score indicates better performance									

The lower performance scores achieved during hypoglycaemia in the Stroop test were not simply because of slower information processing, participants made a significantly greater number of errors during hypoglycaemia compared with euglycaemia with significant increases in both self-corrected and uncorrected errors

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(Table 6.4). Participants with diabetes made significantly more uncorrected errors during Stroop A than participants without diabetes.

Table 6.4: Stroop A (combined) error rates				
	Euglycaemia	Hypoglycaemia	Eu- vs hypo-glycaemia (p value)	Diabetes status (Diabetes versus non-diabetes) (p value)
Self-corrected	1.5±1.41	3.87±2.58	$p<0.001$	$p=0.88$
Uncorrected	0.41±0.84	1.94±2.46	$p<0.001$	$p<0.04$
Total	1.91±1.96	5.81±3.93	$p<0.001$	$p=0.24$
Data are mean±SD. Significance level was $p<0.05$. Unpaired t test				

In the *twenty questions* test, responses given during hypoglycaemia are often of a poorer quality, e.g. asking very specific questions that would only eliminate one or two of the remaining objects (i.e. does it fly? is it a bowl? is it orange?). Food words are remembered at a slower rate during hypoglycaemia than non-food words (Brody et al., 2004). Analysis of the quality of responses showed that scores during hypoglycaemia were significantly lower than during euglycaemia (see methods for scoring system) (5.11 ± 1.40 and 6.24 ± 1.48 respectively, $p=0.003$, unpaired t test).

Significant glycaemic condition by diabetes status interactions were observed for *Stroop A*, *Stroop B* and the *sorting test* (time taken) ($p=0.02$, $p=0.002$ and $p=0.004$ respectively). This suggests that in these tests, the effects of hypoglycaemia differ significantly between participants with, and without, diabetes. Participants with diabetes were affected by hypoglycaemia to a greater degree than those without diabetes (Figures 6.3 & 6.4). When the NART scores are entered as a covariate, participants with diabetes continued to experience a greater detrimental effect of

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hypoglycaemia than those without diabetes in the *sorting test* ($p=0.02$) and *Stroop B* ($p=0.01$), but not for *Stroop A* ($p=0.12$).

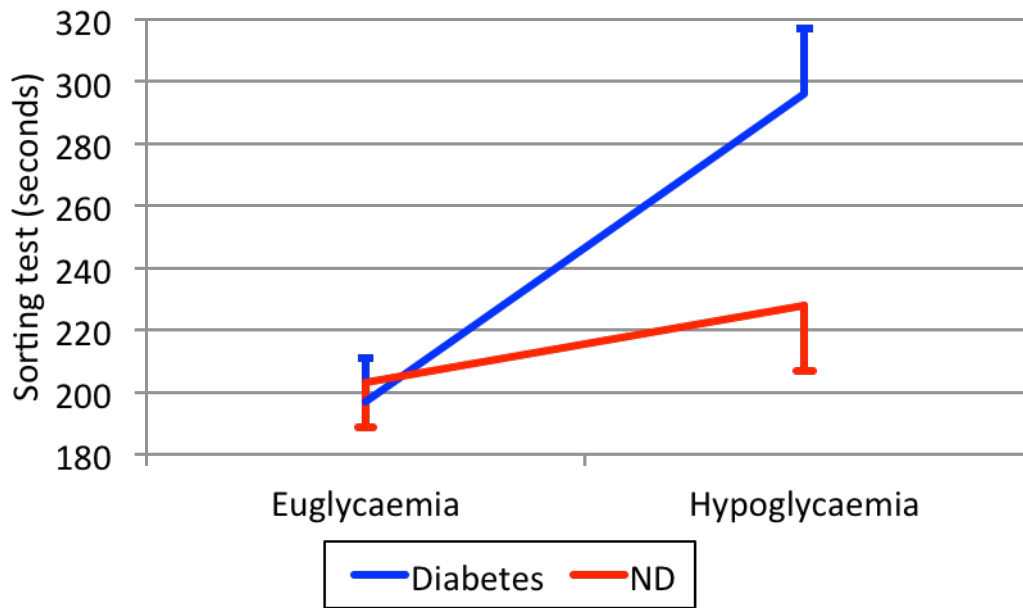


Figure 6.3: Time taken to complete the sorting test (mean(SE)) during hypoglycaemia and euglycaemia according to diabetes status; a lower score denotes better performance. Diabetes: participants with diabetes; ND: participants without diabetes.

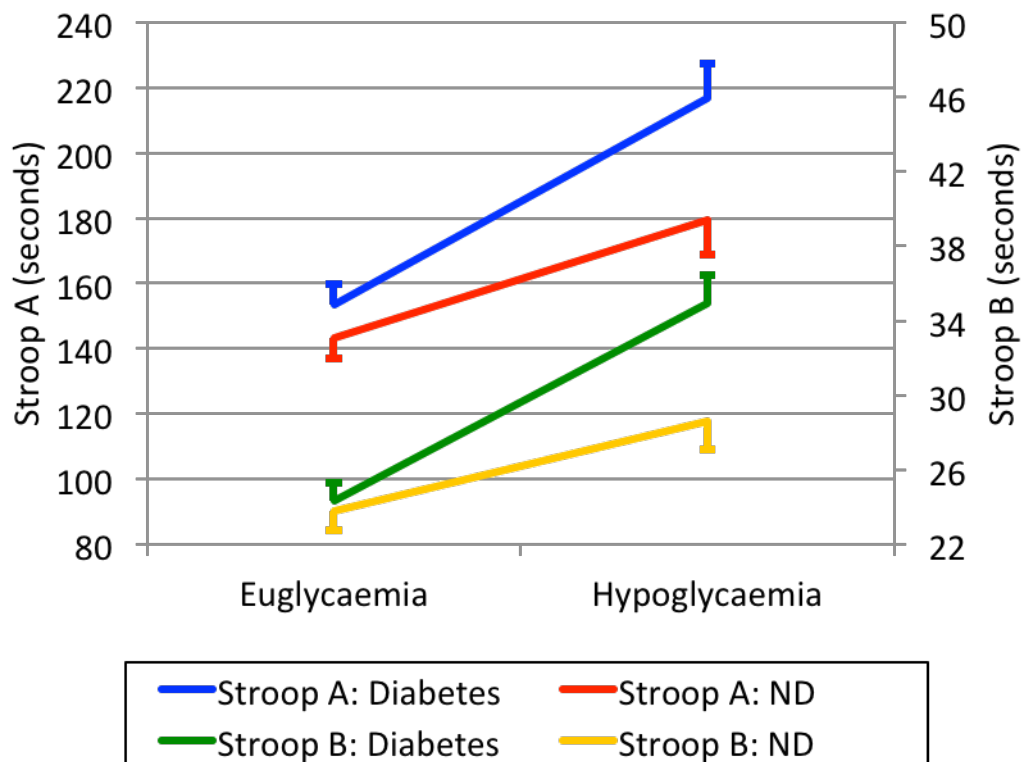


Figure 6.4: Comparison of performance (mean(SE)) during Stroop A & B during hypoglycaemia and euglycaemia according to diabetes status; a lower score denotes better performance. Diabetes: participants with diabetes; ND: participants without diabetes.

Significant glycaemic condition by diabetes status interactions were observed for uncorrected errors for *Stroop A* suggesting that the effects of hypoglycaemia differ significantly between participants with, and without, diabetes. Participants with diabetes were affected by hypoglycaemia to a greater degree than those with diabetes and made more self-corrected errors (Figure 6.5).

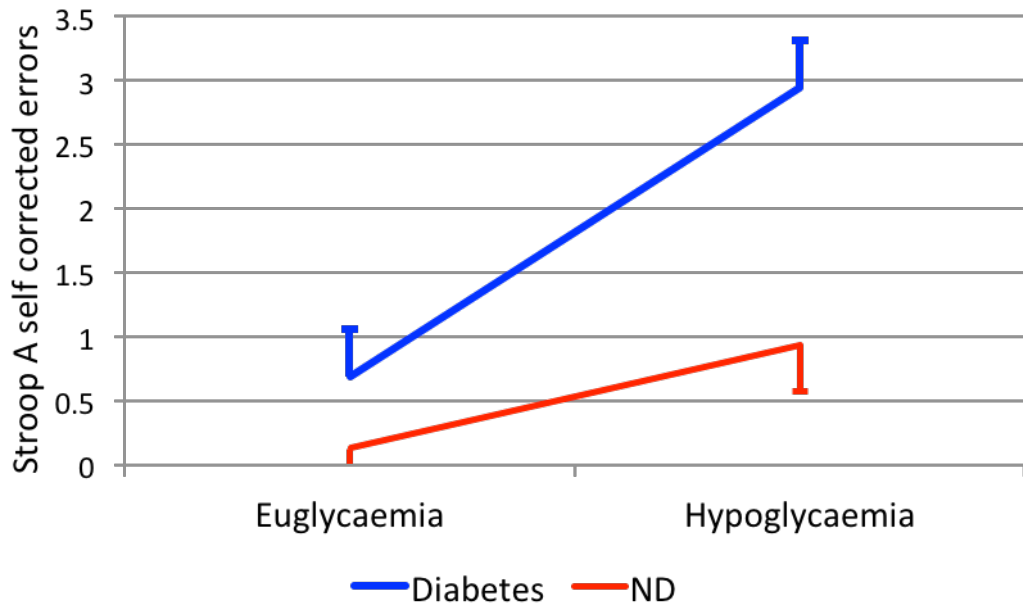


Figure 6.5: Number of self-corrected errors during Stroop A (mean(SE)) during hypoglycaemia and euglycaemia according to diabetes status. Diabetes: participants with diabetes; ND: participants without diabetes

6.4 Discussion

The present study has demonstrated that acute hypoglycaemia markedly impairs performance in almost all the aspects of executive function tested in adults with, and without, T1DM. All domains of executive function were significantly impaired except for *Stroop E*. Where the time taken was a variable rather than a constant, the completion time was significantly longer. The generally large Cohen's *d* values (>0.8) indicate that hypoglycaemia accounted for a large part of the variation in results.

It is debatable as to whether the decrement in processing speed is solely responsible for the observed impairment in executive function (Albinet et al., 2012). However, the present study has demonstrated more specific decrements; the quality of the responses was poorer during hypoglycaemia. In the *twenty questions* test subjects more likely to ask closed questions (i.e. does it have rotor blades?), that would only eliminate a small number of the remaining objects. This trait has been previously noted in people with frontal lobe lesions compared with matched controls with the latter asking more open-ended questions (Baldo et al., 2004). In the Stroop test the number of errors, both uncorrected and self-corrected, were greater during hypoglycaemia. This suggests that during hypoglycaemia, subjects were less aware of an error being made and so were less likely to correct the error; this has been shown previously in driving simulator studies in which participants were less likely to correct any driving errors when hypoglycaemic (Cox et al., 2000).

During euglycaemia, glucose is the main source of energy for the brain. Alternative substrates may be utilised during hypoglycaemia as energy sources, although in general they ameliorate, but do not reverse, the effects of neuroglycopenia (Beall et al., 2012). Administration of some of these alternative fuels (e.g. amino acids or lactate) has been shown to reduce the decrement in cognitive performance observed during hypoglycaemia (Rossetti et al., 2008, Page et al., 2009). In these studies insufficient information was given to determine whether there had been a significant improvement in the quality of the answers given.

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Glycaemic targets were maintained and symptom scores incremented appropriately during hypoglycaemia. The expected decrement in performance during hypoglycaemia in the cognitive ‘marker’ tests was consistent with the results of other similar studies (Geddes et al., 2008, Sommerfield et al., 2003a, Warren and Frier, 2005). Previous studies have shown that several domains of cognitive function are impaired during acute hypoglycaemia, including memory and spatial awareness (Sommerfield et al., 2003b, Wright et al., 2009). Previous research also demonstrated that performance of complex cognitive tasks is preferentially impaired by hypoglycaemia, while simpler tasks such as finger tapping or reaction time are less affected (Warren and Frier, 2005, Geddes et al., 2008).

The executive function tests that were used in the present study examined a series of diverse yet interdependent complex cognitive processes. The category switching part of the *verbal fluency* test examined cognitive switching abilities similar to those examined by *trail making B*. The *sorting test* examined concept-formation and problem solving abilities. The *twenty questions* test assessed the ability to perceive sub-categories within the list of objects presented. The *tower test* assessed spatial planning and the ability to maintain an instruction set. All of these cognitive tests were impaired during hypoglycaemia. Increasing age has been shown to reduce both generalised processing speed and specific executive functioning (Albinet et al., 2012, Troyer et al., 2006, Van der Elst et al., 2006). The groups were well matched in terms of age. While executive function might deteriorate over the age of 60 years, significant deterioration due to age would not be expected with the relatively young study cohort (mean age 29.9 years).

The Stroop test uses a series of combined scores to give an indication of performance in both lower and higher level cognitive functioning (table 6.2); *Stroop C, D & E* can all be considered measures of executive function that aim to remove any contribution from a more basic processing deficit. *Stroop C* measures the classic interference effect and *Stroop D* measures interference and cognitive flexibility; both showed a moderate effect size. *Stroop E* was the only executive function measured not affected by acute hypoglycaemia. *Stroop E* represents the additional time taken to switch between tasks and is thus a measure of cognitive flexibility; it is noteworthy

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that other measures of cognitive flexibility such as *verbal fluency* and *trail making B* were impaired by hypoglycaemia.

The cognitive processes affected will impinge on performance of everyday activities. Impaired ability to switch between semantic categories and retrieval from semantic knowledge would interfere with planning and make it difficult to construct a list of items suitable for a specific purpose (e.g. for a camping trip). In such a scenario, impaired spatial planning and failure to maintain an instructional set would make loading a car or erecting a tent more difficult to undertake.

Compared with their performance during euglycaemia, participants with diabetes experienced a greater detrimental effect of hypoglycaemia than those without diabetes in the *sorting test* (time taken), *Stroop A* (both in terms of scores achieved and number of uncorrected errors) and *Stroop B*. Higher baseline intelligence is known to improve performance during the Stroop test; the effect of higher intelligence scores (in adults) on performance during the sorting test is less clear cut (Van der Elst et al., 2006, Arffa, 2007). Whereas the groups with and without diabetes were otherwise well matched (table 6.1), the significantly lower NART scores (a measure of crystallised intelligence) that were documented in the participants with diabetes may have been a confounding factor. However, when the NART scores are entered as a covariate, participants with diabetes continued to experience a greater detrimental effect of hypoglycaemia compared to those without diabetes in the *sorting test* (time taken) and for *Stroop B*, but not for *Stroop A*. Differential effects of hypoglycaemia between people with and without diabetes were found in a different cognitive domain, psychomotor function. However, in that study, the detrimental effect of hypoglycaemia was greater in participants without diabetes (Geddes et al., 2008). The mechanism underlying this differing effect of diabetes status of performance during hypoglycaemia is unknown.

The euglycaemic and hypoglycaemic hyperinsulinaemic clamp is a well-established tool in clinical research providing a standardised environment with only one variable (i.e. blood glucose concentration) between the two experimental sessions (DeFronzo et al., 1979).

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A possible weakness of the present study is that time constraints allowed each test of cognitive function to be performed only once during each experimental session. Tests to assess several cognitive domains take time to perform and it has been suggested that cognitive adaptation may occur when exposure to hypoglycaemia is relatively prolonged (Kerr et al., 1991, Kerr et al., 1989), although this premise has been disputed (Gold et al., 1995, Evans et al., 2000). Gold *et al* reported no improvement in cognitive function after 40-60 minutes of hypoglycaemia and similarly Evans *et al* reported no cognitive adaptation after 90 minutes of hypoglycaemia. Cerebral adaptation to hypoglycaemia, which results in a lesser magnitude of impairment of cognitive function, is a feature of people with type 1 diabetes who have impaired awareness of hypoglycaemia (Zammitt et al., 2008); individuals with this acquired syndrome were excluded from the study.

6.5 Chapter summary

The present study provides further evidence of a global impairment of most high-level cognitive functions during hypoglycaemia. Both speed of information processing and the quality of answers given were adversely affected by hypoglycaemia. The executive functioning of people with diabetes was affected by hypoglycaemia to a greater extent than those without diabetes. Executive function is essential for many activities (such as driving, analysing data or planning events); its disruption during hypoglycaemia will have a profound effect on the functioning of a person with diabetes.

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Chapter 7: Prevalence of impaired awareness of hypoglycaemia and identification of predictive symptoms in children and adolescents with type 1 diabetes

7.1 Introduction

Hypoglycaemia is the commonest side-effect of insulin therapy and interferes with everyday activities (Gonder-Frederick et al., 2009). Cognitive impairment associated with hypoglycaemia may prevent a child from seeking help and so delaying treatment. Severe hypoglycaemia is inversely associated with age (Wagner et al., 2005) and glycaemic control (Davis et al., 1998), but is not strongly associated with duration of diabetes (Blasetti et al., 2011, Davis et al., 1997). Continuous glucose monitoring (CGM) has suggested that nocturnal hypoglycaemia occurs approximately every third night and is associated with strict glycaemic control and younger age (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010).

In adults, recurrent hypoglycaemia increasingly impairs the normal defences against hypoglycaemia and diminishes the ability to detect hypoglycaemia. The glycaemic threshold at which autonomic symptoms are triggered is re-set at a lower blood glucose level. Cognitive dysfunction can then precede the onset of autonomic symptoms and interfere with the ability to initiate corrective action (Graveling and Frier, 2010).

In adults, symptoms experienced during hypoglycaemia show substantial inter-individual variation but broadly can be categorised into autonomic, neuroglycopenic and non-specific symptoms (Deary et al., 1993). The blood glucose level at which these symptoms are generated is associated with inter- and intra-individual variation according to factors such as level of glycaemic control and exposure to antecedent hypoglycaemia (McAulay et al., 2001). The symptoms of hypoglycaemia differ in children, particularly with respect to age and pubertal status (Ross et al., 2005). While autonomic symptoms cannot be distinguished from neuroglycopenic symptoms by neither children nor their parents, behavioural changes (e.g. becoming

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naughty or irritable) often alert a parent or carer to the onset of hypoglycaemia (Ross et al., 1998, McCrimmon et al., 1995).

