THE EFFECTS of the ENDOLUMINAL DUODENO-JEJUNAL BYPASS LINER on EATING BEHAVIOUR in HUMANS

Werd Al-Najim

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Department of Investigative Medicine

Imperial College London

London

United Kingdom

Supervisors:

Prof. Carel W. le Roux

Prof. Julian Teare

ABSTRACT

Background:

The Endoluminal Duodeno-Jejunal Bypass Liner (DJBL) is a thin, flexible, sleeve-like device, made of a single use 60cm fluoropolymer. The DJBL is inserted endoscopically through the mouth and anchored to the proximal small intestine to acts as a physical barrier between the walls of the duodenal and the food ingested. The DJBL is currently being used for the treatment of diabetes in patients with obesity. Therefore, this device offers the unique opportunity to apply a reductionist approach and interrogates the contribution of bypassing the proximal bowel in the regulation of eating behaviour. This is the first study to assess eating behaviour in DJBL patients using direct and indirect measures of behaviour.

Aims:

To assess whether the DJBL affects eating behaviour 6-months post intervention compared to Best Medical Practice for the treatment of obesity and Type 2 Diabetes.

Objective:

To investigate the effect of DJBL on:

1. Food choices and calories intake
2. Eating behaviour
3. The sensory domain of taste.

4. The appetitive behaviour subdomain of the hedonic ingestive motivation domain.
5. The consummatory behaviour subdomain of the hedonic ingestive motivation domain.

Methods:

This was a randomised controlled study of 42 subjects (23 DJBL, 19 SMT) with Type 2 Diabetes Mellitus who receive the DJBL device or standard medical therapy alone. All patients (40% female) were studied at baseline and followed up for 6-months post intervention. Food choices and calories intake were assessed using Food Diaries, Food

Frequency Questionnaire, and 24hr Diet Recall. Psychology and personality traits linked to eating behaviour were assessed with questionnaires, whereas appetite and hunger scores were assessed with Visual Analogue Scales. The intensity of sweet taste stimuli was measured using (a direct behavioural technique) to determine the taste detection threshold using the method of constant stimuli. The appetitive reward of sweet taste stimuli was assessed using a progressive ratio task (a direct behavioural technique). Finally, the consummatory reward value of taste was assessed using visual analogue scales (indirect behaviour technique).

Results:

1. Total food intake reduced from at 6-months reduced albeit not significantly and DJBL patients had a modest healthier shift in food preferences.
2. A shift towards healthier eating behaviour and psychological factors was found, which was specific to the treatment type. However, no change in the reported appetite ratings was found.
3. No changes in sucrose detection threshold after DJBL.
4. No change in the appetitive reward value of sweet and fatty tastant after DJBL.
5. No change in the consummatory reward value of sweet taste after DJBL.

Conclusion:

I conclude, that despite not adding extra benefits on total weight loss, the DJBL could potentially make weight loss an easier task due to the modest changes in food preferences and eating behaviour and psychological traits. In addition, the DJBL did not affect any of the taste dimensions. Therefore, the bypass of the proximal small bowel is not behind the changes in eating behaviour observed post RYGB or that RYGB alters eating behaviour via a combined/synergistic effect of the multiple components and the profound changes in the GI tract. This study contributes to the clinical benefits of the use of DJBL for weight loss and also to the research field on the physiological mechanisms behind RYGB operation.

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DEDICATION

This PhD is solely dedicated to the greatest influence of my life my mother Nashwa Al-Quraishi, to whom I owe every bit of my achievements. Thank you, mama, for your unconditional love, endless encouragement and for sacrificing all that you have to secure a bright future for us.

STATEMENTS OF WORK BY CANDIDATE

This thesis was part of a large NIHR clinical trial consisting of the main trial plus three mechanistic sub-groups (sub-group 1: fMRI; sub-group 2: insulin clamps; sub-group 3: food preference). The work presented here represents the experiments carried out in sub-group 3: food preferences. My role in this clinical trial was designing and setting-up the experiments for sub-group 3, which are described in this thesis and also formed part of the clinical trial protocol; establishing the Standard Operation Procedures SOPs; carrying out the experiments; collecting and analysing the experimental data; and assisting with the dietetic clinical follow-up visits. Therefore, all the work described in the thesis was performed by the author. All collaborations and assistance are described below.

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ABBREVIATIONS

AUC Area Under the Curve

ARC Arcuate Nucleus

AgRP Agouti-Related Protein

ACTH Adrenoorticorophic Hormone

AEA Anandamide

2-AG 2-Arachidonoylgycerol

BMI Body Mass Index

CHO Carbohydrate

CART Cocaine- and Amphetamine Rrelated Transcript

CNS Central Nervous System

CB1 and CB2 Cannabinoid (type 1 and 2)

DJBL Endoluminal Duodeno-Jejunal Bypass Liner

DMH Dorsomedial Hypothalamic Nucleus

EC50 Half Maximal Effective Concentration

EWL Excess Weight Loss

FM Fat Mass

FFM Free Fat Mass

GI Gastrointestinal

GLP-1 Glucagon-Like Peptide One

HbA1C Haemoglobin A1c

PRO Protein

PYY Peptide YY

POMC Pro-Ppiomelanocortin

PC1 and **PC2** Prohormone Converatse 1 and 2

SMT Standard Medical Therapy

MSHs Melanocyte Stimulating Hormones

MC1R-MC5R Melanocrtin Receptors 1-5

NPY Neuropeptide Y

T2DM Type 2 Diabetes

VAS Visual Analogue Scales

WHO World Health Organisation

CHAPTER 1 INTRODUCTION

1 Introduction

1.1 Eating behaviour

The term eating behaviour describes our relationship with food, and is characterised by physiological, psychological and social drives that are integrated into the brain and determine not only how much we eat, but also what, when, and how we eat (1).

Hunger and satiety are the predominant physiological signals to initiate and stop an eating episode or meal in response to peripheral signals but because food and especially the high-calorie food is now widely available our hunger and fullness can be readily satisfied (2). So the reward value of food has emerged as a major force affecting eating behaviour and in particular food preferences (2). All humans are born with an innate preference for sweet taste and disliking of sour and bitter tastes (3, 4). However, when it comes to preferences for certain foods over others, then intrinsic factors (e.g. liking and wanting) and extrinsic factors (e.g. health values, brand, cost), in addition to social, cultural, and genetic factors, all contribute to the development of preferences ((5) (6)).

Food selection is affected by the sensory properties of food i.e. taste, smell, and texture. When food is ingested, a complex network of taste systems is responsible for the liking or disliking of that particular food, and that is reflected by physiological and psychological responses (7).

1.1.1 Biopsychology of hunger and satiety

Food intake (ingestion of food) is an innate behaviour predominantly regulated by signals of hunger and satiety to initiate and stop an eating episode or a meal. The Satiety Cascade (see the lowest domain of Figure 1) is a concept developed by John Blundell based on the underlying processes controlling food intake, i.e. hunger, satiation, and satiety (8). Hunger is defined as the motivation to seek and consume food, initiating a feeding episode. Conversely, the processes that bring episodes of eating behaviour to an end are termed satiation. It

commences when the gut senses fullness or when the person is satisfied with the amount consumed. It combines all of those events that operate during a meal. These ultimately lead to a state of satiety in which the hunger drive, and consequently eating behaviour, is inhibited (8). The feeling of satiety remains until the occurrence of hunger and readiness for the next meal.

Psychological experiences, peripheral and physiological signals and central neural processes underpin the expression of appetite and interact during an eating episode to form a biopsychological network consisting of hunger, satiation, satiety, and then back to hunger again (Figure 1) (9).

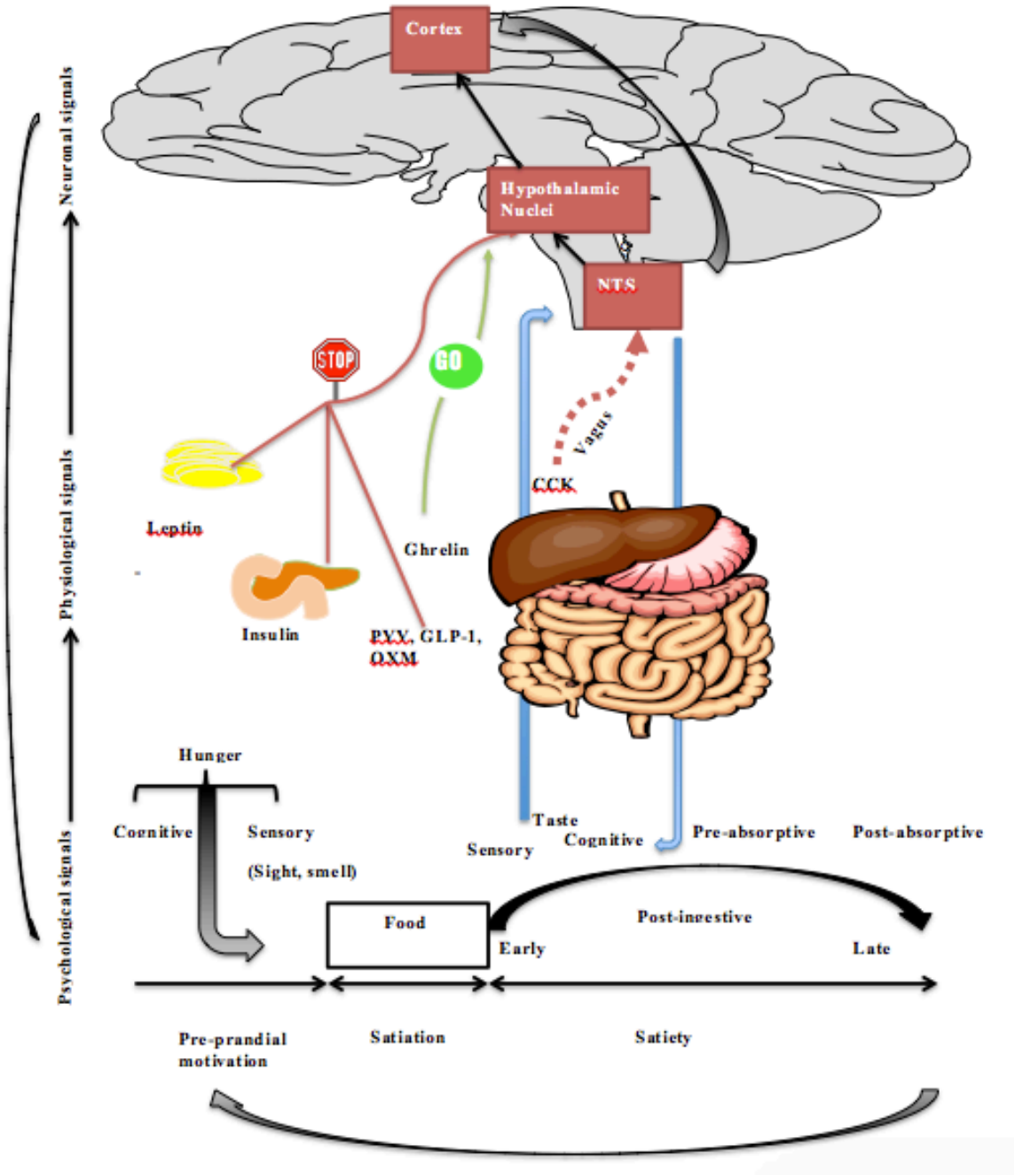
Hunger is the first phase of the satiety cascade and is driven by pre-prandial cognitive and sensory signals to promote food intake and prepare the body for digestion (8). Pre-prandial signals are generated by the peripheral hunger hormone (Ghrelin) (10), hedonic stimulation (the reward system), cognition and learned experiences (e.g. memory of last meal, meal times) and also sensory stimulation (e.g. sight and smell of food) (11). Once the food is present in the oral cavity, and during the early phase of an eating episode, further hunger signals are generated by sensory stimulation caused by the contact of food with the mouth (12).

During the meal (prandial phase) the stomach is the first to sends post-ingestive signals about the amount and the composition of food consumed to the brain via the vagal nerve (13). Gastric distention caused by the presence of food in the stomach is sensed by mechanoreceptors to detect the quantity eaten (14), while chemoreceptors detect the presence of different nutrients in the stomach providing information on the nutritional composition of the food consumed (14).

Finally, prandial and post-prandial signals are generated by the detection of nutrients absorbed from the small bowel into the peripheral circulation. Glucose is immediately absorbed into the bloodstream and carried to the brain to modulate the function of a variety of neurotransmitters and peptides associated with appetite regulation (15). The liver also plays a major role in metabolising glucose, fatty acids and amino acids (16). Hepatic energy

metabolism generates satiety signals (16) that travel from the liver to the CNS via the vagal nerve (15).

Figure 1 Biopsychology of hunger and satiety



Note 1 Figure is my original work

1.1.2 Cognition and learned behaviour

Hunger, eating, and satiety are a result of biopsychological processes. Modern humans do not have to wait for the physiological signals to initiate hunger and satiety. Instead, we also rely on psychological processes to initiate an eating episode or a meal. Those psychological processes are a result of the learned and cognitive components of hunger and can affect what, when, and how we eat (17).

Unlike any other beings, we humans learn to follow a personalised routine and use a clock to time our daily tasks including when to sleep and when to eat. For instance, most of us would feel hungry at 12 pm and have lunch just because we learned that this is our lunchtime. To challenge this, Shachter & Gross (1968) carried out a study where they manipulated the cognition of their participants by leading them to believe that they were eating either before, or after, their usual dinnertime. They found that participants adjust their food intake based on the time presented on the clock rather on their actual physiological need (18).

In our current obesogenic environment, we are regularly being reminded about the importance of healthy food choices and controlled portion sizes. Which may play a role in altering the real physiological hunger and satiety signals by using our cognition. People can adjust their food intake based on their awareness of its energy content. Wooley S. C. (1972) reported that people ate less after a preload that was designed to appear high in calories, compared with a preload that was designed to appear low in calories, although actual manipulation of the calorie content of the preload had no effect on food intake in the subsequent meal (19). Similarly, Capaldi *et al.* (2006) found that when foods perceived by participants as meals were consumed as a preload, this suppressed subsequent intake more than in a group who perceived the same foods as snacks (20). Wansink has argued that, rather than closely monitoring what is being eaten, people tend to use shortcuts to estimate how much they have consumed, such as “eating until their plate is cleaned” (21). In support of his argument, Wansink has reported that when people eat soup from bowls that are surreptitiously refilled, they can be induced to eat a large amount (22).