Impaired awareness of hypoglycaemia (IAH) is a syndrome in which the ability to detect the onset of hypoglycaemia is diminished or absent and is discussed further in chapter 4 (Graveling and Frier, 2010). Counter-regulatory hormonal failure is not the direct cause of IAH as avoidance of hypoglycaemia results in improved symptom perception without restoration of the normal counter-regulatory response (Dagogo-Jack et al., 1994). Nevertheless, the two are closely related, usually co-segregate and probably share a common pathogenesis (Ryder et al., 1990). In adults, IAH carries up to a six-fold higher risk of severe hypoglycaemia (Gold et al., 1994, Geddes et al., 2008).

The prevalence of true IAH is uncertain in children. The recognition of hypoglycaemia involves a complex interplay of psychological and physiological factors. Some children may fail to interpret symptoms and react appropriately; this does not mean that they do not experience symptoms of hypoglycaemia. The present study investigated the prevalence of IAH in children with T1DM using two methods of assessing awareness status that have good concordance in adults with T1DM (Geddes et al., 2007). Secondary aims were to assess the frequency and symptomatology of hypoglycaemia in children and to determine which symptom group best predicts awareness of hypoglycaemia.

7.2 Methods

7.21 Participants

Children and adolescents attending paediatric diabetes clinics in the Lothian region of Scotland were recruited; the clinic population was approximately 340 and had a mean DCCT-aligned HbA1c of 71 mmol/mol (8.62%) in the year of survey. Inclusion criteria were T1DM of at least six months duration and measurement of blood glucose three or more times per day with no exclusion criteria. Permission for the study was obtained from the Lothian ethics advisory committee.

Each participant and one of their parents were asked to complete baseline questionnaires with a researcher present to answer any queries; the participant completed their questionnaire without assistance from their parent(s). The questions were read out to the participants if the participants were unable to read it for themselves; the questions were not paraphrased. The baseline questionnaire is reproduced in appendix one. Recognising that the paediatric population often requires assistance to treat hypoglycaemia, severe hypoglycaemia was subdivided into events requiring third party assistance and those requiring hospital attendance.

Awareness of hypoglycaemia was assessed using two validated questionnaire-based methods that have been compared in adults, designated the “Clarke” and “Gold” methods, after the first author of each paper (Clarke et al., 1995, Gold et al., 1994, Geddes et al., 2007). The Clarke questionnaire uses eight questions to determine awareness status whereas the Gold questionnaire uses a simple 7-point Likert scale (1 = always aware of hypoglycaemia, 7 = never aware of hypoglycaemia). Both methods result in a score between 1 and 7. American terminology was modified where necessary to reflect British vocabulary. Although not explicitly stated in the original papers the original validation of both the Gold and Clarke questionnaires gave 3 possible awareness outcomes: “aware” for a score of 1 or 2 and “impaired” for a score of 4 or more with participants who scored 3 placed in an undetermined or “intermediate” awareness category. When submitted for publication, careful discussion based on comments received during the peer review process regarding reducing the number of awareness states led to the intermediate (score = 3) and

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impaired awareness (score ≥ 4) groups being amalgamated. With both methods a score is calculated; a score of 1 or 2 was classified as *aware*, a score of 3 or more classified as *IAH*.

Typical clinical features observed by parents and experienced by children during hypoglycaemia were based on a previous study by our group (Ross et al., 1998); in a similar cohort of children and parents, good correlation existed between clinical features perceived by the children and observed by their parents. Because parents cannot directly observe some of the possible symptoms (e.g. headache) they were encouraged to use their own observations and determine which symptoms were present in conversation with their children. Although pallor is a sign, all clinical features in this present paper are referred to as “symptoms” to maintain consistency with previous literature (Ross et al., 1998, McCrimmon et al., 1995). Symptom intensity was estimated using a 7-point Likert scale (1=symptom not present, 7=very intense) (Likert, 1932).

Based on the first few responses of the child to the baseline questionnaire, it was left to the discretion of the parent and the researcher as to whether the participant was likely to understand the remaining questions. If it was evident that they did not understand the questions, then only the parental questionnaire was completed. Participants were asked to record blood glucose at least three times per day, for four weeks. For any blood glucose readings < 4 mmol/L, both the parent and participant were asked to complete hypoglycaemia questionnaires prospectively, to document blood glucose, hypoglycaemia recognition (self, third party or meter), assistance required (self-treated, third party or hospital attendance) and symptoms experienced (using a 7-point Likert scale). This biochemical level was chosen to determine potential hypoglycaemic events because 4.0 mmol/L is the alert level for avoidance of hypoglycaemia recommended by Diabetes UK, the principal diabetes charity in the UK. The hypoglycaemia questionnaires for both children and their parents form appendix two.

Retrospective review of case records and growth charts were used to determine whether peak height velocity (PHV) or menarche had been achieved. Male participants were classified as pre-pubertal if they were < 10.5 years old when

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surveyed and those aged ≥ 10.5 years who had not reached PHV within 6 months of survey were considered to be of uncertain pubertal status. Male participants were considered pubertal if PHV was achieved within six months of survey. Female participants were classified as being pre-pubertal if they were < 9.5 years old and those aged ≥ 9.5 years who had not achieved PHV were considered to be of uncertain pubertal status. Female participants were considered pubertal if they had reached menarche or PHV.

7.22 Specimen processing

HbA1c was measured by ion exchange HPLC using a haemoglobin testing system (Bio-Rad Laboratories, Munich, Germany; non-diabetic reference range 31-43 mmol/mol (5.0-6.05%); results were DCCT-aligned.

7.23 Statistical analysis

Results were analysed using SPSS (version 18 for Windows, SPSS, Chicago, IL) and R, version 2.10 (R Development Core Team, 2010). Categorical variables were analysed using Fisher's exact test and continuous variables using an unpaired t-test. Spearman's rank correlation was used to analyse reported symptoms and method of assessing awareness status. Principal Components Analysis was used to examine how symptoms aggregate; the number of factors was determined using a scree plot. A loading of > 0.3 was considered significant (a loading is the strength of a given variable's relationship with the underlying factor and may take a value from -1.0 to +1.0). Multinomial logistic regression models were used to predict which aggregate of symptoms best predicts awareness status. Data are shown as median (range) or mean \pm SD, unless otherwise stated. A *p* value < 0.05 was considered to be significant.

7.3 Results

7.31 Participant demographics

The actual response rate to the invitation handed out by clinic staff is not known. The local clinic population of 340 would be expected to attend clinic 3 or 4 times per year. An estimate of the response rate would be about 40%, perhaps 200-250 children would have been invited to participate over the five-month period. Ninety-eight participants completed the baseline questionnaire; 57 completed blood glucose diaries prospectively and questionnaires about any episode of hypoglycaemia that had occurred over the subsequent four weeks. The principal reason given for non-completion was time constraint. No significant baseline differences between completers and non-completers were found. Approximately half of the participants (n=52, 52.5%) were taking a biphasic insulin in the morning followed by a short-acting insulin before their evening meal and a basal (long-acting) insulin in the evening. Most other participants (n=44, 44.4%) used a basal bolus insulin regimen and one used CSII with an insulin pump.

7.32 Awareness status

Satisfactory completion of the questionnaire by the child was deemed to have occurred if their awareness status according to the Clarke method could be determined. Awareness status could be determined in 70 children (98.6%) aged nine or over but in only seven (25%) under the age of nine. Table 7.1 shows baseline demographics by awareness status (Clarke method); both younger age and younger age at diagnosis were significant predictors of IAH. No difference in awareness status was found between different insulin regimens (basal-bolus vs. biphasic, $p=0.81$, Fisher's) or between those completing versus those not completing the period of blood glucose monitoring ($p=0.14$, Fisher's).

Table 7.1: Baseline characteristics of study participants			
Awareness status (Clarke method)	Aware	Impaired Awareness of Hypoglycaemia	<i>p</i> value
n (% female)	76 (52.6%)	22 (45.5%)	<i>p</i> =0.63
Current age (years)	12.0 (10.5-13.3)	8.2 (5.7-10.5)	<i>p</i> =0.0001
Duration of diabetes (years)	4.1±3.2	3.2±2.0	<i>p</i> =0.24
Age at diagnosis (years)	7.4 (4.1-10.1)	4.2 (2.7-6.7)	<i>p</i> =0.012
HbA1c at clinic (mmol/mol(%))	74±9 (8.9±1.0)	72±9 (8.7±1.0)	<i>p</i> =0.46
Family history of T1DM* (n (%))	8 (10.5%)	3 (13.6%)	<i>p</i> =0.71
Data are median (interquartile range) or mean ± SD unless otherwise indicated			
*parent or sibling with T1DM			

7.33 Clarke and Gold Methods compared

Figure 7.1 displays a comparison of self-reported or parentally determined awareness status using both the Gold or Clarke methods. Using the Clarke method, 22 (22.4%) parental responses indicated that IAHD was present compared with 67 (68.4%) parental responses using the Gold method. A significant association was observed between the parents' and children's responses when using the Clarke method ($p < 0.001$, $r_s = 0.55$, Spearman's) but no positive correlation was found using the Gold method ($p = 0.28$, $r_s = 0.12$, Spearman's). No linear correlation was found

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between the two methods ($p=0.14$) with little or no positive correlation ($p=0.14$, $r_s=0.25$, Spearman's).

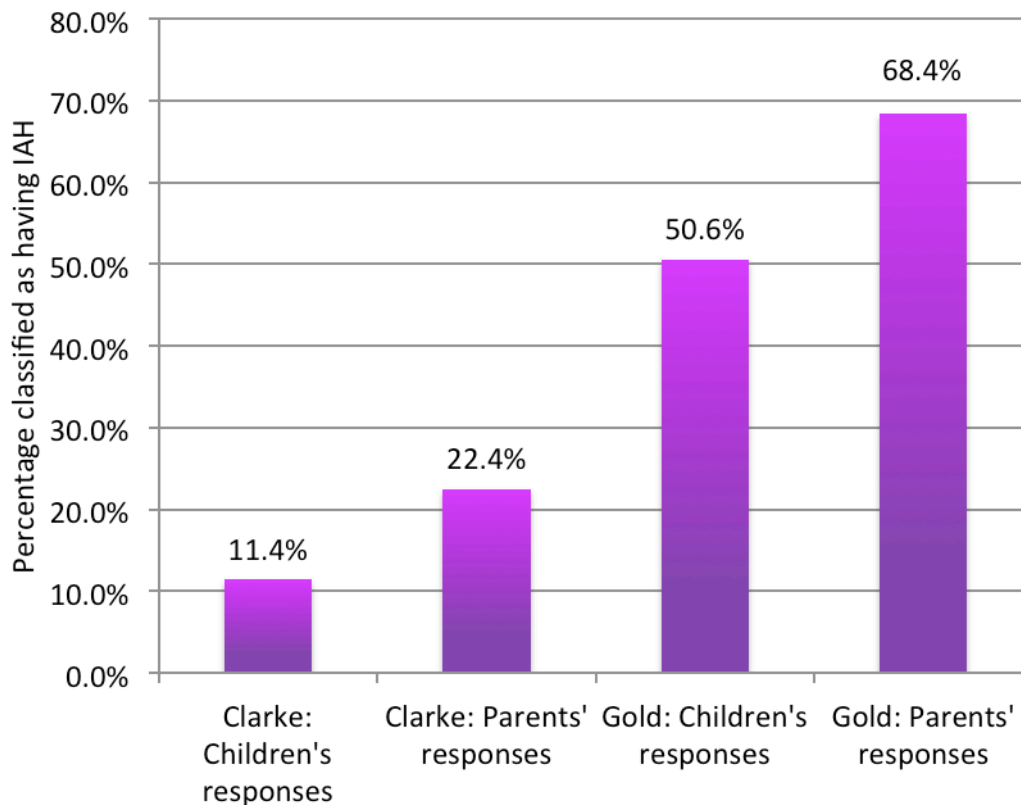


Figure 7.1: Percentage classified as having impaired awareness of hypoglycaemia according to Clarke or Gold methods using parental or child responses (of those able to answer)

Previous studies have demonstrated that young people with IAH have an increased risk of hypoglycaemia requiring medical attention (Ly et al., 2009). While this was evident when participants were classified using the Clarke method (see below), it was not apparent when using the Gold method (Aware vs. IAH, $p=1.00$, Fisher's). Similarly, no significant increase was observed in hypoglycaemia requiring third-party assistance between those with normal awareness or IAH using the Gold method ($p=0.08$, Fisher's). Therefore the Gold method did not show any of the expected differences in baseline demographics between awareness states.

The methods section (section 7.21) discusses the cut-off used to define impaired awareness of hypoglycaemia. During the publication process (see Appendix 4 for

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published manuscript) peer reviewers commented on the number of groups used to define awareness status and the cut off used. If a cut-off of 4 or greater is used to define impaired awareness of hypoglycaemia then 9.2% (n=9) of participants had impaired awareness of hypoglycaemia using the Clarke method and 35.7% (n=35) had impaired awareness using the Gold method. Table 7.2 shows the proportion of participants requiring 3rd party assistance or hospital admission using the revised cut-off. Using the Gold method table 7.2 illustrates that the proportion requiring 3rd party assistance or hospital attendance is very similar whether a participant is categorised as having normal or impaired awareness; this is at odds with the expectation that the impaired awareness group would have a greater risk of significant hypoglycaemia. Using the Clarke method, despite the small numbers in the impaired group, the difference between the groups requiring 3rd party assistance remains significant (p=0.001, Fisher's) but there is no significant difference between the groups in terms of requiring admission to hospital (p=0.23, Fisher's).

Table 7.2: Proportion of participants requiring 3 rd party assistance or hospital admission according to awareness status (using score of ≥ 4 for both methods)		
	Required 3 rd party assistance	Required hospital admission due to hypoglycaemia in the 12 months preceding the survey
Normal awareness of hypoglycaemia using Clarke method n(%)	29 (32.6%)	21 (23.6%)
Impaired awareness of hypoglycaemia using Clarke method n(%)*	9 (100%)	4 (44.4%)
Normal awareness of hypoglycaemia using Gold	24 (38.1%)	16 (25.4%)

method n(%)		
Impaired awareness of hypoglycaemia using Gold method n(%)	14 (40.0%)	9 (25.7%)

For the reasons outlined above, the Clarke method, assessed using parental responses, was considered a more effective and reliable predictor of awareness status in this paediatric cohort and so was used hereafter to categorise awareness status.

7.34 Recognition and frequency of hypoglycaemia

Participants completed a mean of 4.4 tests per day over the four week period with mean (\pm SD) blood glucose 9.7 mmol/L (\pm 4.8) with no difference in testing frequency between awareness states ($p=0.67$, t-test). Almost all participants (97%) experienced hypoglycaemia (defined as blood glucose <4.0 mmol/L) while more than two thirds (70.2%) had experienced at least one blood glucose <3.0 mmol/L. Over the four week period the mean (\pm SD) number of blood glucose readings <4.0 mmol/L and <3.0 mmol/L were 10.2 (\pm 7.3) and 2.3 (\pm 2.6) respectively. Table 7.3 shows the mean number of blood glucose readings per participant according to awareness status. The number of blood glucose readings less than 3.0mmol/L, per participant, was not affected by insulin regimen (basal-bolus vs. any biphasic, $p=0.70$, t-test), awareness status ($p=0.11$, t-test), age (<10 years compared with >12.65 years, $p=0.93$, t-test), HbA1c <69 mmol/mol (8.5%) compared with >78 mmol/mol (9.3%), $p=0.65$, t-test) or duration of diabetes (<2 years compared with ≥ 5 years, $p=0.18$, t-test).

Table 7.3: Frequency of hypoglycaemia according to awareness status			
Biochemical cut off (capillary blood glucose)	Mean number of hypoglycaemic episodes over 4 week period per participant		
	Aware	IAH	t test

BG<4.0 mmol/L	11.0±6.9	8.9±7.9	<i>p</i> =0.72
BG<3.5 mmol/L	6.7±5.6	4.0±3.5	<i>p</i> =0.34
BG<3.0 mmol/L	2.7±2.9	1.44±1.1	<i>p</i> =0.11
Data are mean ± SD			

During the period of prospective monitoring, hypoglycaemia questionnaires were completed for 490 of 583 (84.0%) episodes of hypoglycaemia recorded in the participants' blood glucose diaries; three of these events required hospital admission. Hypoglycaemia was most frequently reported in the late afternoon with 31.8% (n=156) of events occurring between 15:00h and 18:59h, and was least commonly reported overnight with 9.2% (n=45) of episodes between 23:00h and 06:59h (Figure 7.2).

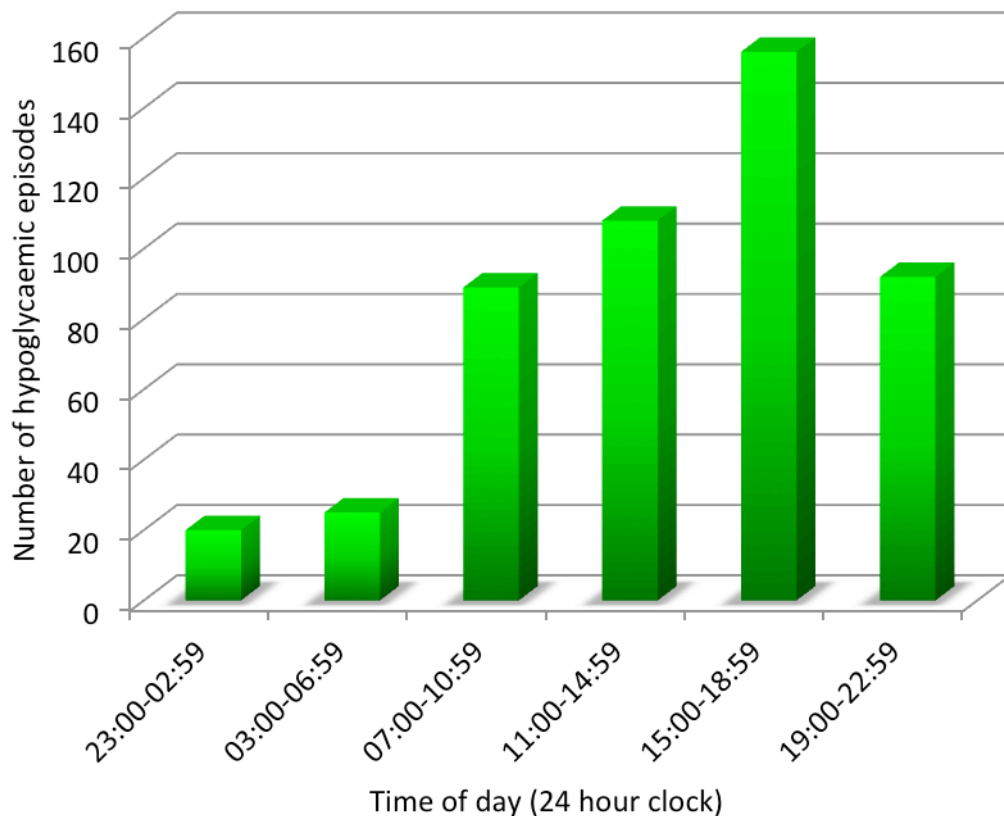


Figure 7.2: Number of hypoglycaemic episodes occurring according to time of day

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Participants with normal awareness were more likely to recognise hypoglycaemia themselves, with 48.2% of hypoglycaemic events being recognised by children in the aware group compared with 37.5% in the IAH group ($p < 0.05$, Fisher's). All parents (or another third party) were poor at recognising hypoglycaemia with 3.7% of parents recognising hypoglycaemia in the aware group compared with 6.3% in the IAH group ($p = 0.29$, Fisher's); the remaining episodes were incidental findings on routine biochemical testing (Figure 7.3).