The importance of memory as an influence on food intake and preferences has long been appreciated. As humans and animals evolved, they had to learn which food in the wild was safe and which food was not safe to eat (23). Taste (discussed in details later in this thesis) provides critical initial signals about the safety of the food. Sweet taste often indicates that the food is energy dense and safe, whereas, bitter taste often indicate toxicity and potentially hazardous (24). However, taste is only the initial indication, once the food is consumed further consequences can be generated. For example, nutritious food will suppress hunger and provide energy and therefore, it will be labelled as ‘familiar and safe’ but if the food

results in gastrointestinal malaise will be labelled ‘familiar and not safe’, which is referred to as Conditioned Taste Aversion (CTA) (25).

Conditioned taste aversion is a form of classical conditioning, which is the simplest form of associative learning (23). The acquisition of conditioned taste aversion occurs when the subject associates the novel taste of a new sickness induced food (unconditioned stimulus) with nausea generated from its consumption (unconditioned reaction). ‘Unconditioned’ is a term used for first time exposure to the stimulus and reaction. However, futures exposures become ‘conditioned’ as the subject has learned what reaction would be elected (23). Avoiding the conditioned stimulus in the future is a sign of an established conditioned reaction and is referred to as conditioned taste aversion (23).

CTA is of particular interest in obesity and obesity surgery studies as patient often report changes in their likes and dislikes of certain types of food. Sclafani & Koopmans (1981) was perhaps one of the first researchers who reported that a jejunoileal bypass surgery in rats produces a strong and persistent conditioned taste aversion to novel-flavored solutions (26). This reaction may be due to the exaggerated peripheral hormones produced after obesity surgery. Several studies have confirmed this by showing that peripheral administration of $PYY_{3–36}$ (27) and CCK (28) causes CTA in animal studies.

In contrast, conditioned taste avoidance refers to the conscious avoidance of palatable food due to certain adverse reactions like lactose intolerance or nut allergy. The two terms ‘conditioned taste avoidance’ and ‘conditioned taste aversion’ are often used interchangeably. However, studies with rats indicate they have different processes (29). Aversion to food is accompanied by a strong dislike or disinclination to the stimuli whereas avoidance of food happens as oneself is stopping the consumption of the food despite its palatability.

Facial and somatic reactions of rats were used to determine taste avoidance and aversion in a taste reactivity test (TR test) **(30)**. When rats are exposed to a flavoured solution like sucrose, which does not induce abnormal feelings, they develop a ‘liking’ towards the solution. However, if the rats are then injected with a drug that induces nausea, they will feel endangered and develop a taste aversion to the same solution, expressed by conditioned disgust reactions such as mouth gaping **(29)**. On the other hand, if taste avoidance occurs

then the animal may still like the food and choose it over others but tries to avoid it. In further tests, *Suncus murinus* (house musk shrew) were tested with a sucrose solution paired with amphetamine, cocaine, or morphine. The shrew showed positive, euphoric reactions to solutions. However, they reacted to the change in their physiological state as a sign of danger and thus avoided approaching these solutions. The shrew yet preferred the solution that it had taste avoidance towards rather than the other solution it had a learned taste aversion towards **(29, 31, 32)**.

1.1.3 Social factors

Cognitions present at the time of eating alters eating behaviour based on what constitutes socially acceptable (17). Humans, unlike animals, have social, religious, and culture pressure that influences our food choices, time of eating, people we eat with and how much we eat.

In our western culture, sociocultural norms of thinness value the thin body and shun the overweight body. Being thin provides one with sexual confidence, power and security, whereas being overweight makes one untrustworthy, ugly and weak (33).Therefore, social pressure on body image and portion size particularly for women (34), often result in inhibited or reduced food intake in the presence of others (35) especially in the company of people we feel attracted to (36, 37). People are increasingly conscious during social events and are worried about being judged by what they eat. Evidence showed that people match their intake to that of other diners during social events (38, 39). The influence of other people on eating is not restricted to situations in which those individuals are present because providing information about the consumption of previous participants in an experiment can alter the food intake of participants who are given this information (40).

Similarly to culture, religion inevitably affect an individual's self-identity by providing a set of ethical and value-based criteria of what behaviour is and is not acceptable (9). Probably the best examples of the effect of religion on eating behaviour are the prohibition of eating certain types of food for some religions but not others; restricting food consumption during certain periods of the year or times of the day; preparation methods; and enforcing the selection of specific food for religious values (41). Kim K. H. (2006) investigated the role of religion in eating behaviour, body image and dieting (42). The study showed that religion was

significantly related to greater body satisfaction and less dieting. The author suggested that religion affects eating behaviour indirectly by impacting on an individuals' self-esteem (42). These results are consistent with prior findings from Platte *et al.* (2000) (43).

1.1.4 Psychological traits

Eating behaviour is influenced by a number of personality-specific psychological traits of which some have been used to identify disordered eating behaviour that may lead to over-eating and thus obesity (44). Dietary restraint, disinhibition, hunger are some of the most commonly researched personality-specific psychological traits related to obesity (44).

The dietary restraint theory has been established in the 70s to describe an eating style that is driven by cognitive control rather than physiological control (hunger and fullness) to control body weight (45). Repeated dietary restraint can lead to reduced sensitivity to internal cues for satiety, resulting in disinhibition (loss of control) and overeating in situations where cognitive control is weak (46). Dietary restraint creates the conditions for craving the forbidden foods by increasing their appetitive value similar to "the grass is always greener on the other side of the fence" effect (47). Relaxation of restraint around food was promoted as the path to healthier body image, less disorganised eating patterns and eventually to more realistic weight control (48).

Dietary restraint, disinhibition and hunger are usually measured via questionnaires, the most common psychometric questionnaire used in the field of obesity is the Three Factor Eating Questionnaire that assesses all these three elements (49, 50). Those elements have inconsistent findings in being predictors of how well dieters could do in maintaining their long-term weight loss. Sarwer *et al.* (2008) found that greater baseline dietary restraint results in enhances weight loss after RYGB as a consequence of better adherence to the postoperative diet (51). However, based on the restraint theory, Polivy and Herman (1985) argued that high dietary restraint could lead to increased durations of overeating, resulting in higher consumption of calories following dieting (46). A previous study carried out by our group is consistent with this theory and suggests that high baseline dietary restraint can negatively affect long-term weight loss results (52). Disinhibition before obesity surgery may positively predict postoperative weight loss (52). Disinhibition results in irregular eating and

unplanned meals and is correlated with binge eating, a higher BMI, and obesity (53). Obesity surgery, and in particular RYGB, results in decreased disinhibition and improved eating behaviour, which may contribute to weight loss (54, 55). However, this was inconsistent with previous findings that showed disinhibition prior to a weight-loss program is not a prediction factor of weight loss and long-term weight maintenance (56, 57). The difference is using disinhibition to predict weight loss after bariatric surgery and conventional weight-loss programs may be attributed to the effect of some bariatric surgeries, particularly RYGB, on the hedonic value of food (55).

Another questionnaire commonly used is the Dutch Eating Behaviour Questionnaire (DEBQ) to measure dietary restraint, emotional and external eating (58, 59). The DEBQ is more internally consistent and reliable across subjects of different weight and gender compared to other questionnaires (60).

External eating is a measure of eating in response to external cues such as the sight or smell of appetising food rather than physiological signals. Centring food around external cues can result in increased food craving (61) which may lead to overeating and obesity (62, 63), but this remains unconfirmed (64). Eating can also be in response to emotional cues such as sadness, anxiety, stress and anger as a strategy to escape the negative affect (65). Emotional eating is commonly referred to as comfort eating and is associated with depression and elevated BMIs (66). Emotional eaters tend to have more difficulty in controlling their body weight and struggle with weight control programmes, while also negatively impacting on weight loss following obesity surgery and diet (67). Stress is a stimulus for the over-consumption of energy-dense food (68-70). A few studies have reported the importance of cognitive and behavioural coping strategies during weight loss and weight loss maintenance (71-74). Common strategies suggested in those studies include exercise, mindful eating, conscious relaxation and management of emotionally induced eating.

Depression has also been for long associated with obesity. Whether depression causes weight gain due to stress and unhealthy eating style or whether weight gain is a result of the negative affect of depression are controversial (75, 76). The Beck Depression Inventory (BDI-II) can be used to identify symptoms of depression and has been used extensively in

the context of obesity (77-79). In a randomised clinical trial Fabricatore *et al.* (2009) reported that baseline BDI-II score (higher total scores indicate more severe depressive symptoms) was a strong predictor of weight loss success with each additional point on the BDI-II reduced the odds of success by 4% (80).

Higher impulsivity and delayed discounting are also associated with overeating and obesity (81, 82). Impulsivity refers to the initiation of eating for immediate gratification without considering the long-term consequences (83). The Barratt Impulsivity Scale has been used as a tool to reliably measure impulsivity in the context of obesity and binge eating disorder (84, 85). Delayed discounting refers to the inability to resist a small immediate reward instead of a larger reward that will be available in the future (81, 82). Delayed discounting tasks require participants to make choices between rewards that are smaller but immediate versus rewards that are larger but delayed, greater discounting indicates greater impulsivity (86, 87). Impulsivity has been associated with greater snack intake (frequency and total energy intake) in laboratory settings (88), however, in real world consumption it was only associated with higher energy intake from away-from-home and ready-to-eat foods but not with the frequency of eating (89). Higher energy intake and irregular meal frequency, especially of the 'wrong' food, can result in insulin resistance and long-term health complication (90).

None of the above psychological entities works in isolation. Instead, they interact in the same individual and have additive or synergistic effects.

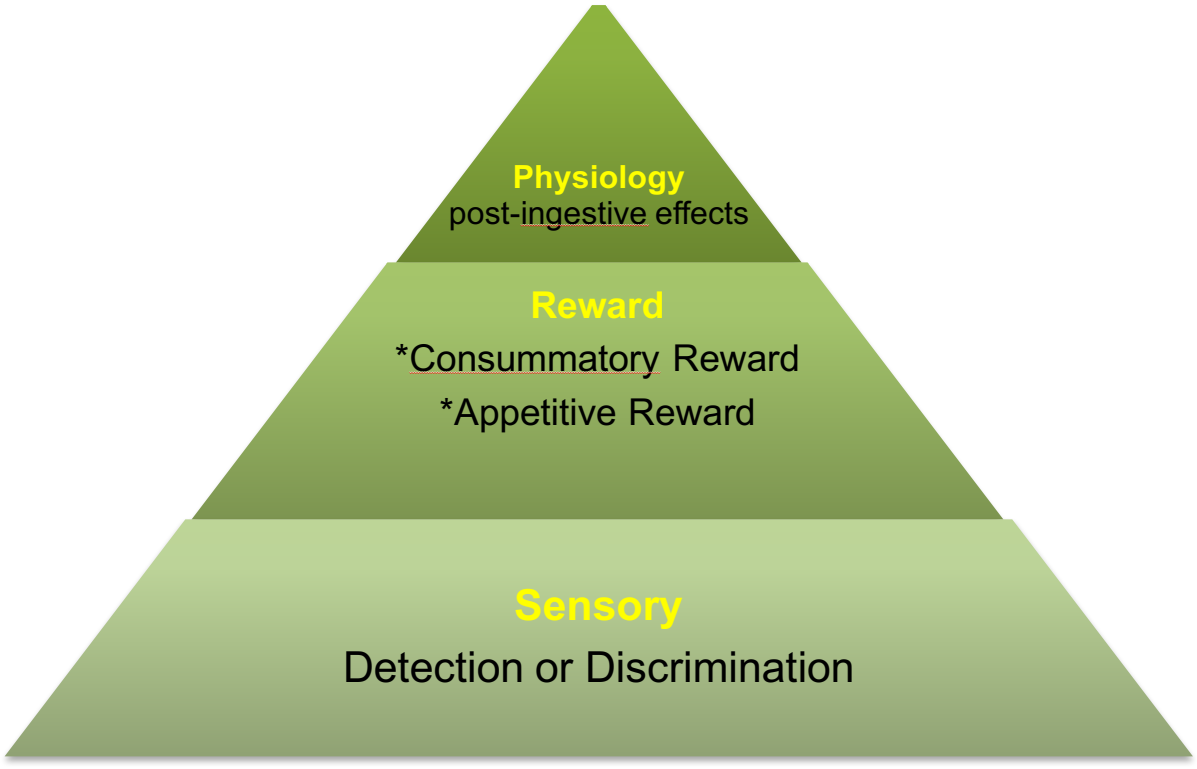
1.1.5 Taste

Taste affects food preference and food intake thereby directly influencing eating behaviour. Taste is the sensation produced when a substance enters the mouth and reacts with the taste receptors cells located on the taste buds. Taste buds are not only found on the tongue, but they are also located in the nasal epithelium, trachea, stomach, bile duct, and on the K- and L- cells in the intestine (91).

In the mouth, the majority of the taste buds are located in the papillae, which are thousands of small bumps on the tongue (91). Taste buds can differentiate between the five basic tastes (sweet, sour, salty, bitter, umami) by specific substance interaction (92).

Once the taste is identified, signals are sent to the NTS in the hindbrain to determine the appropriate responses. Hedonic responses are classified into aversive or appetitive, depending upon the effect the stimulus have on the hedonic system. Physiological responses are in turn the body's way of preparing the digestion and ingestion of that particular stimulus (93). Those three functional domains (figure 2) are equally important for the function of taste. Therefore, generally speaking, the taste systems can be broken down into three main functional domains: Stimulus identification, Ingestive motivation and Digestive preparation.

Figure 2 The taste domains



Note 2 As described by AC Spector (2000) (93)

1.1.5.1 Stimulus identification

The stimulus identification domain or 'sensory domain' encompasses the sensory function of the taste system. Here different tastes "sweet", "salty", "bitter", "sour", and "umami" (e.g. monosodium glutamate taste) are detected. The sensation of taste is encountered when the chemical concentration of a tastant reaches a threshold level that activates taste receptors to generate action potentials in gustatory nerve fibres that are potent enough to elicit a taste perception (94). Taste sensitivity ranges from the lowest concentration of taste stimuli that can be detected (taste detection thresholds) to the intensity perceived for that stimulus (above-threshold responses) (95).

Many researchers believe that taste can contribute to the development of obesity; however, it is difficult to assess whether hypogeusia (reduced taste sensation) causes hyperphagia and weight gain or vice versa. Bartoshuk *et al.* (2006) quoted "The obese live in different orosensory and orohedonic worlds than do the non-obese" (96).