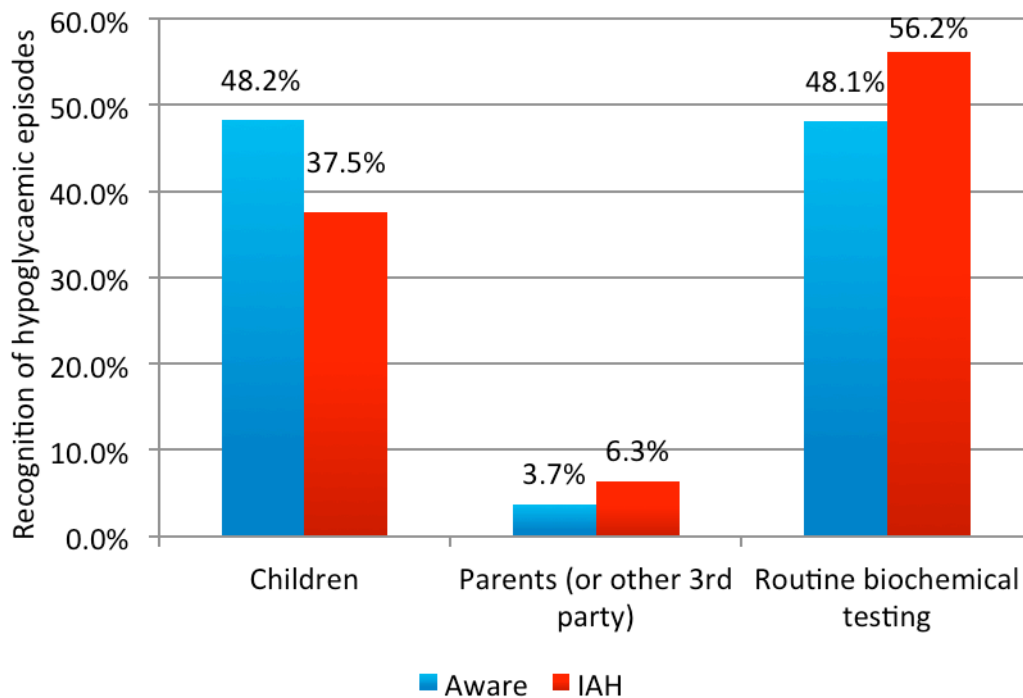


Figure 7.3: Source of recognition of each hypoglycaemic episode according to awareness status

7.35 Hypoglycaemia requiring third-party assistance or hospitalisation

Third-party assistance was more commonly required in those categorised as having IAH (Figure 7.4) and in younger participants ($p = 0.0001$, t-test). Increasing independence of children as they became older was demonstrated: 82% of the lower age tertile required assistance to treat hypoglycaemia in the preceding six months compared with 15% of the upper age tertile ($p = 0.0001$, Fisher's). Hospital data were reviewed for each participant in the 12 months preceding clinic attendance. Seven participants (7.1%) required hospital treatment for hypoglycaemia-related

events in the 12 months before admission, one participant attended twice. Two of these episodes were associated with seizure and six participants required in-patient admission. A significantly greater proportion of participants with IAH required hospital treatment compared with those with normal awareness (Figure 7.4). Accurate retrospective parental recall of hypoglycaemia requiring hospital treatment was demonstrated with eight parents reporting hypoglycaemia requiring hospital attendance in the preceding 12 months; one parent falsely attributed the primary cause of the admission to hypoglycaemia.

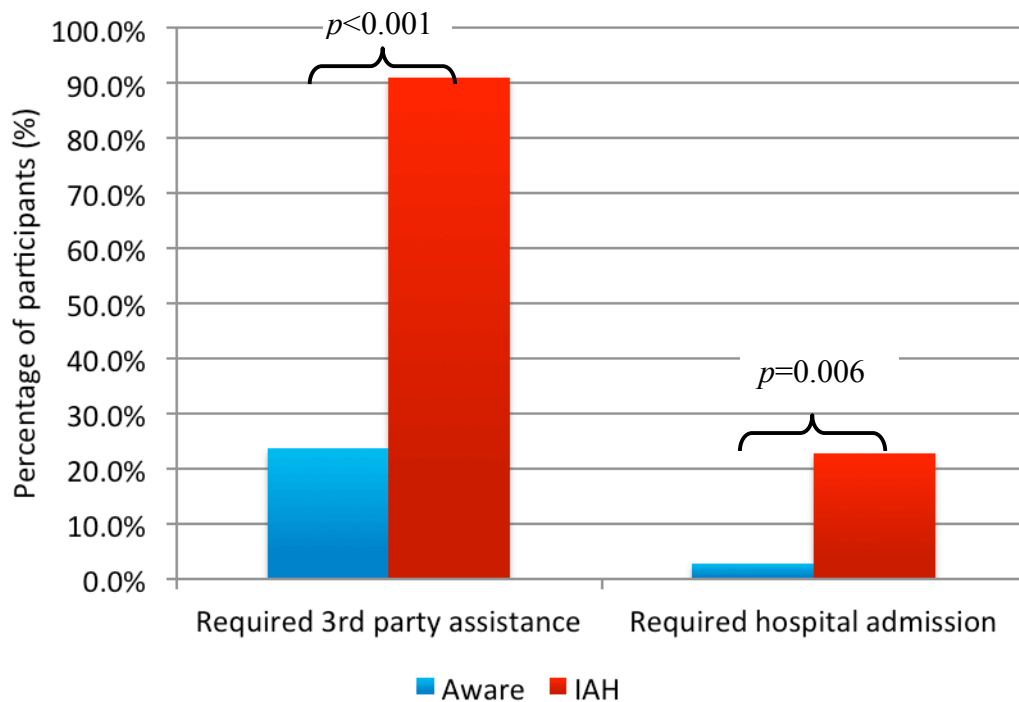


Figure 7.4: Proportion of participants requiring 3rd party assistance or hospital admission according to awareness status (*p* values given above, Fisher's)

7.36 Symptomatology of hypoglycaemia

Symptoms listed in the hypoglycaemia questionnaires are reproduced in appendix two. The most commonly reported symptoms by children were trembling (82.3%) and weakness (70.6%) (Figure 7.5). Parents more commonly observed behavioural symptoms including irritability (66.7%) and aggressiveness (46.5%) (Figure 7.6);

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pallor as a feature of hypoglycaemia was reported by just over half of the parents (51.5%).

Certainly in adults, loss or diminution of symptoms is thought to be a fundamental part of the development of IAH. Participants with IAH were more likely to report loss of symptoms with normal awareness when compared with those with IAH (31.8% versus 7.9% respectively, $p=0.008$, Fisher's). Diabetes duration or current age did not affect the likelihood of symptom loss ($p=0.10$ & $p=0.19$ respectively, t-test).

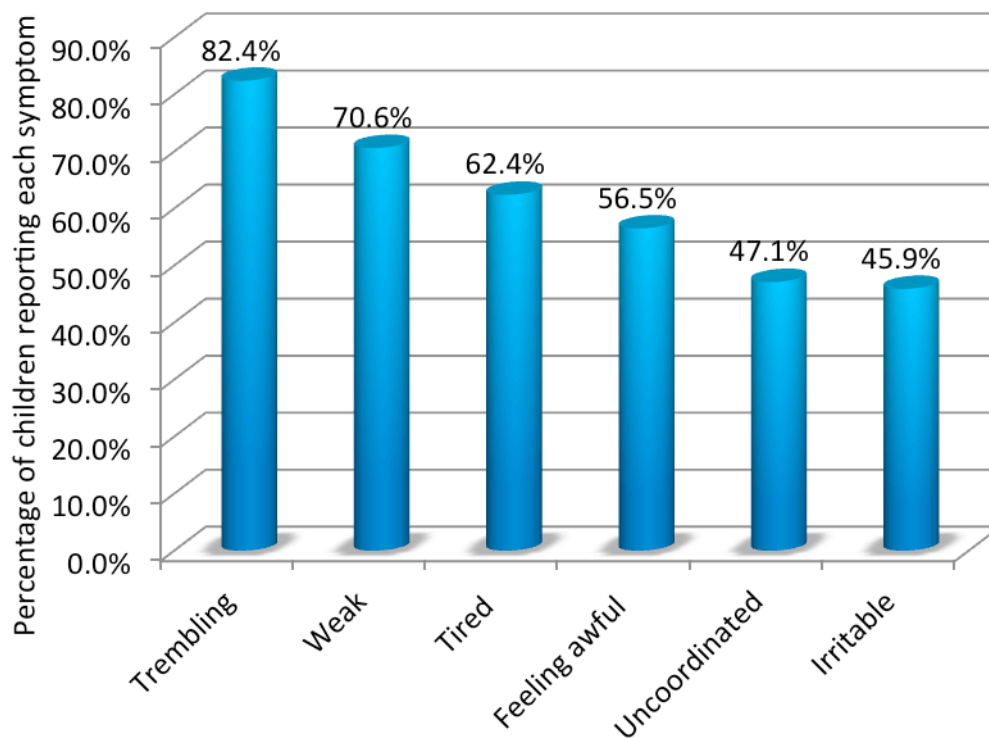


Figure 7.5: Most frequently reported clinical features by children

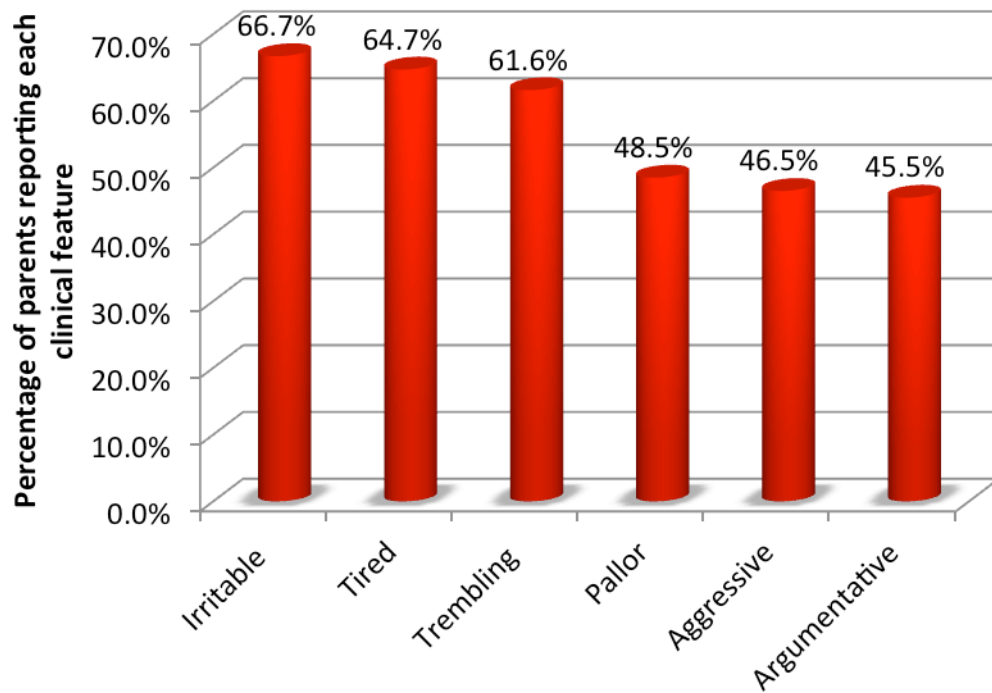


Figure 7.6: Most frequently reported clinical features by parents

Principal components analysis (PCA) was used to identify subgroups of symptoms. Two separate PCAs were performed; scree plots suggested that parentally reported symptom data could be adequately explained by four components and self-reported symptoms by three components. The respective number of components was then extracted using PCA, followed by Varimax rotation with Kaiser Normalization. Using parental reporting the symptoms segregated into “autonomic”, “neuroglycopenic”, “behavioural” and “non-specific” rotate components and using self-reporting the symptoms segregated into “autonomic/neuroglycopenic”, “behavioural” and “non-specific”. Once segregated into these components, the loading patterns were used to form symptom scores for each rotated component.

Parentally reported symptom intensity scores were significantly lower in participants with IAH for autonomic symptoms ($p=0.006$, t-test) but not for neuroglycopenic or behavioural symptoms ($p=0.09$ and $p=0.20$ respectively, t-test).

Multinomial logistic regression is a classification method used to predict the possibilities of the different possible outcomes of a categorically distributed variable,

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given a set of independent variables. Multinomial logistic regression models were fitted to data using the “mlogit” library of “R” (R Development Core Team, 2010). Parentally reported symptom subgroups (“behavioural”, “neuroglycopenic”, “autonomic” and “non-specific”) were compared as predictors of awareness using four models to predict the probability of a particular outcome (i.e. parentally reported awareness of hypoglycaemia), from the factor score in each of the four symptom classes. Factor scores for each of the four symptom classes were conventionally derived from factor analysis by regression method. Each model is a multinomial logistic regression model of a symptom subgroup in which the factor score is the predictor of a multinomial outcome consisting of two awareness states; aware and impaired. Consequently each model estimated a slope coefficient representing change in relative risk of choosing aware over impaired for unit increase in the factor score. The model-predicted probability of the particular outcome choice "aware" was obtained from the relative risks over a range of factor scores.

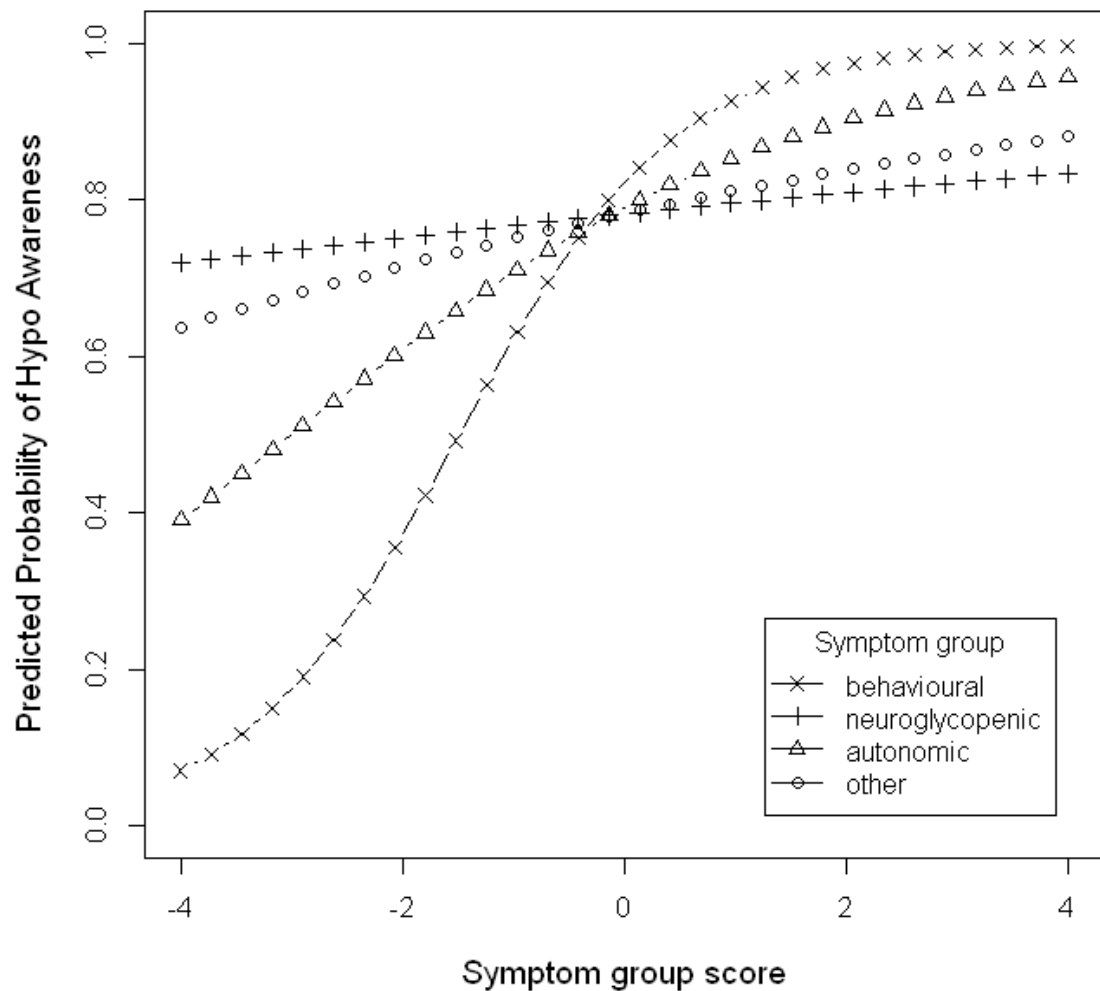


Figure 7.7: Probability of each symptom group predicting awareness status (Clarke method using parental responses)

Figure 7.7 shows the model-predicted probability of choosing aware over impaired as a function of the factor score in each of the four symptom groups. The best fitting model used behavioural symptoms as a predictor and was the only model to achieve significance ($p < 0.01$), according to the chi-squared likelihood ratio test comparing the full model with an intercept-only model (Nagelkerke R-squared for the behavioural model was 0.18). The behavioural group of symptoms was therefore the best predictor of awareness status. The same procedure was then used to compare how the behavioural symptom group predicted hypoglycaemia awareness as determined by the Clarke and Gold methods, either self- or parentally-reported; the two that used the Clarke method were significant ($p < 0.05$). The use of behavioural

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symptoms and the Clarke method, whether obtained from the parent or the child's observations, were better at predicting awareness status than the Gold method (Figure 7.8).