Many studies have shown associations between taste thresholds and weight e.g. (97-99). Kawai *et al.,* (2000) found that leptin, a satiety hormone made by adipose cells, inhibited specific sweet taste responses in lean mice but not in obese diabetic (db/db) mice, suggesting a role of this hormone in sweet taste sensitivity (100). Kawai *et al.* (2000) found that Ob-R, a leptin receptor, is also found in the taste cells of circumvallate papillae in mice in addition to where it has previously been suggested to be present at i.e. the central nervous system (101), peripheral cells, such as T-cells (102), vascular endothelial cells (103), muscle cells (104), and pancreatic cells (105), indicating that taste cells are a site of leptin action (100). It is not surprising that the taste cells of obese diabetic mice were not influenced by the injection of leptin, due to peripheral leptin resistance in obese mice and humans (106). Obese rodents and humans have increased levels of circulating leptin compared to normal weight subjects (107). During weight gain, basal plasma leptin levels would gradually rise, and at the same time, sweet taste sensitivity reduces. The chronic adaptation to high concentrations of leptin may elicit leptin resistance in the taste cells as suggested by Yoshida *et al*. (2015) (108). This means that any further increases in leptin concentration would not elicit further suppression (100).

During weight loss, leptin levels decrease and sweet taste sensitivity improves i.e. decreased thresholds, in invasive- i.e. surgical induced weight loss (109-111) and non-invasive- i.e.

Diet-induced weight loss (112) procedures. Taste sensitivity is also correlated with the reduction in leptin levels (112).

Several gut peptides, including GLP-1 (113), neuropeptide Y (NPY) (114), glucagon (115), and ghrelin (116) (discussed in details in section 1.2) are secreted in response to various taste stimuli and may contribute to taste quality coding (117, 118). A recent study by Takai *et al.* (2015) found that GLP-1 is released from the sweet-sensitive taste cells (T1R3) immediately after stimulation with sweet compounds, indicating that GLP-1 might activate sweet-sensitive gustatory nerve fibres (119). RYGB patients have increased postprandial GLP-1 levels (120), which may contribute to the increased sweet taste sensitivity reported in the previously mentioned studies.

Obesity is associated with many related comorbidities including Type 2 Diabetes Mellitus. Fabbi (1954) was the first researcher who suggested that patients with diabetes may have impaired taste function (121). It was later suggested that this abnormality might be due to the elevated levels of blood sugar that cause a 'satiation effect' towards sweet taste and/or neuropathy causing a reduced taste sensitivity overall (122). A number of studies were then carried out to confirm those finding and it is now well established that T2DM patients have higher thresholds for glucose and sucrose detection than Type 1 patients and controls (123-126). In addition, hyperglycemia is associated with higher sweet taste thresholds between diabetic and pre-diabetic patients (127, 128). This adds burden when designing taste studies and thus my experiments in this thesis included only obese diabetic patients with similar levels of hyperglycemia as discussed in the methods chapter.

Nutritional deficiencies may also affect the taste sensitivity, especially Zinc and B12 (129, 130). Decreased plasma zinc and B12 levels have been reported after RYGB (131, 132). However, Burge *et al.* (1995) did not find an association between zinc and taste acuity in RYGB patients, but in his study zinc levels remained unchanged (110). In addition, this deficiency might not be of a clinical significance to cause such dramatic change in taste.

Altered taste has also been reported in depression and anxiety. Severely depressed patients have decreased sensitivity to all tastes, especially sweet (133), which normalises on recovery. They also report lower intensity responses to suprathreshold stimuli (134). Based

on the ‘monoamine theory of depression’ depression is the result of a deficiency in circulating monoamine concentrations and hence reduced neurotransmission of noradrenaline, dopamine, and serotonin (5-HT), and/or reduced sensitivity of their receptors (135). Taste cells express 5-HT, it’s synthetic enzymes, and it’s receptors. Therefore, 5-HT is involved in the taste signalling by altering ion channel function. Measurement of taste function in healthy humans showed that enhancing 5-HT increased sweet taste sensitivity by significantly reducing the sucrose taste threshold by 27% (136).

The participation of 5-HT in the development of anxiety and stress has also been well acknowledged (137). Anxiety and stress, similarly to depression, often leads to increased intake of high sugary food (138, 139) which could be a result of the reduced sweet taste sensitivity caused by the reduction in 5-HT (136).

Many antidepressants modulate monoamine function, and their use is associated with dysgeusia, an impairment of the sense of taste (140). This will be taken into consideration in this thesis when analyzing the results; history of depression and anxiety and all current antidepressant medication will be reported.

1.1.5.2 Ingestive motivation

When a taste is detected in the stimulus identification domain, another domain comes into action to promote or discourage the ingestion of food, and that is the ingestive motivation domain or ‘reward domain’ (93), please see figure 2 and 3. The ingestive motivation domain differs from the stimulus identification domain in that it represents the hedonic aspects of gustation (93). For example, we can distinguish between the different taste qualities of food and drinks regardless of whether they taste nice or not (pleasant or aversive) by the stimulus identification domain; however, we will only ingest what is determined to “tastes pleasant” by the ingestive motivation domain.

Spector A. C. (2000) described the taste related ingestive motivation as having two sub-domains or two components: the appetitive behaviour and the consummatory behaviour (93). The appetitive behaviour describes the ‘wanting’ actions that bring the animal into contact

with the stimulus e.g. searching, foraging, approaching a drinking spout, whereas the consummatory behaviour represents the final act elicited by the contact of the stimulus, in other words, the 'liking' of the stimulus (93).

In research, the two ingestive behaviour components can be studies in combination but also in isolation, depending on the outcome required. The brief access test is an experimental test used for measuring both components of the ingestive motivation domain (141). In this test, a very small sample of a taste stimulus is presented for a brief duration (e.g. 10 sec) and the animal's unconditioned licking responses are measured using a lick monitoring system (gustometer). Therefore, it assesses how much the animal 'wants' the taste stimulus by approaching it, and also how much the animal 'likes' the stimulus by measuring the number of tongue protrusions over the duration of the test (142). The brief access test minimises any post-ingestive effects of the taste stimuli as only small amounts are ingested (143, 144).

When the appetitive and the consummatory behaviour components of the ingestive motivation domain are studied in isolation, different experimental tests and tools are required. The appetitive behaviour can be assessed using the progressive ratio task which was originally designed by Hodos in 1961 for the use in animal studies (145). This task has also been adopted for the use in human studies for the same purpose (146). During this task, the animal or the subject is required to perform a certain number of responses to obtain a reinforcer (i.e., a reward). After delivery of each reward, the response requirement progressively increases until it is so great, the animal stops responding, which is referred to as the breakpoint. The number of responses completed for the last reward received can be used as a proxy of the reward value of the reinforcer and is a pure assessment of appetitive responsiveness driven by properties of the reinforcer such as its taste (146). This task will be used in this thesis to assess the changes in appetitive behaviour towards a fatty/sweet taste in EndoBarrier patients; therefore, it will be explained in more details in the methods chapter.

On the other hand, the consummatory behaviour component can be assessed using a taste reactivity test (142). This test has been commonly used in animal studies, where an intraoral cannula infuses a taste stimulus directly into the oral cavity and the facial reactions are videotaped and analysed by the investigator (30). Common ingestive (i.e. positive) animal reactions include tongue protrusions and paw licking. While the common aversive (i.e. negative) reactions include gapes and chin rubbing (147). Our research group has adopted

this test for the use in human obesity studies ((148) (unpublished work)). In this human study, a 50ml chocolate milkshake flowed directly into the subjects' mouths using gravity to deliver a rate of 25mL/minute from an 'IV giving set bag'. Subjects' facial expressions were recorded on a camera and were later analysed using a Facial Expression Food Preference Rating Scale ((148) (unpublished work)). Common ingestive human facial reactions to pleasant stimuli include tongue protrusion, mouth movements and ingestion of the stimuli. While aversive facial reactions include gaping, head shaking, wrinkling of the nose, retraction of the head away from the source and fluid expulsion (4, 149, 150).

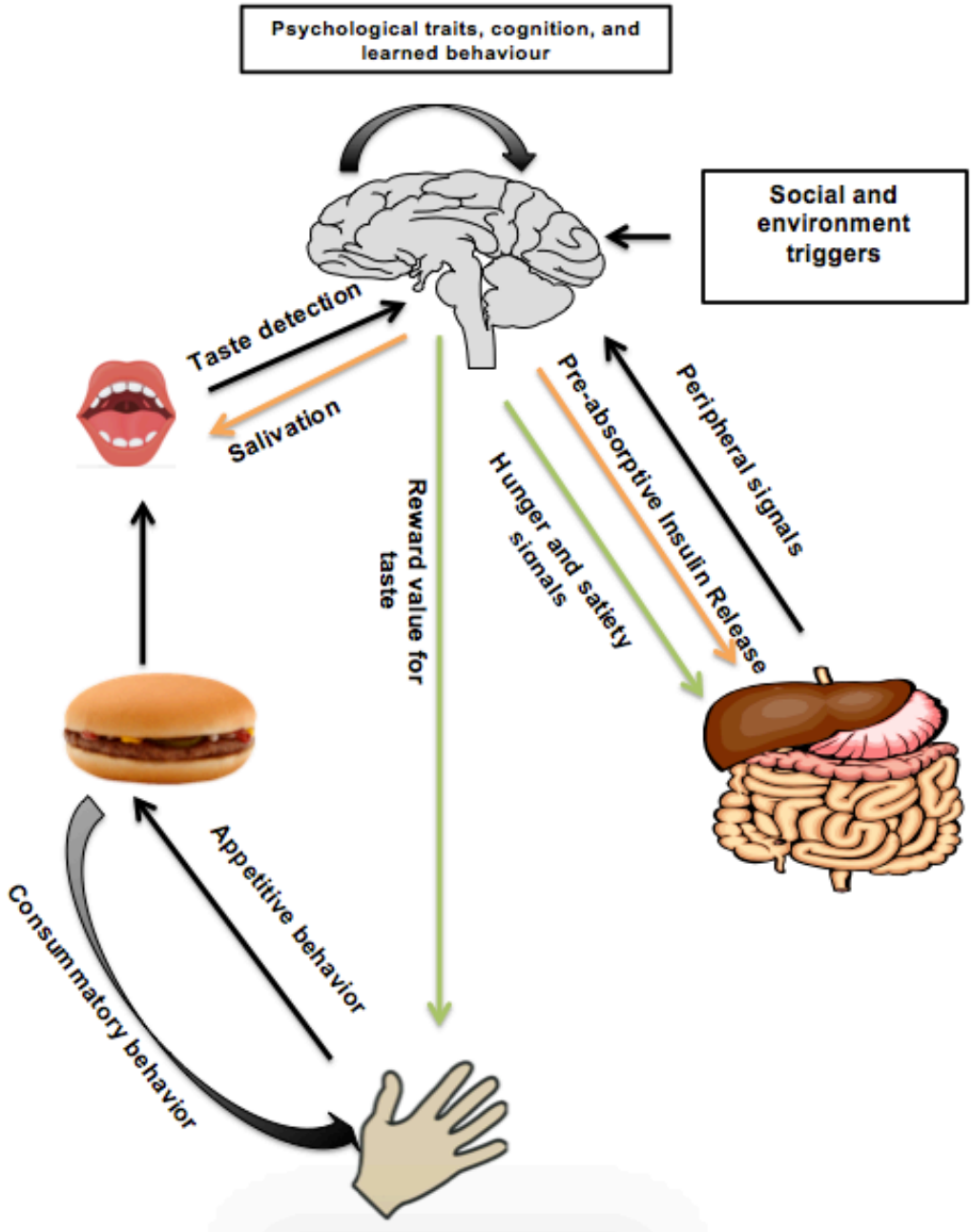
1.1.5.3 Digestive preparation

Taste plays an important role in preparing the body for the digestion of a meal. Once the food is present in the mouth, a number of physiological reflexes can take place as part of what is known as the cephalic phase responses (figure 3). Salivation, is the most obvious cephalic response (151), it can be triggered by the mere thought of food but increases mostly when food is present in the oral cavity (152). Powley (1977) suggested that cephalic phase responses are increased with the appetite for food (153), however, subsequent studies found that salivation rate is not dependent on the level of hunger and appetite (154, 155). The rate of salivation does differ based on the taste of stimuli with the highest saliva stimulation produced by a sour taste, followed by salt, sweet, and bitter (156, 157). This rate is increased with higher concentration of the stimuli (158, 159). A number of studies have suggested that body weight can affect salivation with obese subjects having a higher salivation rate, this can be explained by obese individuals having higher responses to food cues and higher food reinforcing value (160-162). Obese individuals also have a slower habituation rate (reduced salivation to the same ingested food) which can partially contribute to increased food intake (160, 163).

Additional evidence supports the existence of other taste-related physiological reflexes such as delayed increase in blood triacylglycerol levels (164), secretion of gastric acid (165), amylase, gastrin, cholecystokinin, glucagon and pancreatic polypeptide (166). Another taste related cephalic response is pre-absorptive insulin release, which has been studied extensively in animals (167-170) and humans (171-174). Measuring pre-absorptive insulin release can be challenging and require a large sample size and careful protocol consideration as suggested by Teff *et al.* (1991) (174).

The three functional domains discussed above integrate together via multiple signals sent to the brain to determine the reward value for taste of the ingested food (figure 3). Any change to one, or all domains, can alter eating behaviour and thus obesity.

Figure 3 The integration of the three functional domains of taste in eating behaviour



Note 3 Figure is my original work. Black arrows represent triggers of eating behaviour, green arrows represent response signals from the brain to initiate or terminate an eating episode, and orange arrows represent cephalic phase responses.

1.1.6 Studies of eating behaviour

The eating behaviour section in this chapter discussed the complexity of this feeding behaviour as it results from a complex and sophisticated interaction of physiological, psychological, and social factors. The exact behaviour of food intake is a simple action of bringing food to the mouth, and in theory, it should be a simple matter to determine the frequency, size and content of each eating episode. However, under the natural free-living conditions, it is extremely challenging to measure habitual food intake.

Cognition plays a great role in human eating behaviour. Humans have the conscious ability to adopt their food intake based on their environment. This is particularly critical when it comes to extrapolating human food intake data, as it does not reflect the free-living conditions. Cognition, impacts not only on humans but also on animals but its role is greater in human behaviour. Therefore, studies on animals may lack generalisability if compared to humans. Hense, it cannot be assumed that what is true of animals is the same for the far more complex human brain.

Different methodological approaches can be applied to the study of human eating behaviour, but they can be classified into verbal reports or direct behavioural measures. Verbal reports are subjective as they are affected by the awareness of social influences, whereas direct behavioural measures are objective as they measure the physiological or psychological factors by limiting the interference of the social aspect, to a certain extent. Both methodologies carry strengths and weaknesses and their use is determined based on the research question. So far, research in this field has revealed that no single experimental design can answer all research questions. Each research question posed will require a specific study design that will limit the findings of that study to those particular conditions. For example, choices will be made among the use of laboratory or free-living studies, the duration of examination, appropriate measurement techniques and investigative methodologies employed.

Visual analogue scales (VAS) are commonly used in human behaviour studies. They provide a quantifiable objective measure translated from subjective sensations. The origin of VAS in eating behaviour research dates back to Silverstone and Stunkard (1968) (175). Since then, VAS has been employed as the standard methodology to measure the motivation to eat. Rogers and Blundell (1979) (176) developed the original version of a portfolio of VAS questions that have since been adopted by many researchers. They generally include six questions, which relate to states of the motivation to eat. However, more recently questions include: How hungry do you feel now?; How full do you feel now?; How strong is your desire to eat now?; and How much food do you think you could eat now? This last question is also known as prospective consumption.

VAS typically take the form of a 100mm horizontal straight line which is unbroken and unmarked, with the two extreme states (minimum and maximum) anchored at either end by a question associated with a particular state (e.g. hunger). Variations in VAS exist. However, the 100mm horizontal, unmarked line with anchored labels at the extreme is the widely accepted form of VAS.

A series of reviews and discussions have been dedicated to interrogating the validity and reliability of the VAS (177-179).

A number of studies have assessed the use of VAS as predictors of food intake (total daily food intake or at a subsequent meal). The findings are mixed but the majority of studies found that VASs can be used as predictor of energy intake in controlled laboratory conditions (180-182) but not with reported energy intake in a free-living context (183) or at least to a lower extent as suggested by Drapeau *et al.* (2007) (181). Mattes, 1990 pointed that the use of VAS to predict food intake in free-living individuals would not be accurate due to the natural setting people often eat when they are not hungry and sometimes do not eat when they do feel hungry (183).

In terms of reproducibility, VAS is better used for within subjects test-retest due to the genuine differences in individuals' interpretation of the scale. Stubbs suggested that VAS

ratings are consistent and highly reproducible when subjects are fed to energy balance on fixed meals at fixed meal times (177).

The use of VAS in research carries its advantages and disadvantages and those are listed here:

Advantages

- VAS is a reproducible method of assessing subjective appetite sensations – which is strengthened using within-subjects designs
- Easy and quick to use
- Simple to Interpret
- Standardised format

Disadvantages

- Subjective measure affected by social influences
- Sensitive to study manipulation
- Across-group comparisons are invalid or deceptive due to individual interpretation differences

VAS can be optimised by the use of additional tools to increase its accuracy for example by measuring appetite hormonal levels in laboratory studies. In addition, Bartoshuk *et al.* (2005) suggested the use of General Labelled Magnitude Scale (gLMS) where the sensation of interest is compared is relative to an unrelated standard (184). This scale allows a valid group comparison, as the standard will be equivalent across the group. Bartoshuk *et al.* (2005) suggested that this type of scale is not only valid for sensory comparison i.e. appetite but also for hedonic comparisons i.e. liking (184). An example of the gLMS is shown in Appendix 5.

1.2 Regulation of food intake and body weight

Food intake (ingestion of food) is an innate behaviour regulated by two complementary drives, the homeostatic and hedonic pathways (185). The homeostatic pathway regulates energy balance by raising the motivation to eat following exhaustion of energy stores or meal termination in response to physiological hunger and satiety signals (186). In contrast, hedonic or reward pathway integrates the sight, smell and taste of food, along with emotional and social factors to impact upon food intake (186). The hedonic pathway can override the homeostatic pathway during times of relative energy abundance by increasing the desire to consume foods that are highly palatable (186).

1.2.1 Homeostatic regulation of food intake

In the hypothalamus, the arcuate nucleus (ARC) is the main region involved in the homeostatic control of food intake (187). Within the ARC, two groups of neurones are prominently implicated in the regulation of feeding. One group localised more laterally in the ARC and co-expresses anorexigenic (appetite suppressant) neuropeptides i.e. cocaine- and amphetamine-related transcript (CART) and pro-opiomelanocortin (POMC) (188). The second group of neurones tends to cluster more medially in the ARC, co-expresses orexigenic (appetite stimulant) neuropeptides i.e. neuropeptide Y (NPY) and Agouti-related protein (AgRP) (188). Neuronal projections from the ARC then communicate with other key hypothalamic regions, such as the paraventricular nucleus, dorsomedial nucleus, ventromedial and lateral hypothalamic nuclei (188, 189).

The ARC has an incomplete blood-brain barrier that allows peripheral signals such as insulin secreted by the pancreas and leptin secreted by the adipocytes to gain access to the signalling pathway that regulates appetite in the ARC (190). In addition, the vagus nerve and the sympathetic fibres from the nervous system transmit peripheral signals produced in the gastrointestinal tract to the nucleus of the tractus solitarius (NTS) in the brain-stem where signals then integrate with those of the hypothalamus to control appetite (191). Hormones like Leptin and Insulin regulate long-term energy balance (15). While short-term energy balance require a number of signals that send information to the brain on meal-to-meal basis and include nutrients such as glucose, and non-esterified fatty acids (NEFAs), and hormones

such as ghrelin, cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), pancreatic polypeptide (PP) and peptide tyrosine-tyrosine (PYY) (15).

1.2.2 Hedonic control of food intake

Feeding is a required survival mechanism in all mammals just like breathing, and elimination. However, up to relatively recently within human evolution, the concept of food intake was limited to the perception of hunger and fullness as the major driving forces. As a result, only within the last century, food, and in particular high-calorie food, has become so easily available in many parts of the globe. Now that our hunger and fullness can be readily satisfied, the reward value of food has emerged as a dominant force affecting eating behaviour and in particular food preferences (192).

If feeding were solely based on the homeostatic mechanism, we would have all managed to maintain our ideal body weight. However, in our days hedonic eating, that is eating for pleasure, play a vital role in feeding mechanism and can sometimes override the homeostatic control, making energy balance and weight maintenance a very hard task.

Hedonic eating which consist of the emotional and cognitive aspects of food as well as learning and memory are processed in the mesocorticolimbic regions of the brain, collectively called ‘the reward system’. The reward system includes the orbitofrontal cortex, amygdala, insula, anterior cingulate cortex, dorsal striatum, nucleus accumbens, and prefrontal cortex (193). Because the brain is highly complex and regions included in the reward system are interconnected and are not limited to the control of ingestive behaviour, a simplistic approach to describe this pathway will be used in this section for a better understanding of this region of the brain in an attempt to further understand eating behaviour.

1.2.2.1 Orbitofrontal cortex

The orbitofrontal cortex (OFC) received its name from its position above the eye orbits and the sphenoid bone. Its position in the skull makes it susceptible to head injuries and traumas. The orbitofrontal cortex receives information on all sensory modalities (taste, olfaction, touch, hearing and vision), in addition to visceral sensory signals (194-196). A complex integration of signals in different parts of the orbitofrontal cortex leads to the final outcome of decision-making and expectations. Therefore, brain traumas in this area would result in impaired decision-making without necessarily impacting on cognitive abilities (197).

This region of the brain plays an important role in eating behaviour and food choices. Human studies have showed that damage of the orbitofrontal cortex caused by lesions not only result in impaired decision-making but can also lead to weight gain and a preference for sweet foods (194-196). In addition, Goldstone *et al.* (2009) found that healthy non-obese adults have increased activation of OFC when subjected with high-calories food cues than low-calories ones in an fMRI study (198).

Early studies on eating behaviour found that OFC processes information on 'sensory specific satiety' which is a term given when satiety to the food eaten occurs yet other food can still be consumed (199). Small *et al.* (2001) assessed this in humans using positron emission tomography (PET) and found that healthy volunteers that reached sensory specific satiety from chocolate had decreased blood flow to the medial orbitofrontal cortex but increased flow to the lateral orbitofrontal cortex (200). The lateral orbitofrontal cortex not only responds to a taste reward but also to the anticipation of palatable food taste (201), and its activation correlate with future weight gain (202).

1.2.2.2 Insula

The insula is a cerebral cortex structure within the temporal lobe and the frontal lobe; it consists of two parts a large anterior insula and a small posterior insula. The anterior insula appears to integrate visceral and autonomic signals into motivation and emotion, and the posterior to integrate somatosensory, motor and vestibular signals (203). Other studies have also supported its role in risk taking, anticipation, decision-making and addiction (203, 204). However, predominantly the insula is considered the primary gustatory cortex and is involved in taste sensory (detection), taste memory, and taste aversion, without conveying the reward

value of taste (23, 203-205). Instead the insula send signals to the orbitofrontal cortex for encoding of the taste reward (206). The insula is similar to the hypothalamus, in such that the hypothalamus play the key role in integrating the homeostatic functions, the insula integrates the neural signals involved in the processing of external sensory information linked to reward processing (207).

The insula is activated in response to sight and smell of food (208, 209), food craving (210), imagination of saltiness and sweetness (211), and to pleasant food rating (chocolate) (200). In addition, obese subjects have increased insula activation in response to anticipation and tasting food than lean subjects (212).

1.2.2.3 Anterior cingulate cortex

The anterior cingulate cortex is located at the front of the corpus callosum, in the medial frontal lobe. It can be divided into the ventral and dorsal subdivisions (213, 214). Emotional assignments and motivation to food are processed in the ventral subdivision, whereas the dorsal subdivision is responsible for processing cognitive control (213, 214). Both subdivisions integrate together to interpret and regulate emotional responses and motivation for a specific cue, in addition to the assessment of reward and risk (213).

The anterior cingulate cortex is activated in response to the anticipation of palatable food cues as assessed by fMRI in healthy volunteers, together with the medial orbitofrontal cortex and amygdala (215). In obese adults, reduced weight loss at 12 weeks and 9 months follow up of a lifestyle and psychosocial intervention is correlated with higher baseline activation of the anterior cingulate cortex, insula and nucleus accumbens (216).

1.2.2.4 Prefrontal cortex

The prefrontal cortex (PFC) is the cerebral cortex that covers the front part of the frontal lobe. It consist of three main inter-connected neocortical regions, the lateral prefrontal cortex, orbitofrontal cortex, and the meidal frontal cortex, dimensions such as medial/lateral,

rostral/caudal, and ventral/dorsal are used to describe the relative positions of these main divisions (217). Those neocortical regions communicate with all cortical sensory and motor systems as well as subcortical structures via afferent and efferent signals (218). The prefrontal cortex does not process simple automatic behaviour but rather has a critical role in higher cognitive control (referred to as hardwired connections) this is when behaviour is based on an internal physiological signal, cognitive intention or in novel situations. It is also involved in reward processing and particularly in the expectancy and anticipation of a reward (196, 219). The orbitofrontal cortex is the primary site for encoding reward values of reinforces but the lateral prefrontal cortex specifies the expectancy and the type of the reward (220). On the other hand, the dorsol prefrontal cortex controls the inhibition of actions and emotions. DelParigi *et al.* (2007) suggested that successful dieters have increased neural activity in the dorosol prefrontal cortex region in response to food cues than non dieters as a results of restraint eating behaviour (221). This region together with inferior frontal gyrus, dorsal striatum and orbitofrontal cortex is also activated in the conscious application of restraint during presentation of favourite food pictures as assessed by fMRI in normal weight and obese women (222).

1.2.2.5 Amygdala

The amygdala is almond shaped groups of nuclei located deep and medially in the anterior temporal lobe. It consist of the right and left amygdala; the right amygdala induces negative (unpleasant emotions) especially fear and sadness, whereas the left amygdala induces both positive (pleasant emotions) such as happiness and negative emotions as well as processing reward, motivation and learning (223, 224). The amygdala receives information from all sensory systems that process the external world (visual system, the auditory system, olfactory, touch, and hearing) and respond with emotional reactivity. However, it is critically involved in response to sources of danger and that is why its considered the alarm system for the body's organs (225). Animal studies have shown that monkeys with amygdala lesions are fearless with impaired emotional learning and memory for emotional events (226).

In human studies, it has been proved that the amygdala is activated is response to viewing and tasting food using fMRI studies (227-229). It is also not a surprise that it is activated in response to both pleasant and aversive tastants as a way of assessing danger or reward reactions (230-233). The amygdala functions in collaboration with the OFC in the association

between sensory cues and reinforcers (234) and encoding of the reward value of food. Interestingly, Green & Murphy (2012) and Rudenga & Small (2012) found that habitual consumption of non-calorific sweeteners, for example diet coke, can alter the activation of amygdala when real sugar is consumed, suggesting a role of the amgydala in sweet food preferences (235, 236). A recent lesions study by Yesoshima *et al.* (2015) investigated the specific area in the amygdala that can potentially play a role in sweet preferences and found that lesions of the basolateral amygdala (BLA) is specifically involved in the selective sweetener preference between sucrose and saccharin (237).

1.2.2.6 Striatum

The striatum comprises of the ventral striatum and the dorsal striatum. The dorsal striatum consists of the caudate and putamen subdivisions. The dorsal striatum mediates cognition involving motor function, certain executive functions, and stimulus-response learning. Those functions are mediated through the release of Dopamine in response to specific cues, for example hunger (238, 239). The release of dopamine in the dorsal striatum in healthy volunteers also correlates with the subjective pleasantness of food in a seminal PET study (240). The caudate is activated when healthy volunteers are asked to imagine the sensory properties of their favourite food similarly to the insula and hippocampus (210).

It has been suggested that the severity of obesity is associated with neuroadaptation in the dorsal striatum (241). This is based on studies showing that food addiction and compulsive eating induces greater involvement of the dorsal striatum (241, 242). Obese subjects perceive high-calorie food as less pleasurable and its consumption is rather strongly driven by habits (243, 244). Obese subjects show increased dorsal striatum activation in response to food cues (212, 245-247) and lowered activation during food receipt (212, 245).

The ventral striatum is composed of the nucleus accumbens and olfactory tubercle. The nucleus accumbens is made up of the core and shell which have different functions based on their neuronal population. However, as a whole the nucleus accumbens play a major role in cognitive processing of aversion (248), motivation, pleasure, reward and reinforcement learning, and goal directed behaviour (249-251). The nucleus accumbens responds directly to both the appetitive and consummatory reward aspects of food and taste and forms parts of

both the dopaminergic and opioid/endocannabinoid system (249). When a new stimuli is tasted, the nucleus accumbens initiates seeking behaviour and motivation to the stimulus based on its reward value (249, 250).

A study of healthy women, showed that activation of the nucleus accumbens in response to food pictures can predict subsequent snack intake independent of subjective ratings of their desire to eat (252). Activation of the nucleus accumbens was also associated with increased BMI in individuals reporting low self-control (252). Demos *et al.* (2011) compared the activation of the accumbens in dieters and non-dieters based on their scores from the restraint scale. Dieters had higher activation following a milkshake preload whereas non-dieters had the highest activation following a water preload (253). Dieters often have the desire to consume large amounts of high calorific food when their diet is violated, in this study the restraint dieters diet was violated by the consumption of the milkshake preload and thus they had higher activation in the nucleus accumbens. This study suggests a role of the nucleus accumbens in diet success (253).