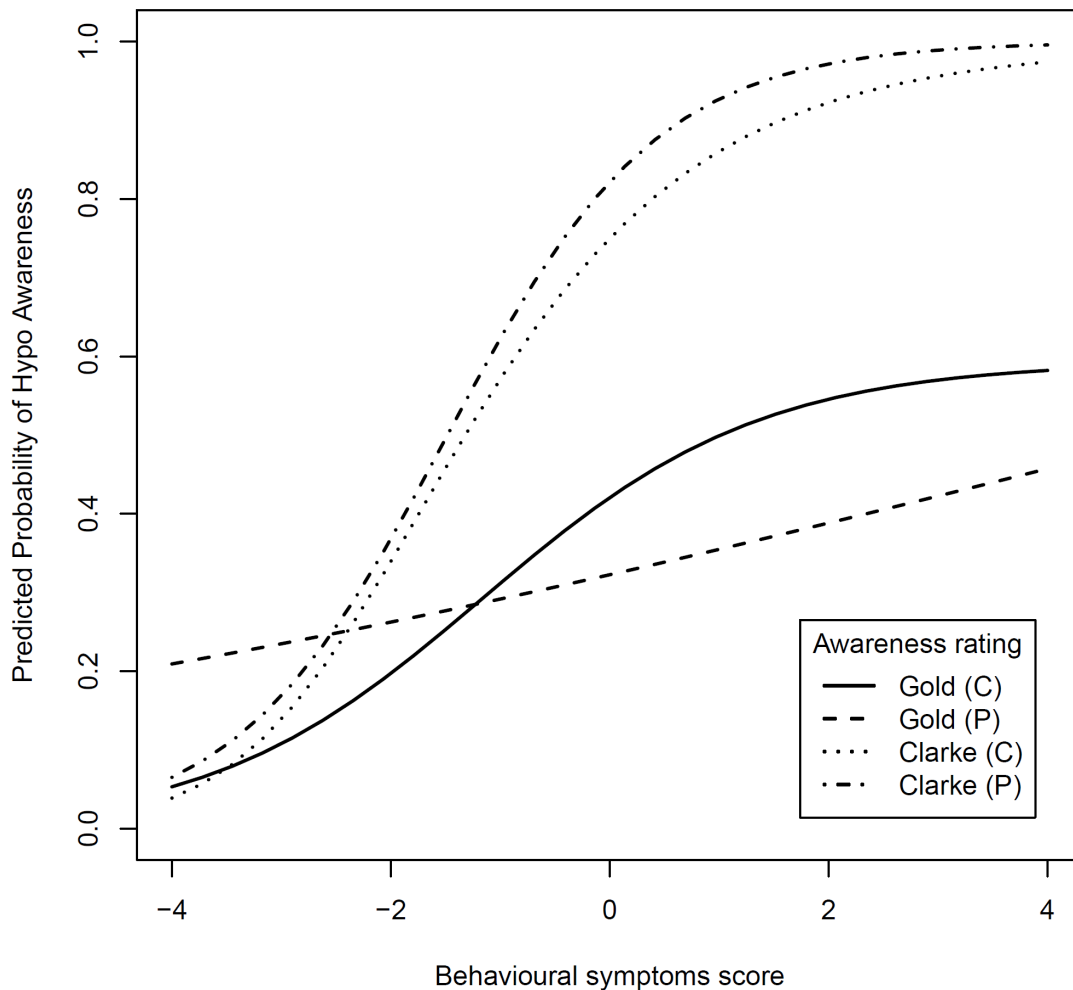


Figure 7.8: Probability of predicting awareness status using behavioural symptoms using the different methods and assessors of hypoglycaemia awareness

7.37 Effect of puberty on hypoglycaemic symptoms

A greater proportion of female participants in the present study had reached puberty in comparison with male participants (62.8% vs. 47.9% of participants respectively). Participants of uncertain pubertal status were excluded from further analysis (n=9 (9.1%) of whom 5 were male). Total symptom scores increased significantly in participants that had reached puberty (pre-pubertal vs. pubertal or post-pubertal,

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$p < 0.001$ for both parental and self-reporting of symptoms, t-test). Sweating and trembling showed the largest increments in symptom score (Figure 7.9).

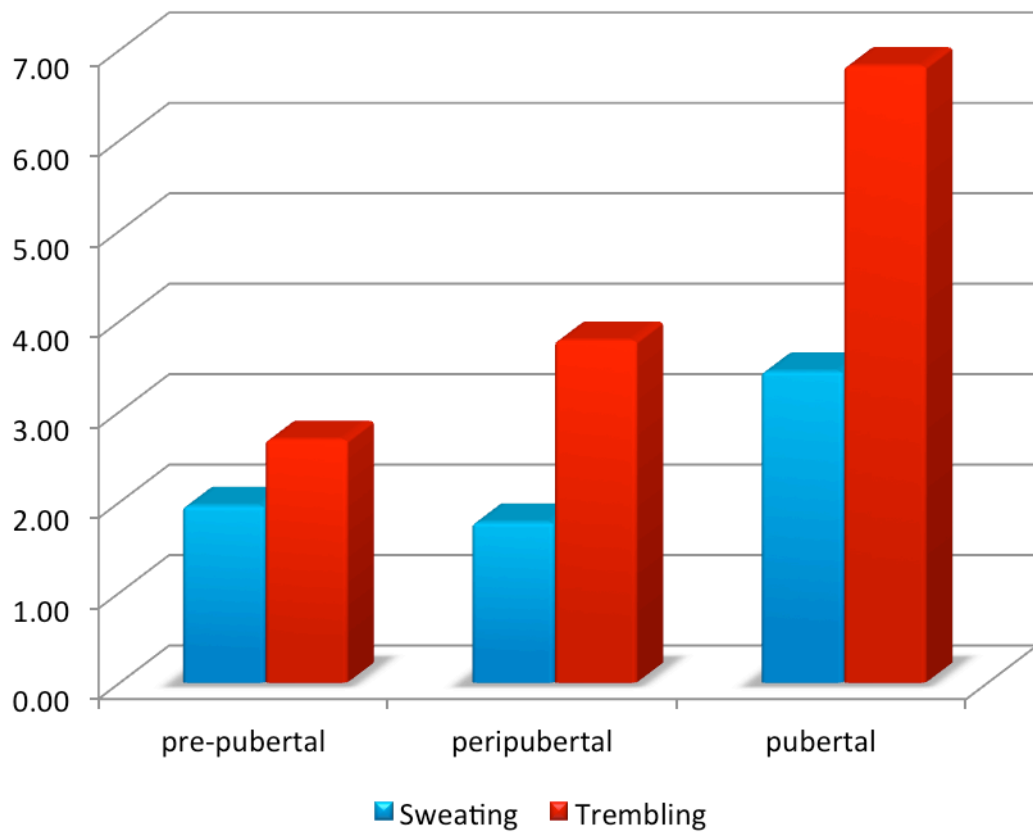


Figure 7.9: Change in intensity of symptoms scores (sweating and trembling) with pubertal status

7.4 Discussion

In the present study, two questionnaires used in adults to assess hypoglycaemia awareness were applied to a paediatric cohort to evaluate their value in assessing awareness status in children and adolescents. In contrast to observations in adults in which these two methods showed good concordance (Geddes et al., 2007), the results correlated poorly in children with T1DM (Figure 7.1). When categorised using the Clarke questionnaire, participants with IAH had a significantly greater risk of requiring third-party assistance or hospital admission to treat hypoglycaemia, thus identifying an “at risk” subset of children that was not identified using the Gold method. Children may have difficulty in comprehending the solitary wide-ranging question of the Gold method compared with the closed and specific questions of the Clarke method.

7.41 Prevalence of IAH

The prevalence of IAH obviously depends on the cut off chosen to represent impaired awareness. Both the current study and the Ly *et al* study reduced the number of possible awareness states from 3 to 2 (Ly et al., 2009). The Ly *et al* study amalgamated the normal awareness and intermediate awareness group and therefore a score ≥ 4 was taken to indicate impaired awareness rather than ≥ 3 used in the current study. In children with T1DM of relatively short duration (mean 3.9 years), the present study indicated a prevalence of IAH of 22.4% (using the Clarke method with a cut off of ≥ 3) falling to 9.2% when using the Clarke method with a cut-off of ≥ 4 . An Australian study (mean duration of diabetes 5.4 years, mean age 12.8 years) used the Clarke method and reported a slightly higher prevalence of 29%; in both studies, the participants with IAH were significantly younger. In the Ly *et al* study the older age and longer duration of diabetes in participants may have affected the percentage of participants assessed as having IAH. The development of IAH was attributed to progressive counter-regulatory hormonal failure, although no relationship was found between IAH and duration of diabetes. As in the present study, IAH was associated with a higher frequency of severe hypoglycaemia (37.1 vs. 19.3 episodes per 100 patient years) (Ly et al., 2009).

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A Hungarian group used a single question to determine awareness status; the 36.9% of participants who were “sometimes” or “never” aware of hypoglycaemia were classified as having impaired awareness (Barkai et al., 1998). The DirecNet study group claimed that Hypoglycaemia Associated Autonomic Failure (HAAF) was present in one third (Diabetes Research in Children Network Study et al., 2009). Limitations with the DirecNet study design make the results difficult to interpret; the mean blood glucose nadir in this cohort with good glycaemic control, may not have been sufficiently low to provoke a counter-regulatory response (Graveling et al., 2010). While counter-regulatory hormonal failure does co-segregate with IAH in adults with T1DM it is not the cause of IAH *per se* (Dagogo-Jack et al., 1994, Ryder et al., 1990). Taken as a whole, the above studies would suggest that the prevalence of impaired awareness in children is 22-37%.

7.42 Identification of hypoglycaemia

Hypoglycaemia may be difficult to identify in a younger age group because of limited vocabulary and an inability to describe subjective sensations as specific symptoms. In the Australian study only children between the ages of 10-12 years and their parents were both asked to complete the questionnaire; older children completed the questionnaire by themselves while the parents did this on behalf of the younger children (Ly et al., 2009). The present study demonstrated that children aged 9 years or above can provide sufficient information to allow an accurate assessment of their awareness status and that their assessment closely matched that of their parents.

All participants in the present study, but particularly those with IAH, were poor at self-identification of hypoglycaemia with most episodes being detected by an observer or by biochemical measurement. This suggests that asymptomatic hypoglycaemia is common, and this has been confirmed using CGM (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010, Amin et al., 2003). Other studies have reported poor recognition of hypoglycaemia, with parents and children failing to detect hypoglycaemia in >50% and >40% of instances, respectively (Gonder-Frederick et al., 2008). A much earlier study also noted that both parents and children were poor at estimating their blood glucose level

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and recognising hypoglycaemia (Eastman et al., 1983). A very recent study using CGM in children <7 years old found that only 32% of hypoglycaemic events were detected (Sundberg and Forsander, 2014).

Parents were also poor at recognising hypoglycaemia in the current study (Figure 7.3). Factors that might impair a parent's ability to recognise a hypoglycaemic episode in their child might include distraction, educational attainment and the level of independence of the child with regard to self-management of their diabetes. Parents' retrospective recall of hypoglycaemia requiring hospital treatment was confirmed to be robust for up to 12 months.

7.43 Frequency of hypoglycaemia

Almost all participants experienced at least one episode of confirmed hypoglycaemia (blood glucose <4.0mmol/L) over a 4-week period with two thirds experiencing at least one blood glucose <3.0 mmol/L. This compares with 52% experiencing at least one blood glucose \leq 3.0mmol/L over three months in a Finnish study (Tupola and Rajantie, 1998). The present study reported the lowest frequency of hypoglycaemia when children were asleep. However, overnight blood glucose testing was not undertaken routinely and so only symptomatic episodes causing the participant to awaken were identified. This would underestimate the frequency of nocturnal hypoglycaemia. Catecholamine responses to hypoglycaemia are attenuated or absent during sleep and asymptomatic nocturnal hypoglycaemia is common (Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study, 2010, Jones et al., 1998).

7.44 Symptoms experienced during hypoglycaemia

Commonly experienced symptoms during hypoglycaemia in children have been documented previously, with strong agreement in terms of symptom intensity being demonstrated between children and their parents (McCrimmon et al., 1995, Ross et al., 1998). Good concordance between parental and self-reported hypoglycaemia symptoms was noted in 40 pairs of children and parents with a similar age, disease duration and level of glycaemic control (Chiarelli et al., 1998). In the present study

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pallor was observed by 51.5% of parents, consistent with previous reports (McCrimmon et al., 1995).

In a cohort of T1DM adults with a short duration of diabetes (mean 3.9 years), with the exception of glucagon deficiency, the prevalence of counter-regulatory hormonal deficiencies would be anticipated to be low (Cryer, 2012). A small proportion of the present study cohort (n=11, 11.1%) had a clear diminution or absence of hypoglycaemia symptoms; hormonal responses were not measured so co-existing counter-regulatory failure cannot be excluded. With increasing duration of diabetes and exposure to antecedent hypoglycaemia, some reduction in symptom intensity might be expected; this is apparent in adults with T1DM, where the prevalence of IAH rises progressively with duration of diabetes (Pramming et al., 1991, Olsen et al., 2014).

Principal components analysis (PCA) was used to show the latent structure of hypoglycaemic symptoms. As reported previously (McCrimmon et al., 1995), the children were unable to distinguish between autonomic and neuroglycopenic symptoms, resulting in three symptom subgroups (“behavioural”, “neuroglycopenic/autonomic” and “other”) in comparison to four subgroups with parental reporting. In contrast, comparative factor analysis performed by a Canadian group segregated symptoms into 3 subgroups for both adults and children (“behavioural”, “neuroglycopenic/autonomic” and “other”) with no separation of neuroglycopenic and autonomic symptoms (Amin et al., 2014). Tupola *et al* (1998) did not ascertain the full contribution of behavioural symptoms when assessing episodes of hypoglycaemia (Tupola and Rajantie, 1998). Multinomial logistic regression showed that autonomic and behavioural symptom groups, whether experienced by the child or perceived by the parent, could be used to predict awareness status using the Clarke method (Figure 7.8). In contrast with the adult population, behavioural symptoms were the most useful in predicting awareness status, which may suggest that a behavioural component may contribute to the development of IAH. Behavioural symptom intensity was not significantly reduced in participants with IAH.

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Parental involvement has been shown to increase frequency of SMBG and improve glycaemic control although a need to transfer responsibilities to the child is recognised (Anderson et al., 1997, Palmer et al., 2004). Coping strategies would need to take into account the level of cognitive maturity of each child with T1DM; the quality of the parent-adolescent relationship is an important factor (Band and Weisz, 1990, Berg et al., 2011). Social conflict between peers was shown in a review of qualitative studies to have an impact on glycaemic control with a beneficial effect noted with good relationships (Palladino and Helgeson, 2012, Pendley et al., 2002).

7.45 Impact of puberty on hypoglycaemic symptoms

When the effect of puberty on hypoglycaemia symptomatology was examined previously in a small group of children and adolescents with T1DM, sweating was not observed during hypoglycaemia in pre-pubertal children (Ross et al., 1998). Maturation of sweat glands occurs during puberty, which may augment the sweating response. In the present study symptom intensity increased significantly with puberty in all symptom categories, with scores for trembling and sweating showing the largest increments. The generally higher symptom scores could be attributed to increased physical and emotional maturity. The effect of ageing on symptom scores has been reported previously (Tupola and Rajantie, 1998), and with increasing independence and self-treatment, a parent would become less cognizant of the type and intensity of the symptoms experienced by their child.

7.46 Study limitations

The main limitations of the present study are the small sample size and completion rate of 58%. Despite these limitations, many findings were highly significant and consistent with those reported previously. Care was taken to obtain answers from children without the help of their parents although inevitably children did attempt to seek some guidance from their parents. Parents were asked to let their children answer but non-verbal communication may have influenced some of the answers. Performing the interviews separately might have helped but may have been less acceptable to the participants and their parents.

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The present study was pragmatic, so nocturnal blood glucose testing was not obligatory and CGM was not utilised as neither are part of routine clinical care. The frequency of asymptomatic hypoglycaemia may therefore have been underestimated, particularly during sleep. Continuous glucose monitoring technology may have been useful rather than self-monitoring of capillary blood glucose to provide a more complete picture of participants' glycaemic profiles. In particular it would have provided more information regarding asymptomatic episodes of hypoglycaemia particularly at night. There are however issues with the performance of CGM in the hypoglycaemic range and sensor failure rates may have been higher in children not used to wearing the blood glucose sensors. Real time CGM is also likely to affect the participant and their parent's behaviour, for example being alerted to the occurrence of asymptomatic hypoglycaemia. The CGM data would therefore ideally have been blinded rather than real-time.

An Australian group conducting a similar study had reduced the number of awareness states from 3 to 2 previously. In retrospect defining the impaired awareness group with a cut off of 4 or more would have allowed easier comparison with the Ly et al (2009) group. Both studies can be criticised for having an unvalidated group (the "aware" group in the Ly et al study and the "impaired" group in the current study).

In retrospect, pubertal assessment using a recognised staging method would have reduced the proportion of participants in whom pubertal status was uncertain (Tanner and Whitehouse, 1976). This would have allowed more accurate assessment of the impact of puberty on hypoglycaemic symptom experienced and their intensity. Pubertal screening is not routinely performed as part of the usual clinic visit and so would have required additional examination. The participants may have found this embarrassing and been less likely to take part in the study.

From clinical practice we know that scrupulous avoidance of hypoglycaemia can restore hypoglycaemia awareness. The assessment of impaired awareness was only done once, at baseline. An assumption was made that the awareness state of the participant would not change over the four-week monitoring period. This criticism could also be levelled at many other studies that fail to reassess awareness status over

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much longer periods of study. A repeat of the baseline questionnaire at the end of the study period could have been considered. Longitudinal assessment of awareness status and how it changes with respect to age and pubertal status merits further research in the paediatric age group.