1.2.2.7 Hippocampus

The hippocampus is located in the medial temporal lobe in the forebrain. It was historically only associated with memory and particularly long term memory. However, recent findings have linked the hippocampus with eating behaviour and food intake by integrating memory of rewards from previous experience with the external sensory context (visuospatial, olfactory, gustatory cues) and the internal context (interoceptive energy status cues) to influence decisions about when, where, what, and how much to eat (254).

Memory is an essential factor in meal initiation and portion size. Hippocampal damage in amensic patients are able to consume consecutive meals with only a short time gap in between those meals (255). However, those patients can still have sensory specific satiety as their food liking rating is reduced in the subsequent meals if they are presented with the same type of food (256).

Long-term memory also results in conditioned feeding behaviour (learned behaviour). This type of behaviour influences the type, flavour, and time of food consumed. The hippocampus does not play a role in the consummatory (257) or appetitive eating behaviour (258) but it integrate the neural signals between the external, internal and the previous food related experiences to decide on food intake (254).

1.3 Obesity

Obesity has been declared to be a chronic medical disease by a number of global health organizations including the World Health Organization (WHO), Food and Drug Administration (FDA), the National Institutes of Health (NIH), the American Medical Association (AMA, the Canadian Medical Association (CMA) (259, 260). It has reached epidemic proportions worldwide, bringing with it a burden of associated comorbidities and negative impact on quality of life. Obesity is a complex disorder involving eating behaviour, appetite regulation and energy metabolism, therefor prevention and management of obesity requires multifaceted approach to achieve realistic goals.

1.3.1 Defining obesity

Obesity as defined by the World Health Organisation (WHO) is 'abnormal or excessive fat accumulation that presents a risk to health' (261). In clinical settings and epidemiological surveys, adiposity assessments requires expensive and unpractical tools therefor, there was a need to establish a valid, reliable, quick and inexpensive alternative to assess obesity. Body mass index (BMI), which is weight (in kilograms) divided by the square of the person's height (in metres) has been used as a substitute measure for obesity since 1972 (262). BMI remains a measure that carries considerable limitations. It has been recognized that BMI association with mortality and morbidity defers according to ethnicity, that's why some Asian countries have established their own BMI cut-offs for risk assessment (263). In addition, as BMI does not measure body fat, muscular individuals and athletes often fall into the overweight category when they are not actually overweight. In addition to the association of body fat with mortality, many studies have shown a direct correlation between fat body disposition and certain obesity related comorbidities i.e. abdominal fat linked to increased risk of diabetes than hip adiposity. People with TOFI phenotype (Thin on the Outside Fat on the Inside) may present at normal BMI but have a high risk of metabolic diseases (264). Conversely, individuals who have low internal fat stores can have lower metabolic diseases even with higher BMI levels (264). Waist circumference can also be used as a strong indicator increased metabolic diseases risk not only in overweight and obese individuals but also in normal weigh individuals (265).

The International classifications of adult BMI categorise is shown in (Table 1-1).

Table 1-1 WHO International Classification of BMI

Classification	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5-24.9
Overweight	25.0-29.9
Obese	≥30

Obesity is a major risk factors for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer and is a leading risk for global deaths; around 3.4 million adults die each year as a result of obesity related disorders (266).

1.3.2 History and prevalence

Obesity has a long history in human beings and is thought to have affected some hunter-gatherers, since the Stone Age. The earliest depictions of obesity is said to be represented by Venus of Berekhat Ram figurine discovered in the Golan Heights, and the Venus of Tan-Tan discovered in Morocco (230 000 to 500 000 BC). More recently and hundred of miles away, figurines that date back to thousands of years later were discovered in Europe with the same body shape, of which the most famous are 'Hohle-Fels Venus' (38 000–33 000 BC) and 'Venus of Willend' (22,000-21,000BC) (267). A scientific debate regarding those figurines has taken place to whether in fact they were representing obesity, fertility or even ancient pornography (267-269). It is however evident, by the increasing number of 'fat' figurines while agriculture settlement started taking over the hunter-gatherers tribes, that obesity became more prevalent (267).

Hippocrates (460- 370 BC) confirmed those speculations of the early humans obesity when he stated that "Persons who are naturally very fat are apt to die earlier than those who are slender" (270).

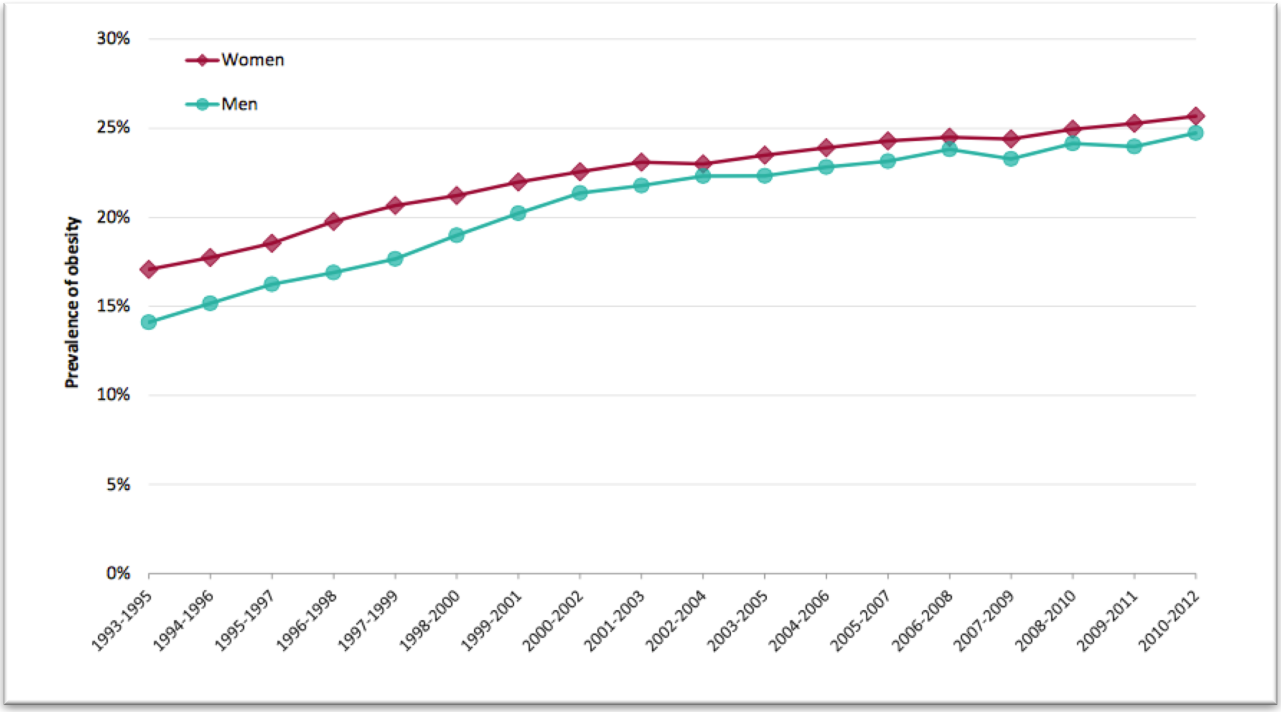
Although, it is very difficult to estimate the prevalence of obesity during those times, due to the lack of statistical evidence, it has been suggested that obesity was a symbol of health,

prosperity, and strength (271). It is not until the eighteenth century when the attitude towards 'fat' started to become altered and eventually in the twentieth century it became considered ugly (271). Subsequently, rates of obesity started to rise in the industrialized countries and by the 1930s life insurance companies were using body weight to determine premiums. Trend in overweight and obesity continued to shift up slowly but it was not until the 1980s when the rise became fundamentally different and 857 million people were classified as overweight and obese, globally (272).

Since the 1980s obesity started to take a different trend, the increase was dramatic and uncontrollable, deaths caused by obesity related comorbidities such as cardiovascular diseases and cancer were on the rise and obesity has received considerable attention as a major health hazard. Overweight and obesity continued to rise in the 90s and have now more than doubled, it currently affect more than 2·1 billion men and women worldwide and is considered a disease in itself (273). In the UK, the Health Survey for England (274) has suggested that a quarter of adults living in the UK are classified as obese, figure 4 shows the increase in the rate of obesity between 1993 and 2012. Those rates are expecting to rise to half of the population by 2030 (275).

It is beyond the remit of this thesis to discuss in full the entire complex reasons for such a rise in the rates of obesity. However, the interaction between an obesogenic environment where an abundance of highly palatable, high caloric dense foods are readily available with the emotional and cognitive brain and how it can make certain individuals more susceptible to increased food consumption is increasingly blamed for such an epidemic (276, 277).

Figure 4 Prevalence of obesity among adults Health Survey for England 1993- 2012



Note 4 Source: Health Survey for England, 1993-2012.

1.3.3 Obesity-related comorbidities

Numerous studies have documented the relationship between obesity and a number of comorbidities such as cardiovascular diseases, dyslipidaemia and type 2 diabetes, and cancer (278, 279) which all may result in increased mortality risk. In addition, obesity is associated with other health conditions that can impact on the quality of life such as osteoarthritis, obstructive sleep apnoea, polycystic ovary syndrome, liver and gall balder diseases, impaired fertility, pregnancy complications, and psychological problems like depression and self-confidence (279-281).

1.3.4 Benefits of weight loss

Weight loss in overweight and obese patients is clinically recommended, especially in those with obesity-related comorbidities (282). The recommendation is based on randomised

clinical trials showing substantial short-term health benefits including improvements in glycemic control, risk factors for cardiovascular disease, quality of life, psychological factors, and other obesity-related co-existing illnesses even by a modest amount of weight loss (283-286). The Action for Health in Diabetes (Look AHEAD) study is the only long-term randomised clinical trial investigated the long-term (11.5 years) benefit of intensive lifestyle intervention through caloric restriction and increased physical activity on cardiovascular morbidity and mortality among overweight and obese adults with type 2 diabetes (287). Although this study was halted 2 years before the original planned date, due to the primary outcome not being met. The study showed that overweight and obese patients were able to maintain an average of 5% weight loss for 11.5 years and modest weight loss was associated with significant improvement in type 2 diabetes for up to a 4 years follow-up period (288), reduction in blood pressure (289), and improvements in urinary incontinence (290) and sexual dysfunction (291).

1.3.5 Treatment of Obesity

Several weight management treatments are available of which lifestyle changes together with diet and exercise are usually considered the first lines of therapy. Frustratingly, the results of these approaches have been disappointing and patients fail to maintain weight loss over the long term. Only around 15% of obese and overweight people who attempt to lose their excess weight by diet therapy can manage to sustain 10% of weight loss over a period of 1 year (292). In those people, lost weight tends to be regained within a year and for the majority it is regained within 3-5 years (293). Obesity surgery is the most successful intervention for the treatment of obesity and weight related diabetes. It is becoming increasingly popular due to sustained post-operative weight loss and improvements in obesity-related comorbidities (294).

1.3.5.1 Dietary therapy

Dietary strategies for the treatment of obesity can be broadly divided into five types. Low-fat diets are focused primarily on limiting fat intake with no recommendations concerning caloric intake; Low-calorie diets reduce the amounts of all macronutrients, including fat, to achieve a daily caloric intake of 1000–1500Kcal; Very-low-calorie diets recommend a daily caloric

intake of <1000Kcal and invariably restrict fat and carbohydrate, but near normal protein intake is maintained; Carbohydrate-restricted diets specify either a modest restriction of carbohydrate and an increase in protein intake or a severe restriction of carbohydrate intake and an increase in protein and fat intake.; Low-glycemic-index diets mostly recommend a diet with a low glycemic load where the carbohydrate intake is maintained but the type of carbohydrate consumed is changed to deliver a lower glycemic load.

Many RCTs have evaluated the effectiveness of those different types of diet on weight loss. Avenell *et al*. reviewed 12 low-fat diet RCTs and found that these diets reduced weight by an average of 5.4 kg at 12 months (295). However, when compared to low calorie diets in a systematic review by Pirozzo *et al*., low-fat diets were shown to be inferior to the low calorie diets with a weight-loss difference of 1.7 kg at 6 months (four studies analyzed) and 1.1 kg at 12 months (five studies analyzed), however, the difference was not statistically significant (296).

The low calorie diet is still a very popular type of diet and based on the evidence report of the National Obesity Education Initiative of the National Heart, Lung, and Blood Institute (NHLBI), in cooperation with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (1998), the report showed that 25 RCT of LCD for more than 6 months resulted in 8% weight loss for up to 1 year.

The LCD just like other types of diets comes with limitations, in this particular type difficulty to comply to smaller portion sizes and to count daily total caloric intake are the most common ones, this in turn effects the duration of the diet per individual. Therefor, the LCD is sometime modified to include low calorie pre-prepared meals or commercial meal replacements. Levy and Heaton (297) reported that in the US, 15% of women and 13% of men who were trying to lose weight were using meal replacements as their weight-loss strategy. A meta analysis of 6 RCTs examining meal replacement as a strategy for weight loss have found that a diet plan including at least one meal replacement daily achieved 2.5kg greater weight loss at 3 months than a food-based diet plan with a reduced energy intake (298). In the Look AHEAD Study the weight loss dietary intervention, for overweight and obese patients with T2DM, included daily meal replacements. This diet has shown to result in an 8.6% reduction in body weight at 12 months and maintaining an average of 5% weight loss for 11.5 years (283, 288).

In some cases a more rapid weight loss is required or desired. Very low calorie diets can result in a higher weight loss in a shorter period of time than low calorie diet. Anderson and colleagues (299) performed a meta-analysis examining weight loss in 4,287 obese patients from the US after 24 weeks of treatment with either low calorie diets or very low calorie diets and found that VLCD can result in 21.3% weight loss compared to 11.4% in LCD. The differences in weight loss between these diets tended to become smaller in the long term (2–5 years) (299).

Many studies have looked at the effect of altering the macronutrient composition within a reduced a calorie diet on weight loss. In a normal diet and a calorie-restricted diet, the protein intake ranges between 12-18% of the total daily energy intake (300). This percentage is increased to about 25-34% in the low carbohydrate diet, the increased protein intake results in increased satiety thus lower total energy intake and longer compliance to the diet.

Nordmann *et al.* compared 5 RCTs investigating the effect of low carbohydrate diet to low fat diet in a meta-analysis with a total of 447 individuals and showed that low carbohydrate diet resulted in 3.3kg higher weight loss after 6 months. However, this difference was no longer present at 12 months (301).

The type of carbohydrate consumed within any diet may also add additional benefits not only on weight loss but also on glycemic control, and possibly on other obesity related health risks (302, 303).

As describes above, all types of diet have weight loss benefits as they all follow the general rule of creating an energy deficit. However, the benefits can only be seen when those diet are followed accordingly and adhered to which is the key to a successful weight management (304).

1.3.5.2 Pharmacotherapy

Several treatments are available for overweight and obese patients who want to lose weight using conventional pharmacotherapy treatments globally. However, in the UK only two medicines are currently approved for the treatment of obesity, those are Orlistat (Xenical) and GLP-1 Analogue (Liraglutide). Those two treatments are effective to result in up to 10 present weight loss but weight tends to plateau after six to eight months. As patients stop taking medication, weight gain usually occurs.

Orlistat is a gastrointestinal lipase inhibitor that primarily inhibits the activity of gastrointestinal lipases, predominantly pancreatic lipase, thereby decreasing the hydrolysis and subsequent absorption of approximately 30% of ingested fat (305) resulting in weight loss in a dose dependent manner (306).

In large multi-centre randomised clinical trials, Orlistat has shown to result in more than 5% weight loss in 65.7% patients treated with the active drug compared to 43.6% on placebo; and more than 10% weight loss in 38.9% in the Orlistat group compare to 24.8% in the placebo group, after 52 weeks (307). Diet modification especially reduced fat intake is an important element to a successful weight loss and to reduce common side effects such as Flatus with discharge, oily spotting, and faecal urgency (307).

Liraglutide, a subcutaneous injection of GLP-1 analogue with 97% homology to human glucagon-like peptide-1, has been used for the treatment of Type 2 Diabetes Mellitus at doses up to 1.8 mg once per day for many years (308) but has only been approved for the treatment of obesity in 2014-2015 by the FDA and the European Medicine Agency . Weight loss with Liraglutide is dose dependent up to 3.0 mg once daily. Liraglutide works by suppressing appetite thus reducing daily energy intake but does not increase energy expenditure. As with Orlistat, Liraglutide should be accompanied with lifestyle and dietary medication for most successful weight results.

The most recent results from a randomised, placebo-controlled, clinical trial to evaluate the efficacy and safety of 3.0mg of Liraglutide injected subcutaneously once daily in non-diabetic obese patients has shown that Liraglutide results in a weight loss of 5% in 63.2% patients taking the active drug compared to 27.1% patients on placebo, respectively; and a 10% weight loss in 33.1% of patients on the active drug compared to 10.6% on placebo, after 56

weeks of continued treatment (309). In addition to weight loss, Liraglutide has shown to result in significant improvement in glycaemic control, cardiometabolic risk factors including weight circumference, blood pressure, and inflammatory markers, and health-related quality of life, especially physical function, compared to placebo (309), those results support previous trials (310, 311).

As all medications come with side effects, the most common ones associated with the use of Liraglutide are nausea and vomiting and possible gallbladder related health events in those who achieved higher weight loss (309).

1.3.5.3 Bariatric/Metabolic Surgery

Obesity surgery is an option for obese patient, where lifestyle and medication have been evaluated but found not be effective. Different procedures are available; they vary with their metabolic benefits, as well as with their surgical risks based on the anatomical manipulation that the operation requires. Different types of obesity operations are available of which some involve the stomach only, others the small bowel only, or a combination of both. However, based on scientific evidence (some are discussed later in this thesis), new concepts for obesity surgeries are rising and S. Santoro (2016) suggested that they should no longer be called obesity restrictive operations; instead they should be called metabolic surgeries (312). His suggestion was based on that obesity surgeries do not cause mechanical restriction but rather a functional one where physiological signals result in food restriction not size of the stomach. In addition using the term metabolic surgery indicate the health benefits rather than disease and illness of a mechanical restrictive or a malabortive operation (312).

Roux-en-Y gastric bypass (RYGB), Gastric Band (BAND), and Vertical Sleeve Gastrectomy (VSG), are the most widely performed surgeries in the UK (313).

The Roux-en-Y gastric bypass (RYGB) is the most popular procedure worldwide and the most performed in the UK due to its high effectiveness in weight reduction (314). Nevertheless, RYGB is a technically demanding procedure and is associated with the profound rearrangement of the normal gastrointestinal anatomy. In this procedure, the

stomach is divided into two parts: a stomach pouch 15 to 30 ml in volume, and a lower larger section, gastric remnant. The stomach pouch is then connected to the mid-jejunum; Gastric, pancreatic and biliary secretions then flow undiluted in the biliopancreatic limb and mix with food in the jejuno-jejunal anastomosis (315). RYGB produces 20-30% weight loss (316, 317) maintained for at least 20 years and improves glycaemic control in 90% of patients (318).

The Gastric Band (BAND) is also a widely performed technique in the UK (314). This procedure involves the insertion of an adjustable hallow plastic and silicone ring near it's upper end, immediately below the gastro-oesophageal junction, creating a small pouch and a narrow passage to the remaining part of the stomach. This procedure causes a delayed emptying of food from the pouch and thus a feeling of fullness (319). The band is adjusted through injections of fluid in a subcutaneous port to change the size of the passage over time (319) causing a reduction of 15-20% in total body weight (317, 320)

Vertical Sleeve Gastrectomy (VSG) is another obesity procedure that has became increasingly popular due to its relative simplicity and good clinical outcomes (321). VSG involves the excision of 70-80% of the stomach to make a small pouch that holds a considerably smaller volume of food that can be consumed. Short-term studies show that VSG is as effective as the RYGB in terms of weight loss and improvement or remission of diabetes (322-325).

1.4 Type 2 Diabetes Mellitus (T2DM)

Diabetes is a chronic metabolic disease that results in increased level of blood sugar (hyperglycaemia). There are two main types of diabetes; Type 1 diabetes is an auto-immune condition in which the cells that produce insulin are destroyed, while Type 2 diabetes mellitus (T2DM) is a progressive disease that occurs when the pancreas stops producing enough insulin for its needs or the body become resistant to the effect of insulin produced (326). T2DM is the only type of diabetes that is associated with obesity therefore type 1 and other types of diabetes like gestational diabetes are beyond the scope of this thesis.

While T2DM is a multi-factorial disease, it is clear that the increase in obesity worldwide is driving the T2DM epidemic. The classic symptoms of diabetes are excessive secretion of urine (polyuria), thirst (polydipsia), weight loss and tiredness (326). However, T2DM can also develop with no early symptoms and only diagnosed several years after its onset, when complications are already present. The main complications include microvascular complications such as retinopathy, neuropathy, nephropathy and macrovascular complications such as stroke, heart attacks and amputation (326).

1.4.1 Defining Type 2 Diabetes

Type 2 Diabetes Mellitus occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin produced which leads to increased concentration of glucose in the blood. The World Health Organization (WHO) diagnostic criteria for T2DM are summarised in Table 1-2 (327, 328).

Table 1-2 WHO Diagnostic criteria for Type 2 Diabetes Mellitus

Type 2 Diabetes Mellitus	
Random venous plasma glucose	≥11.1mmol/l
OR Fasting plasma glucose	≥ 7.0mmol/l
OR 2-h plasma glucose *	≥11.1mmol/l
HbA1c^	≥48mmol/mol (6.5%)

*After ingestion of 75g oral glucose load ^A value of less than 48mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests.

Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG) refer to the levels of plasma glucose above the normal range, but below the diagnostic levels. Table 1-3 summarizes WHO pre-diabetes levels; those levels can predict a higher risk for developing diabetes and diabetes related comorbidities (327).

Table 1-3 WHO CUT-OFF levels for Pre-diabetes

Impaired Glucose Tolerance (IGT)	
Fasting plasma glucose	<7.0mmol/l
AND 2-h plasma glucose*	≥7.8 and <11.1mmol/l
Impaired Fasting Glucose (IFG)	
Fasting plasma glucose	6.1 to 6.9mmol/l
AND (if measured) 2-h plasma glucose*	<7.8mmol/l

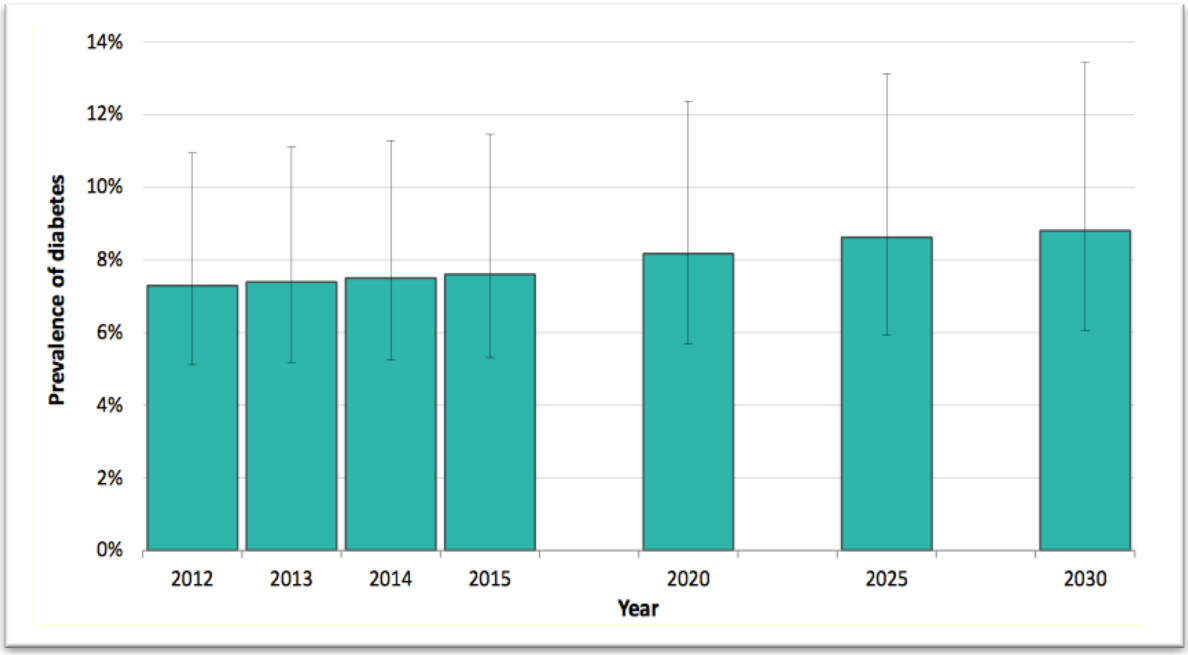
*After ingestion of 75g oral glucose load

1.4.2 History and prevalence

Diabetes prevalence in the UK and worldwide has been on the rise since the 1980s (329). In the UK, there are almost 3.5 million people diagnosed and living with diabetes, out of which 90% are T2DM cases (330). The prevalence of T2DM in the UK is expected to reach 9.5% (4.6M people) by 2030 (331). Figure 5 shows the rise in the prevalence of diabetes between 2012 and 2015 and the expected rise until 2030.

Being overweight or obese is the main modifiable risk factor for type 2 diabetes (332). In England, obese adults are five times more likely to be diagnosed with diabetes than adults of a healthy weight (333). Central obesity adds an additional burden to the risk of developing T2DM, men with a raised waist circumference are five times more likely to have diagnosed diabetes than those without a raised waist circumference and women are over three times more likely (332). Therefore, diabetes will continue to be on the rise as long as obesity is on the rise too.

Figure 5 Adult diabetes prevalence in England 2012-2030



Note 5 Source: Yorkshire and Humber Public Health Observatory (YHPHO) Prevalence Model for local authorities and clinical commissioning groups published November 2012 by YHPHO

1.4.3 T2DM related comorbidities

Diabetes can lead to long term macro- and micro-vascular complications causing a greater risk of a range of chronic health conditions including cardiovascular disease (334),

neuropathy (335), amputation (336), kidney disease (337), and blindness (338), and mortality (334).

The risk of cardiovascular diseases is increased by two-folds in people with diabetes. The health and social care information centre reported that people with diabetes are 48%, 65%, and 25% more likely to be admitted to hospital for a heart attack, heart failure, and stroke, respectively (334). Cardiovascular diseases are a major cause of death and disabilities in people with diabetes accounting for around 52% of fatalities in people with T2DM (339).

Neuropathy is probably the most common complication of diabetes. Studies suggest that up to 50% of people with diabetes are affected to some degree (335). Neuropathy causes nerve damage in the brain, spinal cord, muscles, skin, blood vessels and other organs. Chronic painful neuropathy is the most common type and causes sensory loss and damage to the limbs and feet and increases the risk of ulceration and amputation, this is often referred to us 'Diabetic foot disease'. Diabetes is the most common cause of non-traumatic amputation of the lower limb, over 135 people a week have a limb amputated in the UK as a result of diabetes (336).

The kidneys can be affected by diabetes when the small blood vessels are damaged resulting in kidney diseases or failure (nephropathy). Many people with diabetes may not think of the great risk of kidney diseases as it's development is slow and usually takes 10-20 years for it to develop in people with T2DM (337). Once nephropathy develops, it deteriorates to the next stage at 2-3% rate every year, and in many people treatment will require renal replacement at the developed stages (337). People with diabetes are twice more likely to have a renal replacement therapy that the general population. T2DM is a major cause of end stage kidney disease and accounts for 11% of fatalities in T2DM (340).

Damage to the small blood vessels of the retina (Retinopathy) may result from poor diabetes control. Nearly 60% of all patients with Type 2 diabetes people develop Retinopathy within 20 years of their diabetes diagnosis (338). Approximately 2% of those people become blind, while about 10% develop severe visual handicap (341).

Diabetes can also be fatal, in the UK people with T2DM are 36% more likely to die than the general population of the same age and results is nearly 23,000 additional deaths a year (334). A pooled data analysis of 57 prospective studies and 900,000 adults in 2009 showed that people aged 35-59 years with BMI of 40-50 kg/m^2 were at 22.5% more risk of mortality than normal weight people (342). The National Diabetes Audit suggests a U-shaped relationship between short term mortality BMI, though possibly due to the short time between BMI measurement and death (1-2 year only) (334).

1.4.4 Benefits of good glycaemic control

As presented in section 1.4.3 T2DM is an independent risk factor for macro- and micro-vascular complication. Previous prospective studies have shown an association between the degree of hyperglycaemia and increased risk of microvascular complications (343), neuropathy (344), cardiovascular diseases (345), and mortality (346, 347).