7.5 Chapter Summary

In summary, the recognition of hypoglycaemia by children with T1DM is a dynamic process. Various factors, including the distraction of concurrent physical or mental activities can delay recognition of hypoglycaemia and corrective action. The underlying pathophysiological mechanisms of IAH include a blunted sympatho-adrenal response combined with altered cognitive and behavioural responses to hypoglycaemia. Each factor is modulated by a variety of mechanisms and so may alter in importance with each child as they progress through adolescence into adulthood. Increasing physical and mental maturation may result in improved ability to identify and appreciate the significance of early warning symptoms, allowing earlier corrective action to be taken.

In contrast with the adult population, the ability to predict awareness status is strongest when behavioural symptoms are used. Behavioural patterns are therefore particularly important in the recognition of hypoglycaemia in children and introduce the concept of a “voluntary” component to hypoglycaemia awareness. Behavioural modification techniques could be used to make a potentially rewarding activity (the child receives increased parental attention and a sugary snack) less attractive. Placing more emphasis on the significance of behavioural symptoms, rather than the traditional autonomic symptoms (e.g. sweating and shaking), may improve the ability of parents and health care professionals to identify hypoglycaemia. Clinicians may consider utilising the Clarke questionnaire to screen for IAH allowing the identification of an “at risk” cohort within their paediatric clinic population. The awareness status of children may change over time and therefore longitudinal studies are required to characterise any temporal changes associated with hypoglycaemia awareness.

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Chapter 8: Hypoglycaemia and driving in people with insulin-treated diabetes: self-treatment and adherence to recommendations for avoidance

8.1 Introduction

8.11 Effect of hypoglycaemia on driving performance

Hypoglycaemia is a common side effect of insulin therapy for diabetes and can interfere with everyday activities such as driving (Frier et al., 1980, Eadington and Frier, 1989, Inkster and Frier, 2013, Stork et al., 2006). Laboratory studies have demonstrated that cognitive functions critical to driving (such as visual information processing, attention, reaction times and hand-eye coordination) are impaired by hypoglycaemia (Warren and Frier, 2005, Inkster and Frier, 2012). Studies using driving simulators have shown that driving performance (i.e. inappropriate speed or braking, ignoring road signs and traffic lights and not keeping to lanes) is affected adversely by moderate hypoglycaemia (Cox et al., 1993, Cox et al., 2000). During simulation studies driving itself required higher dextrose infusion rates to maintain euglycaemia compared to watching a driving video; this increased metabolic demand predisposes drivers to hypoglycaemia (Cox et al., 2002). The decision to drive may also be impaired, particularly in those with impaired awareness of hypoglycaemia (IAH). During a driving simulator study only 4.2% of those with T1DM and normal awareness stated that they would drive while hypoglycaemic compared to 42.9% with T1DM and IAH (Stork et al., 2007).

Those with T1DM and a history of driving mishaps in the previous 12 months were compared to those with T1DM but no history of mishaps (Cox et al., 2010, Cox et al., 2003a). Save for a greater risk of severe hypoglycaemia in the later study, the groups were well matched in terms of duration of diabetes, age and glycaemic control. The driving performance of those with a history of driving mishaps deteriorated to a greater extent during hypoglycaemia thus perhaps identifying a subset of drivers particularly vulnerable to poor driving performance during hypoglycaemia.

8.12 Diabetes and the risk of road traffic accidents (RTAs)

A recent review article has examined this subject in detail (Inkster and Frier, 2013). Many studies have reported that overall RTA rates appear to be no higher in diabetic drivers (Stevens et al., 1989, Songer et al., 1988, Cox et al., 2006) whereas some studies have reported an increased risk of RTAs in drivers with diabetes (Songer and Dorsey, 2006, Cox et al., 2003b). The discrepancy is probably as a result of considerable heterogeneity of study design. The most recent UK based study showed that drivers with insulin treated diabetes were not at increased risk (Lonnen et al., 2008). A potential confounding issue was that the percentage holding a driving licence in diabetic and non-diabetic populations was not determined (Major et al., 2009).

The largest study examining RTA risk in drivers with diabetes analysed data from the entire adult Norwegian population (3.1 million) for just over 2 years with just over 170,000 taking diabetes medication (Skurtveit et al., 2009). People with insulin treated diabetes had a slightly increased risk of RTAs compared with the total population with an odds ratio of 1.4 (1.2-1.6), it is worth noting that those taking medication for peptic ulcers or gastro-oesophageal reflux (neither thought to affect driving performance) had a similar elevation in risk with an odds ratio of 1.3 (1.2-1.4). A meta-analysis of data from all these studies failed to show a significant increase in accident rates with a non-significant risk ratio of 1.26 (Bieber-Tregear et al., 2011).

The Canadian National Population Health Survey (large, representative and longitudinal study of Canadians) used self-reporting of diabetes status, insulin treatment and RTA occurrence. The proportion of those with diabetes and/or treated with insulin was not significantly increased in those who self reported a history of RTAs in the preceding 12 months (Vingilis and Wilk, 2012).

Part of the reasoning behind why many studies have failed to show a significant difference in RTA rates at a population level between people at risk of hypoglycaemia (mainly those with insulin treated diabetes) and the general driving population is that many countries introduce additional restrictions on drivers with

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insulin-treated diabetes. Patients with diabetes may also voluntarily restrict their driving activities to avoid putting themselves at risk. In addition, the cause of each RTA is usually multifactorial and there may be difficulty in controlling for concomitant fatigue, weather conditions, drug or alcohol use.

8.13 Hypoglycaemia and the risk of RTAs

Hypoglycaemia is recognised to be the cause of some crashes, people with a history of road traffic accidents exhibited poorer working memory during hypoglycaemia compared with no history of accidents (Campbell et al., 2010). Perhaps the most consistently identified factor that increases risk of RTAs in people with diabetes is severe hypoglycaemia; a history of severe hypoglycaemia in the preceding two years increased the risk of accident four-fold (Cox et al., 2009, Redelmeier et al., 2009). Cox *et al* (2009) prospectively followed 452 drivers for 12 months who reported monthly on any driving mishaps. Driving mishaps included a variety of driving related incidents including experiencing automated driving, someone else taking over driving and experiencing disruptive hypoglycaemia while driving. When adjusted for mileage severe hypoglycaemia, experience of hypoglycaemia while driving and a previous history of an RTA within the last 2 years were associated with an increased risk of driving mishap (Cox et al., 2009). Tighter glycaemic control (HbA1c of 57mmol/mol versus 63mmol/mol) also increased the accident risk although to a lesser extent than a history of severe hypoglycaemia, type of diabetes was not stated although with a mean age of diagnosis of 31.6 years and 80% receiving insulin therapy many will have had T1DM (Redelmeier et al., 2009).

The road traffic accident risk in people with T2DM who do not take insulin therapy is increased almost two-fold in people who have previously required medical attention for hypoglycaemia compared to those with no history of hypoglycaemia requiring medical attention; this difference persisted despite adjustment for potential confounders (Signorovitch et al., 2013). Cox *et al* (2009) found a slightly increased accident rate in those with insulin pump therapy although an earlier study had found no difference in road traffic accidents rates was observed between different insulin treatments (e.g. CSII) (Harsch et al., 2002, Cox et al., 2009).

8.14 Driving regulations for drivers with insulin-treated diabetes in the UK

In the United Kingdom driving licences are either issued as Group 1 licences (i.e. ordinary driving licence for cars, light vans or motorcycles) or Group 2 licences (i.e. vocational which allows lorries or buses to be driven). Treatment for diabetes is the reason for medical notification in almost 1 in 4 of such driving licences issued in the United Kingdom (UK); approximately 575,000 active licences with 13% being for Group 2 licences (Parkes et al., 2014). The European Union has issued directives on driving regarding the issuing of driving licences to individuals with diabetes. The most recent directive follows a European Working Group on Driving and Diabetes with the aim of harmonising the driving regulations applied by member states (Second European Working Group on Diabetes and Driving, 2006, The European Parliament and the Council of the European Union, 2006).

In 2012 the Driver and Vehicle Licensing Agency (DVLA) introduced the requirement that any driver with diabetes and a Group 1 licence who experienced more than one episode of severe hypoglycaemia in any 12 month period must inform the DVLA and be advised not to drive (Gallen et al., 2012). This change in legislation would mean that 44% of the intensively treated and 17% of the conventionally treated DCCT cohort would have lost their licences at some point during the trial period (Kilpatrick et al., 2013). A recent study in Denmark has shown that following implementation of this legislation self-reported rates of severe hypoglycemia have fallen by 55%, suggesting that the licensing change will encourage concealment of severe hypoglycemia (Pedersen-Bjergaard et al., 2014). The requirements for people with a Group 2 licence are more stringent; they must report any severe hypoglycaemic episode and may have their licence revoked after one event.

In the UK, the DVLA receives 30 police notifications per month regarding driving incidents related to hypoglycaemia while driving (Major et al., 2009). Consequently, careful avoidance of hypoglycaemia is recommended before and during driving (American Diabetes Association et al., 2014). This advice is particularly relevant for drivers receiving intensive insulin therapy, who may experience hypoglycaemia more frequently.

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Anecdotal reports suggest that many diabetic drivers do not follow all or any of these local recommendations, or those issued by the DVLA, the government body responsible for issuing driving licences (DVLA, 2014). Many drivers also claim to have received no advice on driving safety from health care professionals or the DVLA. However, the DVLA supplies a fact sheet with this advice with each renewal of a period restricted licence (i.e. every 1-3 years) (DVLA, 2014).

8.15 Study aims

The primary aims of the present study were therefore to assess awareness of, and adherence to, these recommendations for safe driving in people attending our clinic. In the UK, diabetes is considered to be a prospective disability for medical fitness to drive, and ordinary driving licences are period-restricted for insulin-treated drivers. A secondary objective was to determine how many drivers had declared their insulin-treated diabetes to the national licensing authority (DVLA) and to their motor insurance company.

It is important to note that this study predates the changes in driving regulations introduced in the UK in 2012.

8.2 Methods

A structured questionnaire was used to interview adults with diabetes attending outpatient clinics at the Department of Diabetes at the Royal Infirmary of Edinburgh. No patient identifiable information was collected, only anonymous data was analysed. Ethical approval for the study was obtained from the local Research Ethics Committee.

8.21 Subjects

People were eligible if they had been treated with insulin for at least one year, held a current UK driving licence, had driven within the preceding year and intended to drive in future. In total, 205 people were approached without selection during a two-month period, and 202 questionnaires were completed. Diabetes type was recorded, with 115 having T1DM, and 87 having T2DM treated with insulin, 11 of the latter group were taking a combination of oral hypoglycaemic agents and bedtime isophane insulin. One driver held a C1 licence, which permits the driving of commercial vehicles up to 7.5 tonnes, is subject to more strict medical assessment, and must be reviewed annually. Subject characteristics are shown in Table 8.1. The cohort appeared to be reasonably representative of the clinic's population of people with insulin-treated diabetes in terms of sex, age and type of diabetes.

Table 8.1: Subject characteristics			
Characteristic	All subjects (n=202)	T1DM (n=115)	T2DM (n=87)
Number (%) male	143 (70.8%)	73 (63.5%)	70 (80.5%)
Age (years)	51 (21-81)	44 (22-78)	58.5 (34-81)
Diabetes duration (years)	14 (1-55)	17 (1-55)	11.5 (1-35)
Insulin therapy (years)	10 (1-55)	17 (1-55)	5 (1-32)
HbA1c (%)*	8.3 (5.0-14.0)	8.2 (5.0-14.0)	8.4 (5.9-11.0)
HbA1c (mmol/mol)*	67 (31-130)	66 (31-130)	68 (41-97)
Data other than sex are given as median (range)			
*HBA1c DCCT aligned; local non-diabetic range: 31-43 mmol/mol (5.0-6.05%)			

8.22 Questionnaire

Participants were asked about their employment, driving habits, awareness of hypoglycaemia, experience of hypoglycaemia in general, experience of hypoglycaemia while driving and any associated accidents, blood glucose testing in relation to driving, and self-treatment of hypoglycaemia while driving. In most cases questions were not open-ended, but offered a choice of answers from which the participant selected the most appropriate. The questionnaire is reproduced in appendix three. Testing blood glucose before driving was defined as a measurement up to 30 min before the start of the journey. Participants rated their hypoglycaemia

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awareness using a validated scale from 1 (always aware) to 7 (never aware); ratings of 3 or higher were considered to indicate impaired awareness (Gold et al., 1994). To minimise ethical concerns that the driver might reveal unsafe driving practices, once the questionnaire was completed, an information sheet regarding safe driving practice and diabetes was given to all participants.

8.23 Statistics

For simplicity, questionnaire response options were combined into smaller numbers of categories for analysis. Data are presented as numbers of subjects (%) unless stated otherwise. Categorical variables were compared using the chi-square test with Yates' correction, with one degree of freedom. Between-group means were compared using independent-sample t-tests. Statistical significance was accepted at $p < 0.05$.

8.3 Results

8.31 Employment and annual mileage

One hundred and fifty-one participants (74.8%) were in employment. Eighty (53.0%) reported that driving was necessary for their job. Estimated total annual mileages were reported as follows: fewer than 5 000 miles: 68 drivers (33.7%); 5 000 to 10 000 miles: 69 drivers (34.2%); 10 000 to 20 000 miles: 49 drivers (24.3%); more than 20 000 miles: 16 drivers (7.9%).

8.32 Declaration to licensing authority and motor insurer

Almost all participants (195, 96.5%) were aware of the statutory requirement to inform the DVLA of their insulin treatment, but 12 of these individuals reported that they had not done so. A further eight of the 195 participants who were aware of the requirement reported that they had declared, but held licences that were not period-restricted; these individuals had presumably not reported their change from oral hypoglycaemic medication to insulin therapy. The remaining seven participants either were unsure, or believed that there was no statutory requirement, despite which six had declared to the DVLA. In total, therefore, 21 participants (10.4%) appeared not to have declared that they had insulin-treated diabetes.

Almost all participants (194, 96.0%) were aware that they should report their diabetes and insulin treatment to their motor insurance company, and 196 (97.0%) said that they had done so.

8.33 Blood glucose testing habits in relation to driving

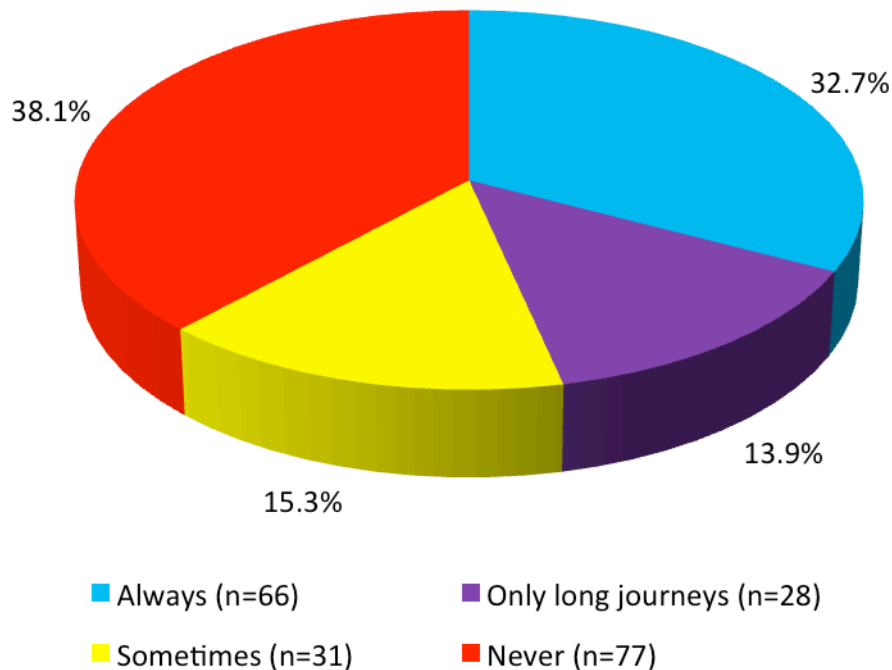


Figure 8.1: Reported frequencies of carrying a glucometer while driving

Figure 8.1 shows the participants' estimated frequencies of carrying glucose meters with them when driving. Sixty-six participants (32.7%) said that they always have a glucose meter with them when driving, and 77 (38.1%) reported never carrying one. The remainder indicated that they would take a meter on some journeys, or only on long journeys. In respect of testing blood glucose before driving, only six participants (3.0%) reported that they always test, with a further 22 (10.9%) reporting that they test on at least half of journeys. The majority (121, 59.9%) reported either that they never test before driving, or test only if they experience symptoms of hypoglycaemia. The reported testing frequency tended to increase with the length of the journey undertaken (Table 8.2).

Table 8.2: Association between frequency of blood testing before driving, and journey duration (percentages sum across rows)

Journey duration (hours)	Testing frequency		
	Never	Occasionally: <1 in 2 journeys	Regularly: >1 in 2 journeys
Long (>2)	70 (34.7%)	42 (20.8%)	70 (44.6%)
Medium (0.5-2)	109 (54.0%)	63 (31.2%)	30 (14.9%)
Short (<0.5)	137 (67.8%)	55 (27.2%)	10 (5.0%)

Participants were also asked whether they measure blood glucose during journeys when driving. Most participants (155, 76.7%) reported that they never test, and the remainder reported either that they would test occasionally or test during long journeys.

8.34 Perceived blood glucose for safe driving

Participants were asked what blood glucose level they considered to be the minimum for safe driving. A value of 4.0 mmol/L or higher was given by 151 (74.8%), 42 (20.8%) gave a value between 3.0 and 3.9 mmol/L, and nine (4.5%) considered levels below 3.0 mmol/L to be compatible with safe driving.

8.35 Experience of hypoglycaemia while driving

Sixty-four drivers (31.7%) had experienced hypoglycaemia while driving at some time previously, with 27 (13.4%) reporting episodes within the preceding year. Seven participants reported having had accidents at some time that they attributed to hypoglycaemia. Details of these individuals and the accidents are shown in Table 8.3.

Table 8.3: Road traffic accidents attributed to hypoglycaemia

Subject	Age (years)	Sex	Type of diabetes	Duration of insulin therapy	Damage from accident	Hypo awareness score (Gold, 1994)	BG testing before driving	Carbohydrate kept in car?
1	31	M	1	31	Vehicle & people	4	Never	Never
2	53	M	1	36	Vehicle	5	Occasionally	Always
3	53	D	2	15	Vehicle	2	Never	Always
4	57	M	1	32	Vehicle	3	Regularly	Always
5	61	M	1	16	Vehicle & people	1	If symptomatic	Always
6	63	M	1	32	None	4	Never	Always
7	64	F	2	10	Vehicle	2	Never	Always

8.36 Treatment of hypoglycaemia while driving

Figure 8.2 shows the participants' reported frequencies of keeping carbohydrate in the vehicle when driving. Carbohydrate was kept available at all times by 177 participants (87.6%), with a further 20 (9.9%) doing so intermittently.

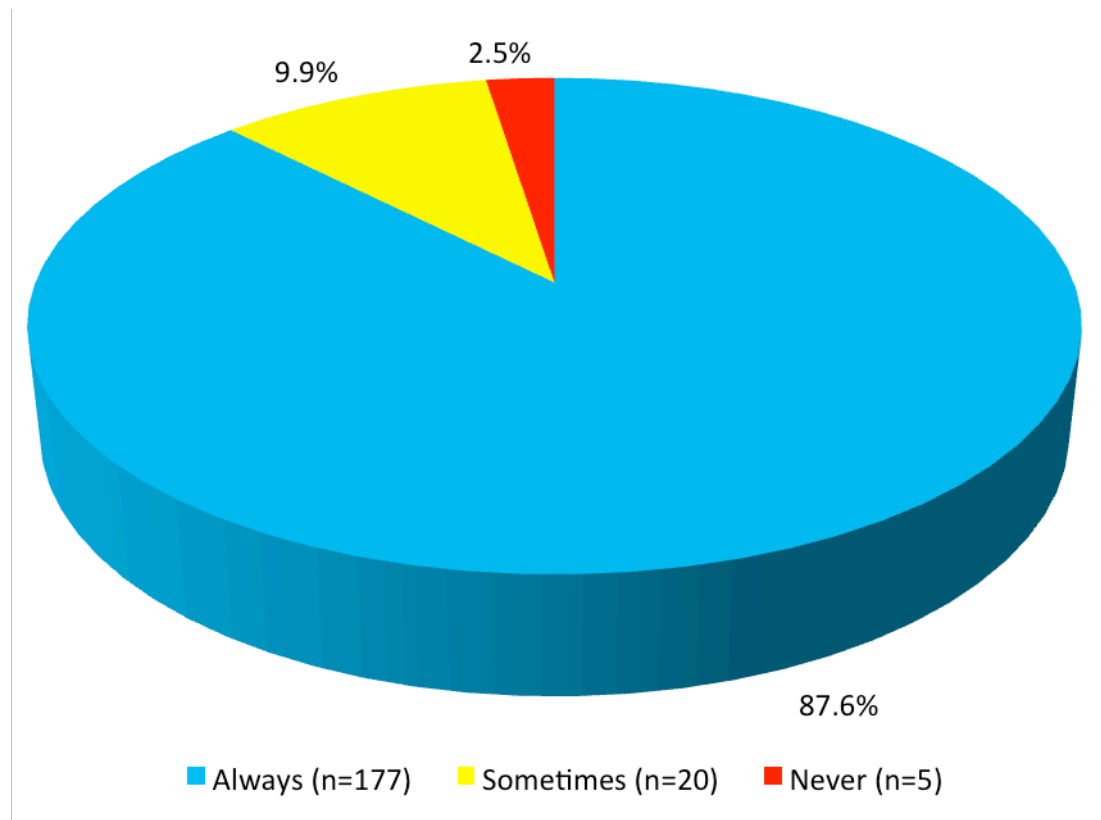


Figure 8.2: Reported frequencies of carrying carbohydrate in the motor vehicle

Participants were asked whether they would stop driving to treat hypoglycaemia, and how long they would wait before resuming their journey. The majority (192, 95.0%) reported that they would stop, but 13 of these (6.4%) reported that they would resume driving immediately after eating a snack. Most participants (128, 63.4%) indicated that they would wait between 10 and 30 minutes, and only 28 (13.9%) reported that they would wait for 30 minutes or more before recommencing driving.

8.37 Subgroup comparisons

Diabetes type

The 115 participants with T1DM were compared with the 76 participants with T2DM who were receiving full insulin therapy. A larger proportion of participants with T1DM were in employment than those with T2DM (88.7% vs 56.3%; $\chi^2=27.5$, $p<0.001$).

Drivers with T1DM were more likely to report experiencing frequent symptomatic hypoglycaemia (more than once per week) than T2DM drivers (37.7% vs 15.7%;

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$\chi^2=10.1$, $p=0.001$), and were more likely to have experienced hypoglycaemia while driving (44.4% vs 17.1%; $\chi^2=15.2$, $p<0.001$). Participants with T1DM reported never testing blood glucose before driving less frequently than those with T2DM (39.1% vs 61.8%; $\chi^2=9.5$, $p=0.002$), and more frequently reported testing before at least half of journeys (20.9% vs 5.3%; $\chi^2=8.9$, $p=0.003$).

Hypoglycaemia awareness

Of the 190 participants with previous experience of hypoglycaemia, 144 (75.8%) were classified as having normal awareness, and 46 (24.2%) as having impaired awareness. Most ($n=35$) of the latter group rated their state of awareness as 3 or 4 on a scale of 7. The drivers with impaired awareness were more likely to have suffered an episode of severe hypoglycaemia (requiring assistance) within the preceding year than the 144 with normal awareness (34.8% vs 13.2%; $\chi^2=10.8$, $p=0.001$). Compared with those with normal awareness, fewer of the drivers with impaired awareness reported that they never measure blood glucose before driving (34.8% vs 52.8%; $\chi^2=4.5$, $p<0.05$), with more reporting testing before at least half of journeys undertaken (23.9% vs 11.1%; $\chi^2=4.7$, $p<0.05$). A similar proportion of each group had previous experience of hypoglycaemia while driving (30.6% normal vs 43.5% impaired awareness; $p=0.15$).

Glycaemic control and previous experience of hypoglycaemia when driving

No significant differences were observed when the cohort was divided on the basis of glycaemic control (HbA_{1c} above and below the median) or previous experience of hypoglycaemia.

8.38 Minimum safe practice

One hundred (49%) of the participants admitted to one or more of the following:

- never measuring blood glucose before any journey of any duration;
- never carrying carbohydrate in the car;
- not stopping if developing hypoglycaemia while driving;

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- the belief that the minimum blood glucose for safe driving was below 3.0 mmol/L.

8.4 Discussion

8.41 Compliance with informing DVLA and motor insurers

In the present survey, almost all drivers had informed the DVLA and their insurer of their insulin treatment, which represents a substantial improvement over the last 30 years (Frier et al., 1980, Frier et al., 1984). A few drivers with T2DM had neglected to inform the DVLA of their conversion to insulin. Drivers with diabetes treated with oral antidiabetic medication are less likely to declare to the licensing authority (Steel et al., 1981), and it is important that this statutory obligation should be re-emphasised at the time of conversion to insulin.

8.42 Experience of hypoglycaemia while driving

Previous experience of hypoglycaemia while driving was reported by nearly a third of drivers, which is consistent with previous surveys in Edinburgh (Frier et al., 1980, Eadington and Frier, 1989) and Belfast (Stevens et al., 1989). More recently a prospective survey reported that over a 12-month period, 41% of drivers reported experienced “disruptive” hypoglycaemia while driving. It is noteworthy that the mean number of episodes reported by each of these drivers was 2.7 with a range of 1-26 (Cox et al., 2009). This would suggest that a subset of drivers experience hypoglycaemia while driving on a frequent basis.

8.43 The decision to drive including testing blood glucose levels before and during driving

To assess the safety of driving, a driver with insulin-treated diabetes needs to know their blood glucose with some accuracy, and appreciate the minimum level compatible with safe driving. Estimates of blood glucose based on symptoms are unreliable (Pramming et al., 1990, Weinger et al., 1995, Cox et al., 1985), and this has also been shown for subjects with T1DM in the context of driving. In a laboratory study by Weinger et al. (Weinger et al., 1999), 38% of subjects felt able to drive safely when their blood glucose was 2.8 mmol/L, and in a driving simulator study three quarters of subjects recognised neither the impairment of their driving performance, nor the presence of hypoglycaemia, at blood glucose levels as low as

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2.8 mmol/ l (Cox et al., 2000). It is therefore preferable that a decision to drive should be based on an actual measurement of blood glucose. Similar findings were observed by Clarke et al. in a prospective study, and diabetic drivers also reported feeling safe to drive on around 25% of occasions when they had already estimated that they were very hypoglycaemic (below 2.2 mmol/ l), suggesting that some errors of judgement result from misperceptions about the safety of driving while hypoglycaemic (Clarke et al., 1999). Automated behaviour as a result of hypoglycaemia (i.e. becoming disorientated, getting lost or arriving at their destination with no memory of how they got there) was reported by 18% of drivers (Cox et al., 2009). In vehicle monitoring has been suggested as a possible solution using technologies such as CGM linked to the car's display systems (Kerr and Olateju, 2010).

While it is reassuring that three quarters of drivers (74.8%) in the present survey gave an appropriate estimate of the minimum blood glucose for safe driving, i.e. 4.0 mmol/ l or higher, this leaves a significant minority who still regard lower levels of blood glucose to be acceptable. It is disconcerting that almost 60% of participants reported that they never test blood glucose before driving, or test only if they feel hypoglycaemic. When completing the questionnaire, many drivers mentioned that they do not test when they believe hypoglycaemia to be very unlikely, such as immediately after a meal. Although testing before driving was more common in participants with impaired hypoglycaemia awareness, only a small minority in this high-risk group reported regular testing. Most participants (77%) also reported never testing during journeys of any length, indicating a lack of vigilance even when the risk of hypoglycaemia is not negligible. This is particularly relevant in view of the metabolic demands of driving itself (Cox et al., 2002).

Failure to measure blood glucose could have major medico-legal consequences. In a previous prosecution in the Edinburgh Sheriff Court, the defendant, a driver with T1DM, was found guilty of causing death by dangerous driving while hypoglycaemic, and was strongly criticised because he had not measured his blood glucose before driving. In passing judgement, the Sheriff stated that there is a risk associated with diabetes and driving, and consequently the privilege of a driving

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licence carries a responsibility to ensure safety by measuring blood glucose. This demonstrates the discrepancy between the limited criteria that must be met for a person with insulin treated diabetes to obtain a licence, and the more rigorous standards that may be demanded by a court of law. It is important that health care professionals should be aware of this divergence of standards, and ensure that the potential legal ramifications are communicated to their patients.

8.44 Treatment of hypoglycaemia that occurs while driving

Appropriate treatment of hypoglycaemia while driving is vital. Most respondents in the present survey carried carbohydrate with them, but very few would wait for more than 30 min after self-treatment before resuming their driving, although previous studies have demonstrated that cognitive function may not recover until 45 min or more after restoration of euglycaemia (Evans et al., 2000, Blackman et al., 1990, Gonder-Frederick et al., 1994). The time required for recovery of sufficient cognitive function for driving has not been fully determined and drivers should be advised to err on the side of caution.

It is disconcerting that several drivers who have had accidents while hypoglycaemic reported persistently unsafe practice. Two self-rated their awareness of hypoglycaemia as impaired, and yet reported that they never test blood glucose before driving. While this behaviour can be regarded as irresponsible, they fortunately comprise a very small minority in this survey. However, a large proportion of respondents were failing in some essential aspect of safe practice. Although the definition of safe practice is debatable, any of the following is unsatisfactory: never measuring blood glucose before driving; never carrying carbohydrate when driving; not stopping the vehicle to treat hypoglycaemia while driving; and belief that a blood glucose level below 3.0 mmol/L is compatible with safe driving. Almost half of the participants were failing to meet one or more of these basic standards in the current study; a study conducted in New Zealand reported that 33% of drivers failed to meet one or more of these criteria (Bell et al., 2010).

8.45 Subsequent changes in the DVLA guidance

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In the United Kingdom, when the medical fitness to drive of insulin-treated diabetic drivers is being evaluated for the issue or renewal of ordinary (non-vocational) licences, the DVLA may require some information from the applicant's medical attendant. This is usually limited to determining whether the applicant has normal awareness of hypoglycaemia and has recently suffered disabling hypoglycaemia. When this study was conducted there was no obligation to test before driving for those holding ordinary (Group 1) licences.

Since this study was conducted the guidance for drivers with insulin treated diabetes has changed from guidelines issued by Diabetes UK to regulations issued by the DVLA (current regulations are reproduced in Table 8.4, the regulations affecting non-insulin treated drivers have also been included). A major change is that people with insulin treated diabetes can apply for Group 2 driving licences; at the time of study only C1 licences could be applied for by people on insulin treatment and so none of the people interviewed had group 2 licences.

Table 8.4: Current standards of fitness to drive for people with diabetes (DVLA, 2014)	
Group 1 entitlement (cars, motorcycles)	Group 2 entitlement (lorries, buses)
Insulin treated	Insulin treated
<p>DVLA must be notified</p> <p>Must have adequate awareness of hypoglycaemia</p> <p>Must not have had more than one episode of hypoglycaemia requiring the assistance of another person in the preceding 12 months</p> <p>There should be appropriate blood glucose monitoring (no more than 2 hours before the start and every 2 hours when driving)</p> <p>Must not be regarded as a likely source of danger to the public when driving</p> <p>The visual standards for acuity and visual field must be met</p>	<p>DVLA must be notified</p> <p>No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12 months</p> <p>Has full awareness of hypoglycaemia</p> <p>Regularly monitors blood glucose at least twice daily and at times relevant to driving, (no more than 2 hours before the start of the first journey and every 2 hours while driving). More frequent testing may be required if for any reason there is a greater risk of hypoglycaemia. At the annual examination by an independent Consultant Diabetologist, 3 months of blood glucose readings must be available</p> <p>Advised to use a modern blood glucose meter which has a memory chip</p> <p>Must demonstrate an understanding of the risks of hypoglycaemia</p>
Managed with tablets that carry a risk of hypoglycaemia (i.e. sulfonylureas or	Managed with tablets that carry a risk of hypoglycaemia (i.e. sulfonylureas or

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glinides)	glinides)
<p>DVLA must be notified</p> <p>Must not have had more than one episode of hypoglycaemia requiring the assistance of another person within the preceding 12 months. It may be appropriate to monitor blood glucose regularly and at times relevant to driving to enable the detection of hypoglycaemia. Must be under regular medical review.</p>	<p>DVLA must be notified</p> <p>No episode of hypoglycaemia requiring the assistance of another person has occurred in the preceding 12 months</p> <p>Has full awareness of hypoglycaemia</p> <p>Regularly monitors blood glucose at least twice daily and at times relevant to driving</p> <p>Must demonstrate an understanding of the risks of hypoglycaemia</p> <p>There are no other debarring complications of diabetes such as a visual field defect</p>
<p>Managed by tablets other than those above or by non-insulin injectable medication</p>	<p>Managed by tablets other than those above or by non-insulin injectable medication</p>
<p>DVLA does <u>not</u> require notification unless develops relevant disabilities.</p>	<p>DVLA must be notified. Drivers will be licenced unless they develop relevant disabilities.</p>
<p>Managed by diet alone</p>	<p>Managed by diet alone</p>
<p>DVLA does <u>not</u> require notification unless develops relevant disabilities.</p>	<p>DVLA does <u>not</u> require notification unless develops relevant disabilities.</p>

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Since this study was conducted the previous suggestion of measuring glucose levels before each journey and at regular intervals during long journeys has been changed to a current requirement of measuring glucose up to 2 hours before the first journey and to then retest at two hourly intervals (DVLA, 2014). Reviewing the data with these changes in mind, even before long journeys (>2 hours) just over a third of drivers (34.7%) would never check. The previously published paper had anticipated this change with the statement that it may also be unnecessary to measure blood glucose before every journey when consecutive short trips are made and that an argument could be made for recommending testing at reasonable intervals (e.g. every two hours) during periods when some driving is taking place (Graveling et al., 2004).

8.47 Other surveys of people's driving practices in relation to their diabetes

After the current study was published (Graveling et al., 2004), a study conducted in Aberdeen examined both patients and healthcare professionals' knowledge of regulations surrounding diabetes driving (Watson et al., 2007). A high proportion of participants (95%) were aware of the obligation to report their insulin treated status to the DVLA and had done so (92%). Only 15% always tested and 24% would never test before driving. Sixty-two percent of healthcare professionals were aware that people with insulin treated diabetes should be advised to test before driving. A more recent survey using a modified version of this current study's questionnaire conducted in Birmingham found similar results with 38% reporting never testing before driving (Bodansky and Bodansky, 2009). A rather poorly worded questionnaire based survey conducted in Liverpool reported that 65% would consider checking before each journey and 68% carried carbohydrate in the car (Jackson-Koku et al., 2010).

8.48 Study limitations

Participants with insulin treated diabetes were approached during their routine diabetes clinic appointment. The high completion rate (n=99%) means that a representative cross-section of the clinic population was interviewed. There was no way of verifying all of their answers although the responses are consistent with

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previous and subsequent studies carried out both in the UK and abroad (Watson et al., 2007).

A score using the Gold questionnaire of 3 or more was used to indicate impaired awareness of hypoglycaemia (Gold et al., 1994). As previously discussed in chapter 7 this is a non-validated cut-off, a score of 4 or more was used in the original validation study. This will have over-estimated the proportion of drivers with impaired awareness of hypoglycaemia.

8.5 Chapter Summary

The present survey has shown that most insulin-treated diabetic drivers understand what is meant by hypoglycaemia and the dangers it can pose in relation to driving. However, most drivers rely on the development of symptoms to detect hypoglycaemia, and rarely test blood glucose either before or during journeys. While the present survey reflects local practice, these results have now been replicated in other centres in the UK.

Patient education should emphasise the importance of using glucose meters to detect hypoglycaemia, particularly for people at high risk of hypoglycaemia, and of treating hypoglycaemia effectively before driving is resumed. Reinforcement is clearly necessary, and a discussion of driving practice should be included as part of the annual review procedure. An advice sheet has been compiled for drivers with insulin-treated diabetes in our clinic, and was given to all participants after the interview.

Following the publication of this study the DVLA updated its guidance to motorists with insulin-treated diabetes (DVLA, 2014). The key changes are a recommendation that blood glucose testing strips are always carried and that blood glucose levels should be checked no more than 2 hours before the start of each journey and every 2 hours while driving. This means that for shorter journeys, it is no longer necessary to check before each journey. The updated DVLA advice is summarised below (Inkster and Frier, 2013, DVLA, 2014):

- You should always carry your glucose meter and blood glucose strips with you.
- You should check your blood glucose no more than 2 hours before the start of the first journey and every two hours whilst you are driving.
- If driving multiple short journeys, you do not necessarily need to test before each additional journey as long as you test every 2 hours while driving. More frequent testing may be required if for any reason there is a greater risk of hypoglycaemia for example after physical activity or altered meal routine.