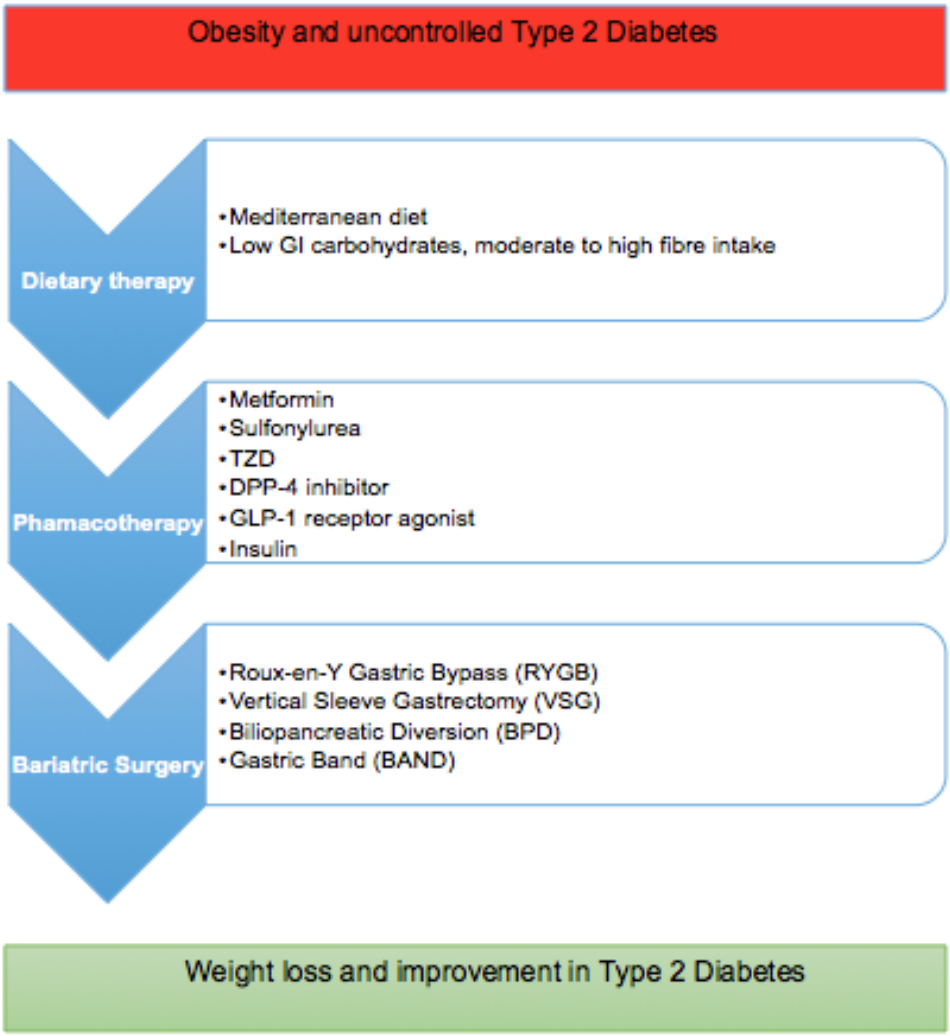
The UK Prospective Diabetes Study (UKPDS) has evaluated the relation between exposure to glycaemia over time and the development of macrovascular and microvascular complications and found that each 1% reduction in HbA1c was associated with reductions in 21% for deaths related to diabetes, 14% for myocardial infarction, and 37% for microvascular complications (348). Intensive diabetes management with the goal of achieving normal glycaemia has been shown to delay the onset and progression of increased urinary albumin excretion, reduced eGFR and diabetic retinopathy in patients with T2DM (339, 349, 350).

1.4.5 Treatments of T2DM

Healthy food choices and weight loss are a major part of the management therapy of Diabetes. Considering that T2DM is associated with body weight and that weight is the main modifiable risk factor for type 2 diabetes (332), weight loss of as little as 5% by conventional weight loss therapies can improve glycemic and metabolic control in patients with type 2 diabetes. However, this may be difficult to sustain for the long-term in all patients and medical treatment would be added in most cases. Patients with poor diabetes control and

diabetes related comorbidities, have been shown to have long-term benefits from surgical options (351).

Figure 6 Summary of treatments recommended for diabetes management



1.4.5.1 Dietary therapy

All dietary therapy recommendations for the management of T2DM primarily aim at achieving modest weight loss and weight loss maintenance (352-355). The Look AHEAD (Action for Health in Diabetes) study was one of the biggest multi-centred randomized controlled trial that investigated the effect of an intensive lifestyle therapy in patients with Type 2 Diabetes (356). Although the primary outcome of this study was cardiovascular morbidity and mortality,

this study showed that participants were able to achieve 8.6% weight loss in one year and sustained a 3.5% weight loss at 9.6 years follow up (287). They showed weight loss was strongly associated with improved glycaemia and that 5-10% weight loss increased the odds of achieving a 0.5% point reduction in HbA1c (357).

Adhering to a healthy dietary pattern without restricted calorie intake has beneficial for the management of T2DM, several dietary patterns have been investigated for this purpose and those are summarized in Table 0-5. The Mediterranean diet has gained increased attention and popularity due to it's great health benefits on improving glycaemia and reducing incidents of major cardiovascular disease events without restricting calorie intake, as evidenced by the PREDIMED trial (358). A RCT of 215 newly diagnosed diabetic patients naïve to T2DM treatment, found that a Mediterranean diet consisting of 50% of daily calories form carbohydrates resulted in better glycaemia control and less patients having to start on diabetes medications at 4 years follow up compared to patients who had a low fat diet (359). A systematic review of 5 RCTs of (restricted and non-restricted calorie intake) Mediterranean diet have supported those findings (360).

Educating patients with diabtese on the quality of specific macronutrients is a very important aspect in the dietary management of T2DM. Carbohydrates can be broadly divided into simple sugars, complex carbohydrates, and fibre which each effect blood sugar differently (361). The effect of food on the rise in blood sugar level is termed Glycaemic Index (GI); a low GI response from food (below 50) is preferred in the management of diabetes. This is obtained from food that is high in complex carbohydrates and fibre as opposed to simple sugars. However, when considering the GI level, portion size should also be controlled as a high portion of a low GI food can result in a high Glycaemic Load (GL), which causes increased need for insulin. Therefore, GI and GL should be considered in combination (355). In addition, breakdown of food during food preparation cause an increase in its GI, for example fruit juices and smoothies have higher GI than whole fruit pieces, and rice crackers have almost double the GI of wild, minimally cooked, long-grain rice (361).

A meta-analysis study carried out by Thomas & Elliott (2010) assessed 12 RCTs with interventions longer than 4 weeks comparing a low-GI diet with a higher-GI diet for type 1 or type 2 diabetes, found a significantly improved glycaemia control on with the low-GI diet than a high-GI diet (362). Some studies combine fiber intake with low GI diet when assessing the

effect of a carbohydrate diet on blood sugar, meta analysis of 13 RCTs found that a diet rich in fiber or fiber supplements resulted in a 4.75% reduction in HbA1C (363), a reduction of 5% is clinically relevant and comparable to some T2DM medication (364).

1.4.5.2 Pharmacotherapy

If diet and lifestyle changes alone are not sufficient to lower blood sugar levels, several medications are available for the management of diabetes (365). Though those medications are effective in controlling glycaemia, it's highly recommended for patients to continue following a healthy eating style and to lose or maintain the weight lost even when they commence on the medication (366, 367).

The National Institute for Health and Care Excellence (NICE) is in line with the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in their general recommendations for the potential sequence of antihyperglycaemic therapy (366, 367). The pharmacotherapy treatment for T2DM is beyond the scope of this thesis so it will not be discussed in details.

1.4.5.3 Obesity/Metabolic Surgery

Some patients will continue to have uncontrolled hyperglycaemia even while on pharmacotherapy, which puts them at increased risk of developing diabetes related comorbidities (368). Pories *et al.* (1995) was the first to show that a 14 years follow up of gastric bypass patients resulted in long term improvement of T2DM (368), In addition, diabetes often improves dramatically within just days following obesity surgery, even before any noticeable weight loss occurred (368). His findings were later verified by another group showing similar astonishing benefits of the commonly performed obesity procedures on T2DM (369). Since then researchers have become increasingly interested in the mechanisms that lead to these clinical results and the durability of these effects.

Long-term case-control studies showed that, compared with conventional care, obesity surgery can lead to major reductions in hyperglycaemia or to diabetes remission in some cases, and can reduce diabetes and obesity related comorbidities and death (370-372). The Swedish Obese Subjects (SOS) is the biggest prospective controlled intervention study of obesity surgery; it showed that obesity surgery resulted in 72% remission of diabetes at 2 years follow-up (373). A Meta analysis carried out by Buchwald *et al.* (2009) reported similar finding with 78% of patients undergoing obesity surgery having very well controlled diabetes (374).

The majority of the published literature supporting diabetes remission after obesity surgery has short- and medium-term follow-up. The longest available follow up is from the SOS study which reported findings from 10 years follow up (373). Despite the rate of very good control dropping from 72% at 2 years follow-up to 35% at 10 years follow-up, this remains a significant and impressive outcome. Unfortunately, data on individual types of surgeries is not available from this study and there is currently a scarce of evidence from RCT comparing all those three different types of surgery for their diabetes remission significance. The By-BAND-Sleeve study is the only currently running randomized clinical trial comparing the RYGB, BAND, and VSG in the UK. The study started in 2012 and will run for approximately 8 years, no results are available as of yet (375).

Roux-en-Y Gastric Bypass (RYGB), Vertical Sleeve Gastrectomy (VSG), Biliopancreatic Diversion (BPD), and Gastric Band (BAND), have all been shown to improve T2DM more effectively than dietary and pharmacotherapy treatments (376-381). Out of those surgery's, RYGB, VSG and BAND are currently the most performed surgeries in the UK (313). RYGB produces 20-30% weight loss maintained for at least 20 years (316, 317), BAND causes a reduction of 15-20% in total body weight (317, 320), short-term studies show that VSG is as effective as the RYGB (322-325). Over the past three years, interest in VSG has increased significantly and recent UK individual surgeon data shows that rates of VSG have now surpassed those of BAND in the NHS (382). It is generally accepted that bypass operations have more powerful effects on T2DM than non–bypass operations, but there are few studies demonstrating this difference (383).

A recent study carried out by Panunzi *et al.* (2016) found that by merging data from the SOS study and two other randomized controlled studies gastric diversion surgeries i.e. RYGB and

BPD resulted in 76% of patients having very good diabetes control compared with Gastric only surgeries i.e. VSG and BAND that resulted in 60% (384). However, a systematic review of 20 RCT comparing different types of obesity surgeries suggested that RYGB was more effective than VBG and BAND in weight loss but did not find any differences in diabetes control or other comorbidities (294).

The emergence of a large body of literature supporting surgical treatment of diabetes has led the International Diabetes Federation (385) and ADA (386) to recognize obesity surgery as an effective treatment option for obese patients with T2DM. The Diabetes Surgery Summit was able to get 42 organizations and professional societies to endorse their recommendations (387).

1.5 Metabolic adaptation to caloric restriction and weight loss

During periods of calorie restriction and weight loss and after achieving a certain amount of weight loss our bodies create responses that aim to resist further weight loss and induce weight regain by metabolic, neuroendocrine, and autonomic systems.

1.5.1 Hormonal adaptation

Weight loss reduces sympathetic nervous system activity, plasma leptin and insulin, all of which inhibit food and energy intake (388). Weight loss improves glycaemic control, which is partly reflected by a decrease in fasting glucose. This might be problematic in a context where a decrease in glycaemia triggers episodes of feeding. It is thus possible that in order to achieve a comparable level of satiety to what was experienced while still obese, a more substantial amount of energy has to be consumed to compensate for the reduced impact of the above mentioned factors on appetite-related variables (388).

Few studies have directly addressed the issue as to whether appetite scores are affected by prolonged energy deficit and consequent weight loss. In this context, Heini *et al.* demonstrated that during controlled weight loss, although no significant changes in hunger-satiety levels were found, some positive correlations were observed between postprandial changes in these variables and fractional changes in glucose and insulin (389). Results from the same group have also demonstrated that during energy restriction lower levels of leptin are accompanied by increased hunger and lower satiety ratings which might partly be explained by the fact the leptin levels were shown to predict palatability scores (390).

1.6 Eating behaviour post obesity surgery

Obesity surgery is the most successful treatment option for the growing number of individuals with extreme obesity. It's profound health benefits, amount and durability of weight loss have surpassed those typically seen with lifestyle modification and pharmacotherapy. Although the majority of patients will benefit from obesity surgery, a significant minority of patients, will experience suboptimal outcomes, including less than expected weight loss, premature weight regain, and frequent vomiting and/or gastric dumping. The reasons for these mixed outcomes are not well understood, but likely involve the same mechanisms.

Obesity surgery was originally designed to mechanically restrict food intake, and consequently caloric restriction. However, the terminology used in obesity surgery literature, including "desire", "not interested", or "intolerance", made it clear that obesity surgery, and specifically gastric bypass, does not just reduce the amount that people eat but also alters the perception of food and possibly eating behaviour. Research in this area has shown that weight loss after obesity surgery is complicated and the different anatomical manipulations in the different types of obesity surgeries result in different effects on appetite, eating behaviour and metabolism, often towards healthier choices. This healthy shift away from high calorie fat and sugar foods to increased consumption of fruit and vegetables could be explained by alterations in any one, or a combination, of functional taste domains: stimulus identification, ingestive motivation, and digestive preparation.

1.6.1 Effect of RYGB on eating behaviour

1.6.1.1 Food intake and preferences

Obesity surgery and particularly RYGB was primarily designed to restrict gastric size, and thereby results and reduced food intake and weight loss. However, humans and animals are able to compensate for smaller meal sizes by increasing the meal frequency (391-393). Despite the smaller size of the gastric pouch, there is usually little restriction as the stoma between the gastric pouch and the small bowel is wide. Thus the effect of the small pouch on

weight loss is potentially small and other mechanisms are likely to be behind the change in eating behaviour and weight loss.

RYGB involves a profound anatomical change to the gastrointestinal tract, which causes a more rapid delivery of nutrients to the distal ileum. An exaggerated rise in a number of peripheral satiety hormones including PYY and GLP-1 was found to occur within days after surgery even regardless of weight loss (394). These hormonal changes affect gastric emptying, subsequently reducing total food intake (395). Delayed gastric emptying results in increased appetite and reduced food intake. However, despite this exciting hypothesis, the rate of gastric emptying post RYGB have been inconsistent in different research studies and was suggested to be due to different surgical techniques resulting in different pouch sizes and distribution of the vagus nerve (396-398).

Different macronutrients, proteins, carbohydrates (high GI and low GI) and fats, play a role in diabetes management, weight loss and weight maintenance in any diabetes and weight loss intervention (399-401). Halmi *et al.* (1981) were the first to show that gastric bypass causes a change in macronutrients selection as patients shifted away from the calorically dense high carbohydrate foods (402). These results led other researchers to investigate the effect of obesity surgery on food preferences and macronutrients consumption.