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- The intention is to ensure that blood glucose is always above 5.0mmol/l while driving. In each case if your blood glucose is 5.0mmol/l or less, take a snack. If it is less than 4.0mmol/l or you feel hypoglycaemic, do not drive.
- If hypoglycaemia develops while driving, stop the vehicle as soon as possible. You should switch off the engine, remove the keys from the ignition and move from the driver's seat.
- You should not start driving until 45 minutes after blood glucose has returned to normal (confirmed by measuring blood glucose). It takes up to 45 minutes for the brain to recover fully.
- Always keep an emergency supply of fast-acting carbohydrate such as glucose tablets or sweets within easy reach in the vehicle.
- You should carry personal identification to show that you have diabetes in case of injury in a road traffic accident.
- Particular care should be taken during changes of insulin regimens, changes of lifestyle, exercise, travel and pregnancy.
- You must take regular meals, snacks and rest periods on long journeys. Always avoid alcohol.

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Chapter 9: Discussion and Conclusions

9.1 Introduction

For people with T1DM the DCCT and follow on EDIC study provided proof that intensive glycaemic control reduced the risk of complications; particularly microvascular complications but also macrovascular disease (DCCT Research Group, 1993, Nathan et al., 2005, DCCT/EDIC Group et al., 2009). The downside of intensive glycaemic control is the substantially elevated risk of hypoglycaemia. The impact of hypoglycaemia on the daily lives of affected individuals is often substantial and ranges from the embarrassment of suffering an episode in a public place to being admitted to hospital with a suspected hypoglycaemic seizure. The first five chapters of this thesis describe the important effects of hypoglycaemia on various parts of the body and mind. These five chapters therefore provide a summary of the background on which the experimental work in this thesis is based.

This thesis presents three main studies: (1) the effect of acute hypoglycaemia on executive functions which are crucial for the performance of many everyday activities; (2) the prevalence of impaired awareness in a paediatric or adolescent population with T1DM with identification of symptoms sub-groups that best herald the onset of hypoglycaemia; (3) a questionnaire based survey of practices in people with insulin-treated diabetes with regard to testing and treating hypoglycaemia while driving.

9.2 Acute hypoglycaemia and executive cognitive functioning in adults with and without diabetes (chapter 6)

The aim of this study was to examine the effect of acute hypoglycaemia on executive function in healthy adults with and without T1DM. The current study showed that executive functions were profoundly affected by acute hypoglycaemia, with moderate to large effect sizes by Cohen's *d* statistic. This is not unexpected given that previous studies have shown that higher order cognitive functions are preferentially and often profoundly disrupted by hypoglycaemia.

Previous research into some other areas of cognitive function (e.g. psychomotor function) has suggested that those with diabetes are less affected by hypoglycaemia than participants without diabetes (Geddes et al., 2008). This was suggested as being a result of a lesser degree of counter-regulatory hormonal release in those with diabetes resulting in reduced amplitude and frequency of tremor. An unexpected finding in the current study was that in a number of tests (sorting test, *Stroop A* and *Stroop B*) the participants with diabetes were affected by hypoglycaemia to a worse degree than those without diabetes. This would suggest that cerebral adaptation does not occur; participants with diabetes would have been expected to have much greater experience of hypoglycaemia than participants without diabetes. In the current study the participants without diabetes achieved higher NART scores (a test of pre-morbid crystallised intelligence). Higher baseline intelligence is known to affect the scores achieved during the Stroop test, although the differences persisted when NART scores were included as a co-variate. Other measures of intelligence could be utilised in future to build a more accurate picture of the pre-morbid ability of the test population. Participants without diabetes might have a greater cognitive reserve. The idea of diabetes acting as a cognitive disruptor during hypoglycaemia is an interesting hypothesis and worthy of further research.

Given the large effect size seen following moderate hypoglycaemia (2.5mmol/L) it would be interesting to determine whether a greater (e.g. 2.0mmol/L) or lesser degree (e.g. 3.0 mmol/L) of hypoglycaemia would alter the findings. The latter experiment would have practical relevance in determining the impact of relatively mild

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hypoglycaemia on higher order cognitive functions and therefore the impact on many daily activities (e.g. composing a shopping list).

In the current study the quality rather than just speed of responses was poorer. Extrapolating these results would suggest that acute hypoglycaemia profoundly disrupts many activities of daily living. Many of these tests assess multiple executive functions and it is therefore difficult to demonstrate specific effects on particular cognitive processes that comprise executive functioning. Their overlapping nature would make it very difficult to design a test battery that examined the individual cognitive processes that comprise executive function. Some of the composite scoring used by the D-KEFS (i.e. for the Stroop test) aims to break down some of the cognitive processes by subtracting scores for lower order cognitive functions to try and better estimate the impact of hypoglycaemia on individual areas of executive functioning although some overlap remains.

Future research could combine executive function testing with functional imaging, although there are several practical difficulties that would need to be overcome. The most obvious hurdle would be performing the cognitive tests while undergoing cerebral imaging which would be difficult in the confines of an MRI scanner. The areas of the brain involved in executive functioning are not as clearly defined as in other cognitive tasks that may make image analysis more difficult.

In summary, further research into the specific cognitive processes involved in executive functioning is indicated although for the reasons outlined above, will be challenging. The mechanism behind the performance difference during hypoglycaemia in those with and without T1DM is unclear.

9.3 Prevalence of impaired awareness of hypoglycaemia and identification of predictive symptoms in children and adolescents with type 1 diabetes (chapter 7)

The aim of the current study was to ascertain the prevalence of impaired awareness in a typical cohort of patients with T1DM attending a paediatric clinic. Symptoms reported by the patients and clinical features observed by parents during hypoglycaemic episodes were also determined. Using the Clarke method the prevalence of IAH in the present study was just over 20%, similar to a previous study of an Australian paediatric population (Ly et al., 2009). The mean duration of diabetes of the current study's participants was shorter than a lot of studies in the adult population with T1DM. Those with IAH had an increased risk of hypoglycaemia requiring third party assistance or hospital admission. The increased morbidity observed in the IAH population increases the clinical utility of targeted screening for IAH, perhaps in children admitted with a hypoglycaemic event. Having identified a group at increased risk the healthcare team could then target this group with specific guidance and intervention to try and reduce the impact of IAH. Further research is urgently required to examine a longitudinal cohort of paediatric patients to determine how awareness status changes over time. It could be hypothesised that younger children would have a higher prevalence of IAH that would reduce over time until they became teenagers, at which point an increased prevalence may then be observed due to behavioural factors.

The cut off employed to define hypoglycaemia awareness considerably affects the prevalence of IAH, whether using the Gold or the Clarke method. A potential weakness of the current study is that the impaired group used the non-validated cut off of ≥ 3 , when the validated cut-off of ≥ 4 was used; the prevalence of IAH fell significantly. The present study showed that in a paediatric population the Clarke method of assessing impaired awareness of hypoglycaemia was more accurate than the Gold method (irrespective of the cut-off used). Whether using the participant or their parent's answers, the Gold method tended to overestimate the prevalence of IAH. This was in contrast to the adult population where good concordance between

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these two methods has been demonstrated (Geddes et al., 2007). The Gold method uses a single question and is therefore simpler to administer than the Clarke method. This makes it popular in research involving adults but on the basis of the current study's findings, it cannot be recommended for use in children. An important point to note for further research is that almost all children aged over 9 years were able to provide sufficient answers to allow their awareness status to be calculated.

Despite the key role that parents play in the management of their child's diabetes, in line with other studies, identification of hypoglycaemic episodes by parents was particularly poor (Gonder-Frederick et al., 2008). Parents of children with normal awareness detected just 4% of episodes, this increased slightly to 6% in parents of children with impaired awareness. Targeted parental support in the identification of hypoglycaemia in their offspring may help improve this percentage. Development of programmes that deliver blood glucose awareness training for parents of children with diabetes may be useful.

Loss or diminution of symptoms was reported by 11% of all the study participants and less than a third of those with IAH; this is a lower proportion than would be reported by an adult population with IAH (Pramming et al., 1991). The classical explanation for the development of IAH is that it arises as a result of reduced counter-regulatory responses seen with established T1DM; this is clearly not the explanation (or at the very least not the whole explanation) for the presence of IAH in children. Given that there is no clear pathophysiological mechanism, further examination of the clinical features observed and reported during hypoglycaemic episodes affecting children is key to advancing our understanding of this condition and these are discussed in the next two paragraphs.

Autonomic symptoms such as tremor are usually readily attributable to the onset of hypoglycaemia. In contrast, behavioural symptoms are less specific and may herald the onset of any number of issues such as tiredness, frustration or jealousy of another sibling or person. This may make it more difficult to promptly attribute these symptoms to the onset of hypoglycaemia. It is noteworthy that the most commonly reported clinical features identified by parents were behavioural (Figure 7.6). A Canadian study compared hypoglycaemic symptoms reported by adults with those

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reported by children. Using a comparative factor analysis, behavioural symptoms (i.e. tearful or aggressive) were more predominant in children than adults (Amin et al., 2014). Perhaps the fact that behavioural symptoms are the most commonly reported symptoms during hypoglycaemia partly explains the poor parental recognition of hypoglycaemic episodes. A recent consensus statement acknowledges the important of behavioural symptoms in the recognition of hypoglycaemia although doesn't cite the present study (Ly et al., 2014).

The symptoms reported during hypoglycaemia segregated into 3 sub-groups when using principal components analysis. Behavioural symptoms were shown to be most useful in predicting awareness status. While this has not been found to be case in adults, there are differences in the behaviour of adults with IAH in terms of adherence to suggested management strategies (Smith et al., 2009). That there might be a behavioural component to the development of IAH raises the question of whether this is a subconscious or deliberate behaviour. If IAH is a voluntary behaviour then this raises the possibility that an individual might choose to ignore the onset of hypoglycaemia. Some children may do this to trigger parental guilt, some might do it in an attempt not to seem different from other children or some might “enjoy” or at least not dislike the sensation of hypoglycaemia. Further research, perhaps using qualitative interviewing, of children and their parents with IAH is indicated.

In summary, further research is indicated into better identification of those with IAH particularly how awareness status changes over time (i.e. the “natural history” of the condition). Closer examination of symptoms, particularly behavioural symptoms is also indicated. Having identified a group of children at increased risk, further research is required into intervention programmes for both the child and their parents with the aim of reducing the morbidity of this condition.

9.4 Hypoglycaemia and driving in people with insulin-treated diabetes: self-treatment and adherence to recommendations for avoidance (chapter 8)

The aim of the current study was to examine participants' management of their insulin treated diabetes in relation to driving. While compliance with reporting their condition to the insurance company and DVLA was excellent, half of the participants reported one or more unsafe practices with regards to driving and diabetes (i.e. not checking a blood glucose level before driving). It is disappointing that subsequent surveys have failed to show a significant reduction in the number of drivers adopting potentially unsafe practices despite many diabetes centres giving advice regarding diabetes and driving (Watson et al., 2007).

Following the European Union legislation regarding diabetes and driving and the subsequent update of the DVLA guidance in 2012 regarding diabetes and driving there have been some key changes that affect car drivers with diabetes. The requirement for testing before driving has been altered to checking blood glucose no more than 2 hours before driving and every 2 hours while driving. It would be useful to repeat the present study following the change in advice to drivers with insulin treated diabetes from the DVLA. This would allow an assessment of awareness and compliance with the change in guidance. From clinical practice it would be suspected that compliance with the new guidance remains poor and that unsafe driving practices persist.

The most contentious requirement has been that if drivers suffer more than one episode of hypoglycaemia in the preceding 12 months they must report themselves to the DVLA. Anecdotally drivers with diabetes are becoming aware of this legislation; recent research in Denmark shows that following implementation of this legislation there has been a 55% reduction in self-reported rates of severe hypoglycaemia (Pedersen-Bjergaard et al., 2014). It would be interesting to perform a similar study in the UK, along with ascertainment of the proportion of drivers with IAH who report themselves to the DVLA.

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The effect of hypoglycaemia on driving performance has not been studied in the UK using a driving simulator. British roads tend to be congested and British cars tend to have manual gearboxes rather than automatic. The seminal driving simulator studies were carried out well over 10 years ago in the United States (Cox et al., 2000), an update of these studies utilising contemporary computer technology would be extremely useful. Different road and weather conditions could be examined (i.e. driving through town or on the motorway, driving in snow or at night). Based on the work showing that more complex cognitive functions are preferentially affected by acute hypoglycaemia it could be speculated that with increasingly levels of driving difficulty would result in a greater decrement in performance during acute hypoglycaemia. Many people with diabetes fail to appreciate the impact of hypoglycaemia on their driving performance and perhaps an update of the driving simulator studies might help convince some of them.

Although the impact of insulin treated diabetes on accident risk is difficult to quantify there is no doubt that any episode of hypoglycaemia while driving will increase the risk of a road traffic accident. The use of emerging technology such as meter downloads or CGM could be linked with driving data from the person's car. While initially confined to the experimental setting, in the future cars may require a safe blood glucose level prior to starting the engine and at intervals during the journey.

In summary, approximately half of a representative cohort of drivers with insulin treated diabetes reported unsafe driving practices. Repeating the study following the introduction of new regulations in the United Kingdom would demonstrate whether there has been any improvement in safe driving practices.

9.5 Chapter summary

Hypoglycaemia continues to be a major barrier to the management of insulin treated diabetes. These three studies examine a different area of how hypoglycaemia affects daily life and the various strategies people employ to deal with it. The cognitive function study (chapter 6) shows that acute hypoglycaemia affects both the speed and quality of thinking when asked to perform complex cognitive tasks. The paediatric study (chapter 7) has determined the prevalence of IAH in a paediatric cohort and examined the symptom sub-groups that may be predictive of this. The driving study (chapter 8) showed that drivers with insulin treated diabetes adopt a number of potentially dangerous practices when it comes to managing their condition while driving. The work contained within this thesis has expanded our knowledge of how hypoglycaemia affects the lives of people with insulin treated diabetes.

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Appendices contents

Appendices

Appendix One: Baseline paediatric questionnaire (chapter 7)

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Appendix Three: Diabetes and driving questionnaire (chapter 8)

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Appendix 1 (Baseline questionnaire)

Appendix 1: Baseline Paediatric Questionnaire

Retrospective Questionnaire

(to be completed at subject recruitment by the researcher)

Year of diagnosis of Diabetes (approximately)

Family history of type 1 diabetes? Yes No

If yes is it parent sibling other

Timing of insulin injections (please write in the name of the insulin and how many units you use):

	Type of insulin	Number of units
Before breakfast	1)	
	2)	
Before lunch	1)	
	2)	
Before evening meal	1)	
	2)	
Bedtime	1)	
	2)	

Other medications (i.e. tablets etc.)

“We are interested in the opinion of both yourself and your child. If it is okay with you I would like to ask each question to your child first and then ask you the same question.”

Appendix 1 (Baseline questionnaire)

1) (CHILD) Can you tell when your blood glucose is low?

- Never Child unable to answer
- Occasionally
- Usually
- Always

1a) (PARENT) Can you tell when your child's blood glucose is low?

- Never
- Occasionally
- Usually
- Always

2) (CHILD) Tick the category that best describes you (tick one only)

- I always have symptoms when my blood glucose is low
- I sometimes have symptoms when my blood glucose is low
- I do not have symptoms when my blood glucose is low
- Child unable to answer

2a) (PARENT) Tick the category that best describes your child (tick one only)

- My child always has symptoms when his/her blood glucose is low
- My child sometimes has symptoms when his/her blood glucose is low
- My child does not have symptoms when his/her blood glucose is low

Appendix 1 (Baseline questionnaire)

3) (CHILD) Have you lost some of the symptoms that used to occur when your blood glucose was low?

Yes Which symptoms have been lost? (e.g. sweating)

No

Child unable to answer

3a) (PARENT) Do you think that your child has lost some of the symptoms that used to occur when their blood glucose was low?

Yes

No

4) (CHILD) How often in the past year have you had a severe hypoglycaemic episode? These are episodes where you were unconscious or had a fit and needed Glucagen® or intravenous glucose.

Never 4 times 9 times

1 time 6 times 10 times

2 times 7 times 11 times

3 times 8 times 12 or more times

Child unable to answer

4a) (PARENT) How often in the past year has your child had a severe hypoglycaemic episode? These are episodes where you were unconscious or had a fit and needed Glucagen® or intravenous glucose.

Never 4 times 9 times

1 time 6 times 10 times

2 times 7 times 11 times

Appendix 1 (Baseline questionnaire)

3 times 8 times 12 or more times

5) (CHILD) In the past six months how often have you had a hypoglycaemia episode where you were unable to treat yourself. You might have also felt confused, disorientated, or lethargic. *This includes episodes of severe hypoglycaemia.*

Never Child unable to answer

Once or twice

Every other month

Once a month

More than once a month

5a) (PARENT) In the past six months how often has your child had a hypoglycaemia episode where they were unable to treat themselves. *This includes episodes of severe hypoglycaemia*

Never

Once or twice

Every other month

Once a month

More than once a month

6) (CHILD) How often in the past month have you had a blood glucose of less than 3.9mmol/L with symptoms?

Never 2 to 3 times/week

1-3 times 4 to 5 times/week

1 time/week Almost daily

Appendix 1 (Baseline questionnaire)

Child unable to answer

6a) (PARENT) How often in the past month has your child had a blood glucose of less than 3.9mmol/L with symptoms?

Never 2 to3 times/week

1-3 times 4 to 5 times/week

1 time/week Almost daily

7) (CHILD) How often in the past month have you had a blood glucose of less than 3.9mmol/L with no symptoms?

Never 2 to3 times/week

1-3 times 4 to 5 times/week

1 time/week Almost daily

Child unable to answer

7a) (PARENT) How often in the past month has your child had a blood glucose of less than 3.9mmol/L with no symptoms?

Never 2 to3 times/week

1-3 times 4 to 5 times/week

1 time/week Almost daily

8) (CHILD) How low does your blood glucose go before you feel symptoms?

3.3-3.8 mmol/L 2.2-2.7mmol/L

2.8-3.3 mmol/L below 2.2mmol/L

Child unable to answer

Appendix 1 (Baseline questionnaire)

8a) (PARENT) How low does your child's blood glucose go before you feel that they develop symptoms?

- | | | | |
|----------------|--------------------------|-----------------|--------------------------|
| 3.3-3.8 mmol/L | <input type="checkbox"/> | 2.2-2.7mmol/L | <input type="checkbox"/> |
| 2.8-3.3 mmol/L | <input type="checkbox"/> | below 2.2mmol/L | <input type="checkbox"/> |

9) (CHILD) Can you tell by your symptoms that your blood glucose is low?

- | | | | |
|-----------|--------------------------|------------------------|--------------------------|
| Never | <input type="checkbox"/> | Often | <input type="checkbox"/> |
| Rarely | <input type="checkbox"/> | Always | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | Child unable to answer | <input type="checkbox"/> |

9) (PARENT) To what extent can you tell by your child's symptoms that their blood glucose is low?

- | | | | |
|-----------|--------------------------|--------|--------------------------|
| Never | <input type="checkbox"/> | Often | <input type="checkbox"/> |
| Rarely | <input type="checkbox"/> | Always | <input type="checkbox"/> |
| Sometimes | <input type="checkbox"/> | | |

Appendix 1 (Baseline questionnaire)

10. (CHILD): Please score how much you experience the following symptoms during a hypo (circle a number for each symptom)

		Not present			Present a great deal			
	<i>Alt wording</i>							
Headache	<i>sore head</i>	1	2	3	4	5	6	7
Irritable	<i>bad tempered</i>	1	2	3	4	5	6	7
Unco-ordinated	<i>clumsy</i>	1	2	3	4	5	6	7
Weak	<i>“floppy”</i>	1	2	3	4	5	6	7
Aggressive	<i>getting angry</i>	1	2	3	4	5	6	7
Trembling	<i>shaking</i>	1	2	3	4	5	6	7
Sleepiness	<i>falling asleep</i>	1	2	3	4	5	6	7
Sweating		1	2	3	4	5	6	7
Blurred vision	<i>hazy sight</i>	1	2	3	4	5	6	7
Tummy pain	<i>sore tummy</i>	1	2	3	4	5	6	7
Feeling sick		1	2	3	4	5	6	7
Yawning		1	2	3	4	5	6	7
Odd behaviour	<i>acting strangely</i>	1	2	3	4	5	6	7
Argumentative	<i>picking a fight</i>	1	2	3	4	5	6	7
Tired	<i>“sluggish”</i>	1	2	3	4	5	6	7
Feeling awful	<i>“yukky”</i>	1	2	3	4	5	6	7

Appendix 1 (Baseline questionnaire)

Other symptoms (e.g. sore legs)? Yes No

Please specify & score as above

_____ 1 2 3 4 5 6 7

_____ 1 2 3 4 5 6 7

_____ 1 2 3 4 5 6 7

Child unable to answer

Appendix 1 (Baseline questionnaire)

10a. (PARENT) Please score how much you feel your child experiences the following symptoms during a hypo (circle a number for each symptom)

		Not present			Present a great deal			
<i>Alt wording</i>								
Tearful	<i>crying</i>	1	2	3	4	5	6	7
Headache	<i>sore head</i>	1	2	3	4	5	6	7
Irritable	<i>bad tempered</i>	1	2	3	4	5	6	7
Uncoordinated	<i>clumsy</i>	1	2	3	4	5	6	7
Naughty		1	2	3	4	5	6	7
Aggressive	<i>getting angry</i>	1	2	3	4	5	6	7
Trembling	<i>shaking</i>	1	2	3	4	5	6	7
Sleepiness	<i>falling asleep</i>	1	2	3	4	5	6	7
Sweating		1	2	3	4	5	6	7
Slurred speech	<i>difficulty speaking</i>	1	2	3	4	5	6	7
Warmness	<i>feeling warm</i>	1	2	3	4	5	6	7
Restless	<i>fidgety</i>	1	2	3	4	5	6	7
Daydreaming	<i>not paying attention</i>	1	2	3	4	5	6	7
Argumentative	<i>picking a fight</i>	1	2	3	4	5	6	7
Pounding heart	<i>'thumping' in chest</i>	1	2	3	4	5	6	7
Confused		1	2	3	4	5	6	7
Tired	<i>'sluggish'</i>	1	2	3	4	5	6	7

Appendix 1 (Baseline questionnaire)

Other (e.g. pallor)? Yes No

Please specify & score as above

_____ 1 2 3 4 5 6 7

_____ 1 2 3 4 5 6 7

_____ 1 2 3 4 5 6 7

Appendix 1 (Baseline questionnaire)

11. (CHILD) Do you know when your hypos are commencing? Please circle a number:

	Always aware					Never aware	
Awareness	1	2	3	4	5	6	7

Child unable to answer

11a. (PARENT) Do you know when your child's hypos are commencing? Please circle a number:

	Always aware					Never aware	
Awareness	1	2	3	4	5	6	7

Appendix 2 (Parental and child prospective hypoglycaemia questionnaires)

Appendix 2: Parental and child prospective hypoglycaemia questionnaire

PARENT

DATE..... TIME.....

BLOOD GLUCOSE VALUE.....

Please score

	Not present				Present a great deal			
Tearful	1	2	3	4	5	6	7	
Headache	1	2	3	4	5	6	7	
Irritable	1	2	3	4	5	6	7	
Uncoordinated	1	2	3	4	5	6	7	
Naughty	1	2	3	4	5	6	7	
Aggressive	1	2	3	4	5	6	7	
Trembling	1	2	3	4	5	6	7	
Sleepiness	1	2	3	4	5	6	7	
Sweating	1	2	3	4	5	6	7	
Slurred speech	1	2	3	4	5	6	7	
Warmness	1	2	3	4	5	6	7	
Restless	1	2	3	4	5	6	7	
Daydreaming	1	2	3	4	5	6	7	
Argumentative	1	2	3	4	5	6	7	
Pounding heart	1	2	3	4	5	6	7	

Appendix 2 (Parental and child prospective hypoglycaemia questionnaires)

Confused	1	2	3	4	5	6	7
Tired	1	2	3	4	5	6	7
Other (1) _____	1	2	3	4	5	6	7
Other (2) _____	1	2	3	4	5	6	7

The reaction was recognised by (please circle one):

Your child Routine testing on meter Someone else

Additional information (Please circle yes or no):

Was the hypo treated according to Sick Kids” Hypo guidelines? Yes No

Did you need to phone the “Emergency Helpline” at Sick Kids? Yes No

Did your child require an injection of Glucagen® (orange box)? Yes No

Did your child require to be taken to hospital? Yes No

Appendix 2 (Parental and child prospective hypoglycaemia questionnaires)

CHILD

DATE..... TIME.....

BLOOD GLUCOSE VALUE.....

Please score the extent to which you experienced the following symptoms during the episode of hypoglycaemia (circle a number for each symptom)

	Not present				Present a great deal			
Headache	1	2	3	4	5	6	7	
Irritable	1	2	3	4	5	6	7	
Uncoordinated	1	2	3	4	5	6	7	
Weak	1	2	3	4	5	6	7	
Aggressive	1	2	3	4	5	6	7	
Trembling	1	2	3	4	5	6	7	
Sleepiness	1	2	3	4	5	6	7	
Sweating	1	2	3	4	5	6	7	
Blurred vision	1	2	3	4	5	6	7	
Tummy pain	1	2	3	4	5	6	7	
Feeling sick	1	2	3	4	5	6	7	
Yawning	1	2	3	4	5	6	7	
Odd behaviour	1	2	3	4	5	6	7	
Argumentative	1	2	3	4	5	6	7	
Tired	1	2	3	4	5	6	7	

Appendix 3: Diabetes and driving questionnaire

Appendix 3: Diabetes and driving questionnaire

Please remember that all information given in this questionnaire is kept confidential

Patient number: _____

Date of interview: _____

Patient Demographics

1) Sex Male Female (please circle)

2) Age ____ years

3) Occupation manual, semi-skilled, skilled, professional, retired, unemployed

Specify _____

Diabetes

4) Date of diagnosis of diabetes _____

5) Type of diabetes (to be completed by the researcher) Type 1 ____ Type 2 ____

6) Date of commencing insulin at diagnosis ____ other date (type 2) ____

7) HbA1c at this/last clinic visit ____ %

Insulin Treatment Regimen

8)

Time of day	Insulin type	Dose (units)
-------------	--------------	--------------

Before breakfast

before lunch

before evening meal

Appendix 3: Diabetes and driving questionnaire

bedtime

Oral therapy (tablets)? Specify _____

Home Blood Glucose Testing

9) Do you measure your blood glucose? (tick description that usually applies)

No, never _____

Only if I think it is too high or too low _____

Less than once a week _____

At least once a week _____

At least three times a week _____

At least once a day _____

Three or more times a day _____

Hypoglycaemic History

10) Have you ever experienced hypoglycaemia (low blood glucose)? Yes ___

No ___

11) If YES, approximately how often do you have a mild hypo? A mild hypo is one that can be treated by yourself. [Question should assess patient's subjective view of hypoglycaemic onset but quote 4 mmol/L if asked for a blood glucose level]

Less than 1 per year _____

Less than 1 per month (1-3 per year) _____

At least 1 per month _____

2 or more per month _____

Appendix 3: Diabetes and driving questionnaire

At least 1 per week _____

3 or more per week _____

12) To what level does your blood glucose fall before you have symptoms of mild hypoglycaemia?

Doesn't measure blood sugar during episodes of hypoglycaemia _____

above 4.0 mmol/L _____ 4.0-3.6 mmol/L _____ 3.5-3.1 mmol/L _____

3.0-2.6 mmol/L _____ 2.5-2.0 mmol/L _____ below 2.0 mmol/L _____

13) If yes to Q11, how many severe hypos have you had in the last year (a severe hypo is one in which you have felt that you needed assistance from another person)

None: _____ One: _____ Two-five: _____ more than 5: _____

14) Do you know when a hypo is starting? (please circle)

always 1 2 3 4 5 6 7 never

15) At what time of day do you usually have hypos? (please tick)

Before breakfast _____ Before lunch _____ Before evening meal _____

At bed-time _____ Through the night _____ Any time _____

16) Do you check your blood glucose while experiencing a hypo? (please circle)

always 1 2 3 4 5 6 7 never

Driving

17) Do you have a current driving licence? (please tick)

Provisional _____ Ordinary _____ C1 _____

18) How long have you held a driving licence?

Appendix 3: Diabetes and driving questionnaire

Less than a year ___ 1-5 years ___ 5+ years ___

19) Is there a period restriction on your licence? Yes ___ No ___

If yes: 1 year ___ 2 years ___ 3 years ___

20) How many miles do you usually drive in a year?

Less than 5,000 ___ 5,000-9,999 ___ 10,000-20,000 ___

More than 20,000 ___

21) Do you travel to work by car?

Yes ___ No ___ Retired ___ Unemployed ___

If YES,

Every day ___ At least twice a week ___

Once a week ___ Less than once a week ___

22) Do you have to drive as part of your job, other than commuting to and from work? (please choose the statement that most closely matches your usual driving habits)

Yes ___ No ___ Retired ___ Unemployed ___

If YES, Everyday ___ At least twice a week ___

Once a week ___ Less than once a week ___

23) Is driving essential for your job? Yes ___ No ___ N/A ___

Blood Glucose Monitoring While Driving

24) Do you carry your blood glucose testing kit with you while driving? (please circle)

Always Only on long journeys (>2 hours) Sometimes Never

Appendix 3: Diabetes and driving questionnaire

25) Do you test your blood glucose level before driving? (please tick statement that most closely applies to your testing habits)

No, never _____

Yes, but only if I think it may be too high or too low _____

Yes, but less than 1 in 10 journeys _____

Yes, about 1 journey in 5 _____

Yes, at least every other journey (1 in 2) _____

Yes, every journey _____

26) If you were about to set off on a car journey lasting more than two hours would you test your blood glucose before you drive?

No, never _____

Yes, but only if I think it might be too high or too low _____

Yes, but less than 1 in 10 journeys _____

Yes, about 1 journey in 5 _____

Yes, at least every other journey _____

Yes, for every journey _____

27) If you were about to set off on a car journey lasting between half an hour and two hours would you test your blood glucose before you drive?

No, never _____

Yes, but only if I think I might be too high or too low _____

Yes, but less than 1 in 10 journeys _____

Yes, about 1 journey in 5 _____

Appendix 3: Diabetes and driving questionnaire

Yes, at least every other journey _____

Yes, for every journey _____

28) If you were about to set out on a car journey lasting less than half an hour would you test your blood glucose before you drive?

No, never _____

Yes, but only if I think it might be too high or too low _____

Yes, but less than 1 in 10 journeys _____

Yes, about 1 journey in 5 _____

Yes, at least every other journey _____

Yes, for every journey _____

29) When driving do you ever test your blood glucose level during a journey?

Always Only on long journeys (>2 hours) Sometimes Never

30) If yes to Q29, for how long would you drive before testing? __ hrs or __ miles

31) If yes to Q29, which statement is most applicable?

always test 1 2 3 4 5 6 7 never test

Driving and hypoglycaemia

32) Have you ever experienced hypoglycaemia while driving? Yes ___ No ___

33) Have you experienced hypoglycaemia in the last year? Yes ___ No ___

34) How many mild hypos have you had in the last year while driving? (A mild hypo is one that could be treated by yourself without medical assistance)

0 ___ 1-2 ___ 3-5 ___ more than 5 ___

Appendix 3: Diabetes and driving questionnaire

35) How many severe hypos have you had in the last year while driving, a severe hypo is when assistance is required from another person?

0 ___ 1-2 ___ 3-5 ___ more than 5 ___

36) Has an episode of hypoglycaemia while driving resulted in an accident? (Includes any accident when they were hypoglycaemic whether they thought they were responsible or not)

No hypos while driving ___ Accident in the last year ___

Accident at any time ___ Episode(s) did not result in an accident ___

37) If YES to question 36, did the accident result in:

Damage to vehicle ___ Damage to person(s) ___ (other than minor cuts & bruises)

38) Did you measure your blood glucose when you had a mild hypo?

No hypos while driving ___ Always ___ Sometimes ___ Never ___

39) Did you measure your blood glucose when you had a severe hypo?

No hypos while driving ___ Always ___ Sometimes ___ Never ___

Action taken if hypoglycaemia is suspected while driving

40) Do you carry some type of carbohydrate in the car for the treatment of a hypo?

Always ___ Only on long journeys (>2 hours) ___ Sometimes ___ Never ___

41) If yes, what type of carbohydrate? (please tick)

Glucose tablets ___

Biscuits ___

Appendix 3: Diabetes and driving questionnaire

- Chocolate bar _____
- Confectionery (sweets) _____
- Soft drink or Energy drink _____
- Other (please specify) _____

42) If you thought you were becoming hypoglycaemic while driving would you...?

- Carry on driving _____
- Continue driving but with increased care _____
- Stop driving, eat some food or have a sugary drink, then carry on driving _____
- Stop driving, eat some food or have a glucose drink and then rest for at least half an hour before driving again _____

43) Assuming you are carrying your blood glucose testing kit, would you measure your blood glucose after treating the hypo? (please circle)

- Always Only if severe Sometimes Never

44) If yes to Q43, how long after treating the hypo would you wait before measuring blood glucose? (please circle)

- Wouldn't measure Immediately 5-10 mins 11-20 mins
- 21-30 mins 31-40 mins >40 mins

45) How long would you wait after treating the hypo before starting driving again? (please circle)

- Wouldn't stop Immediately 5-10 mins 11-20 mins 21-30 mins
- 31-40 mins >40 mins

Appendix 3: Diabetes and driving questionnaire

46) Do you reduce your insulin dose to allow for the increased energy required for driving, especially over a long distance? (please tick)

Always Only if on long journeys Sometimes Never

47) If yes, by how much?

5% ___ 10% ___ 20% ___ >20% ___

Knowledge

48) Below which blood glucose level would you consider it unsafe to drive?

___ mmol/L

49) Have you ever received detailed advice about driving and diabetes? Yes ___

No ___

50) If yes, from what source? (please tick all that apply)

Diabetic clinic doctor ___ Family/Friends ___

Diabetic clinic nurse/dietician ___ Diabetes literature ___

GP ___ Newspaper/magazine ___

GP practice nurse ___ Internet ___

Other medical professional ___ DVLA ___

51) Are you required by law to inform the DVLA that you have insulin-treated diabetes?

Yes ___ No ___ Not sure ___

52) Have you informed the DVLA that you have insulin-treated diabetes?

Yes ___ No ___

Appendix 3: Diabetes and driving questionnaire

53) Are you required by law to inform your motor insurance company that you have insulin-treated diabetes?

Yes ___ No ___ Not sure ___

54) Have you informed your motor insurance company that you have insulin-treated diabetes? Yes___ No ___

If no to Q49, ask where they received the advice concerning the answer to Q51-54 [because several patients reported that they been given no advice, but did in fact know the correct answers, and subsequently agreed that they had been informed by the clinic]

55) From what source? (please tick all that apply)

Diabetic clinic doctor ___ Family/Friends ___

Diabetic clinic nurse/dietician___ Diabetes literature ___

GP ___ Newspaper/magazine ___

GP practice nurse ___ Internet ___

Other medical professional ___ DVLA ___

Unknown source ___

Appendix 4

Appendix 4: Published articles

Articles based on work described in this thesis are reproduced here, with permission of the copyright holder in each case.

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- Page 386 Graveling AJ, Deary IJ, Frier BM. 2013. Acute hypoglycemia impairs executive cognitive function in adults with and without type 1 diabetes. *Diabetes Care*, 36, 3240-3246
- Page 393 Graveling AJ, Noyes KJ, Allerhand MH, Wright RJ, Bath LE, Deary IJ, Frier BM. 2014. Prevalence of impaired awareness of hypoglycemia and identification of predictive symptoms in children and adolescents with type 1 diabetes. *Pediatric Diabetes*, 15, 206-213
- Page 401 Graveling AJ, Warren RE, Frier BM. 2004. Hypoglycaemia and Driving in People with Insulin-Treated Diabetes: Self-Treatment and Adherence to Recommendations for Avoidance. *Diabetic Medicine*, 21, 1014-1019

Podcast on study described in chapter 6

<http://www.alliesvoice.com/tag/diabetes-podcast/>