The current literature provides a large pool of evidence on the effect of RYGB on food preferences, two reviews carried out by our group summarises the available studies (206, 403). In summary, research findings are consistent in showing that RYGB results in a lower consumption and preference for sweet and fatty foods and higher consumption of fruit and vegetable post- compared with pre- operatively. Similar findings were seen when RYGB was compared with BAND and VSG (404-407). The mechanism behind those changes is unknown but there are suggestions for changes in “taste”, “food intolerance/nausea/sickness”, and “loss of interest/desire for food” in the studies mentioned.

Animal data are consistent with the findings from human studies. Rats after RYGB ate less high-fat high-sugar food compared with sham but more chow, demonstrating a shift in food preferences (408-410).

1.6.1.2 Taste detection

Taste affects eating behaviour by directly influencing food preference. DeWys and Walters (1975) were the first to report the connection between taste changes and food aversions. They found that increased taste acuity for urea (bitter) in cancer patients correlated with meat aversions (411). Aversions to sweet foods have been associated with increases in taste acuity for sucrose (sweet) (412). Based on these results, Scruggs *et al.* (1994) were the first to suggest that the changes in food preferences after RYGB may be attributed to the permutation in taste acuity. To test their hypothesis, taste detection and recognition thresholds for the four basic tastes (salt, sweet, sour, and bitter) were assessed using a modification of the Henkin forced choice three stimulus technique before and after RYGB in women (413). This technique involves placing drops of water or tastant on the tongue of the volunteer. The lowest concentration at which the volunteer is able to detect the difference between the tastant and water represents the detection threshold (413). In this study, Scruggs *et al.* found that following gastric bypass surgery, a significant improvement in taste acuity for bitter and sour was observed along with a trend toward a reduction in salt and sweet detection thresholds (109). Methodological limitations of the study include the use of a small sample number (n= 6); use of tiny tastant drops that causes limited receptor stimulation and the lack of control for the effects of repeated testing. Additionally, the concentrations of the solutions used were very high, especially for sucrose (403).

Burge *et al.* (1995) used a staircase method of stimulus presentation and found that sucrose recognition thresholds also decreased after RYGB (110). The group also noted that patients reported that food tasted sweeter, and they modified food selection accordingly. They also found that patients who reported an aversion to meat was associated with increased nausea and vomiting (110).

Using direct measures of behaviour, our research group investigated the effects of RYGB on the sweet taste sensory domain using a method of constant stimuli (111). We found that sweet taste acuity improves after RYGB.

Despite all the previous studies showing improvement is taste acuity after RYGB, the change in taste detection thresholds for sucrose remains controversial. The latest study by Pepino *et*

al. (2014) found no change in detection thresholds for any of the taste qualities (sucrose, glucose, NaCl, and monosodium glutamate (prototypical savory stimuli)) after RYGB and BAND (414). The discrepancy between the earlier studies may be due to differences in the methodologies employed to measure taste thresholds, variation in the diet composition of subjects at the time of testing, time from surgery and sex differences.

1.6.1.3 Consummatory reward value of taste

The consummatory behaviour is one of the hedonic domain's components (consummatory and appetitive) and accounts for how much the stimulus is liked or disliked (95). This ingestive behaviour is actioned by the reward value of the stimuli tasted. When food is in the oral cavity, the taste signal is sent to the orbitofrontal cortex in the CNS to encode the reward value of a food stimulus. The orbitofrontal cortex further communicates with other limbic structures such as the ventral tegmental area, nucleus accumbens, amygdala, hippocampus and ventral striatum with dopamine acting as the primary neurotransmitter. This hedonic activation has led many researchers to focus on neuroimaging in the form of functional magnetic resonance imaging (f)MRI and positron emission tomography scans to investigate the changes in the hedonic value of food post-RYGB.

Indeed, Ochner *et al.* (2011 and 2012) used (f)MRI and Visual Analogue Scales (VAS) pre and 1-month post RYGB and found that the surgery is associated with decreased hedonic value for food and particularly sweet or highly palatable foods (415, 416). Interestingly, the group found that reported 'liking' of food was not changed despite the reduction in hedonic activation (416). These were well-structured studies and showed promising results but did not particularly assess the consummatory behaviour i.e. the liking and disliking of food; they were also based on visual and auditory cues, not taste and therefore, are not an accurate indicator of the actual ingestive behavioural in response to a food. In our research unit, Scholtz *et al.* (2014) compared RYGB to BAND patients and found that RYGB caused a greater reduction in the activation of brain reward areas to high-energy food pictures. In addition, this was the first group to associate the hedonic brain activation with the rating of high-sugar/high-fat food ingestion and found that lower hedonic brain activation was associated with the rating of ice-cream ingestion as 'less pleasant to eat' in the RYGB group (55). The findings of this study were explicable by differences in the anorexigenic plasma gut hormones (GLP-1 and PYY), plasma bile acids and symptoms of dumping syndrome (55).

Another method used to explore consummatory taste behaviour in RYGB patient is the Sweet Taste Palatability Test. In this test subjects rate different sucrose concentrations using VAS or gLMS (described earlier). Our research group carried out this test on RYGB patients and found no changes in the sucrose concentration that is considered as 'just about right' in RYGB patients before and after surgery (111). On the contrary, Pepino *et al.* (2014) carried out a modified version of this test on RYGB and BAND patients and found that RYGB surgery, but not BAND, affected the consummatory component of sweet taste perception, characterized by a rapid shift in sweetness palatability from pleasant to unpleasant when repetitively tasting sucrose (414).

Taste reactivity test to assess facial expressions for liking and disliking of sweet/fatty stimulus has not been used for the study of consummatory reward in RYGB patients as yet.

In animals, the investigation of effects of gastric bypass surgery on sweet and/or fat taste reward has yielded mixed results. Some groups have shown postoperative decreases in consummatory responsiveness to high concentrations of sucrose (417-419) and a fat emulsion (417), and in one case, at low concentrations of these stimuli, rats increased their licking responses after a gastric bypass (417). Still, other authors have shown no changes in consummatory responsiveness to these stimuli (420, 421).

In summary, the studies demonstrate a possible unique effect of RYGB that might further decrease the ingestion of sweet foods and increase adherence to a low-calorie diet.

1.6.1.4 Appetitive reward value of taste

The appetitive behaviour is the second component of the taste hedonic domain and accounts for how much the stimulus is wanted (95). Visual Analog Scale (VAS) techniques, including the generalized labeled magnitude scale (gLMS), have been used to measure the consummatory hedonic evaluation of taste in RYGB patients. However, a more direct approach was used to assess the appetitive hedonic value in human studies through the use

of Progressive Ratio schedule of reinforcement Task (PRT). Miras *et al.* (2012) was the first to use PRT in humans and found that gastric bypass surgery (RYGB) resulted in the selective reduction of the reward value of a sweet and fat tastant (146). This application of the progressive ratio task provided an objective and reliable evaluation of taste-driven motivated behaviour for food stimuli after RYGB. Importantly, the same task could, in principle, be conducted in an animal model of gastric bypass, which may open up the field to a more in-depth interrogation of mechanisms that underlie the change in behaviour (146).

In animal studies, there has been mixed findings as some have shown increases in appetitive responsiveness to sweet-tasting stimuli (392, 421), but other studies have not (419). However, the studies varied in their research methodologies.

In this subsection, most studies demonstrate the possibility of RYGB in decreasing the motivation to seek for sweet foods and therefore contribute to a better adherence to a low-calorie diet.

To summarise the evidence of the effect of RYGB on changes in eating behaviour, I conclude that sufficient evidence is available on the effect of RYGB in reducing total energy intake. It is still unclear whether the reduction in total energy intake is due to changes in food preferences away from high energy dense food or simply a reduction from all macronutrients. Studies using direct measurements of food intake are required. In terms of potential mechanisms involving changes if taste, the results are promising towards positive change in the detection and hedonic domains. However, the available evidence is limited to a few studies carried out by the same groups of researchers. More studies with larger groups of subjects are required to reach consensus.

1.6.2 Effect of VSG on eating behaviour

1.6.2.1 Food intake and preferences

Vertical Sleeve Gastrectomy (VSG) is an obesity surgical procedure limited to the modification of the stomach, and like RYGB, this procedure induces loss of weight and fat mass, and improves glucose tolerance in humans and in rodent models (422-424).

Despite the fact that this procedure was designed to reduce the gastric size in an aim to reduce food intake and thereby weight loss. Furnes *et al*. suggested that the weight loss observed after VSG is independent of the food reservoir function of the stomach (425). In addition, Wilson-Pérez *et al.* (2013) hypothesised that if VSG would result in reduced portion sizes due to the reduced gastric size then patients would develop a compensation reaction by increasing their fat intake in order to maximize caloric intake (426). Wilson-Pérez *et al.* (2013) used a rat model of VSG to investigate this hypothesis. It was not surprising to find that those rats not only restrict their food intake but also preferred the less calorically dense food available (426). In addition, despite the markedly different surgical manipulations, VSG and RYGB rats had remarkably similar changes in food choices i.e. less fat and more carbohydrates when compared to sham operated rats (426). Suggesting a common underlying mechanism in those two procedures.

Improvement in gut hormones is a key factor in weight loss and diabetic improvement in patients undergoing RYGB. It is postulated that this occurs through change in the gastrointestinal tract anatomy. Recent evidences suggest that VSG also leads to similar improvement in gut hormones (427, 428) possibly caused by the faster gastric emptying and earlier presentation of food to the duodenum (429-431).

Alterations in gut hormones can partially explain the changes in food preference that occur following obesity surgeries. VSG is relatively a new procedure; therefore, there is a scarce of scientific evidence on the long-term effects of this procedure on food intake and food preferences in human studies. In addition, all the available short-term evidence lacks a large sample size and is based on verbal reports.

Ammon *et al.* (2015) used a Food Preference Questionnaire and VAS to assess changes in preference for different types of food varying in their macronutrient composition 6 weeks post VSG. They found that postoperative hedonic ratings were significantly decreased for foods

high in fat and carbohydrate content. (432). A few months later Primeaux *et al.* (2015) published a study where they followed the same method but compared VSG to RYGB and found that VSG decreased the hedonic rating of most macronutrient profiles as opposite to RYGB, which was more selective (433). Caution should be taken in assessing their results as they used a 1-3M follow up period and a small sample size. Postoperative diet changes dramatically within this long follow up period which can affect the interpretation of the results (434).

A number of studies have shown no difference between RYGB and VSG in terms of food preferences. A retrospective cross sectional study compared food intake and food preferences at 1 year follow up for VSG and RYGB patients. There were no major differences in dietary intake and food preferences between RYGB and VSG groups (435). This is in agreement with the longest follow up study (5 years) also comparing VSG and RYGB in a Spanish population (436). However, both studies lacked the comparison of preoperative and postoperative measurements.

A recent 2-year follow up study carried out by Coluzzi *et al.* (2016) assessed changes in food intake associated with changes in taste using verbal reports. They found that six months after surgery, the daily caloric intake reduced by 68% and the reduction was maintained until 24 months. In addition, 75% of the patients reported changes in taste which was associated with reduced interest in sweets, high fat food, and alcoholic drinks (437).

Our research group has recently demonstrated that VSG changes eating behaviour and, specifically, reduces *ad libitum* meal size, meal duration and rate of eating. Together with decreased emotional eating and unconditioned eating and increased cognitive restraint. VSG patients also reported reduction in intake of fat and high glycaemic index carbohydrates, with an increase in low glycaemic index carbohydrates and unchanged protein consumption ((148) (unpublished work)).

In general, research findings are consistent in showing that VSG causes a shift in food preference to healthier choices similar to that seen post RYGB.

1.6.2.2 Taste detection

The current literature lacks any studies on taste detection in VSG. Our research group carried out the first taste detection experiment on VSG adolescents in Saudi Arabia by following the same protocol we have previously used on RYGB patients. G. Abdeen *et al.* (2016) found that VSG did not have an effect on the detection threshold for sucrose in adolescent patients (148). This is in contrast to our findings in adults after RYGB where we found an increase in sensitivity of sucrose detection.

Our results suggest that VSG might not fundamentally shift the sensory domain of taste, but food preference changes may instead be related to other factors such as conditioned avoidance.

1.6.2.3 Consummatory reward value of taste

As discussed in section 1.6.1.3 (the effect of RYGB on consummatory behaviour), this sub-domain of the hedonic reward domain accounts for how much the stimulus is liked or disliked (95). Different methodological studies have been carried out to assess the consummatory behaviour in animals and humans including fMRI, PET scans, VAS, and taste reactivity tests. However, only limited studies have been carried out to assess this behavior post VSG.

The first study to assess the affect of VSG on the consummatory behaviour was carried out by Wilson-Pérez *et al.* (2013) in animal models. This study particularly investigated the effect of VSG on food aversion as compared to RYGB surgery using a conditioned taste aversion paradigm in which a novel flavor (0.15%. sodium saccharin) was paired with an intra-gastric infusion of 1ml peanut oil, 1ml water or 1ml of the malaise-inducing agent lithium chloride (0.15 M LiCl) as a positive control. The group found that there was a positive aversion towards intra-gastric oil administration in VSG rats but not in RYGB rats (426). This study initiated a path for other researchers to investigate this field further.

In recent years, VSG became a popular surgical option for the treatment of obesity due to its significant benefits on weight loss. This has enabled the use of neuroimaging to assess the hedonic changes in VSG human studies, which generally require a large sample size. Hedonic activation in response to food cues occurs in the hedonic reward systems that consist of the ventral tegmental area (VTA), nucleus accumbens (NAcc), orbitofrontal cortex (OFC), prefrontal cortex (PFC), and limbic nuclei. Faulconbridge *et al.* (2016) compared the neural response to pictures of high- and low-calorie foods (HCF and LCF), before and 6 months after surgery, in RYGB, VSG and non-surgical weight-stable control participants. RYGB and VSG participants lost 23.6% and 21.1% of initial weight, respectively, at 6 months, and controls gained 1.0%. Liking ratings for HCF decreased significantly in the RYGB and VSG groups but remained stable in the control group, indicating a specific reduction in liking of highly palatable foods after obesity surgery. However, blood oxygen level dependent (BOLD) response, which represents activation, in the ventral tegmental area (VTA) to HCF (vs. LCF) declined significantly more at 6 months in RYGB compared to control participants but not in VSG participants (438). There was no significant changes in any of the other regions relevant to reward processing (438). Further fMRI studies are required to confirm these findings.

Our research groups carried out a pilot study to investigate facial expressions in obese adolescent VSG patients in response to high fat/high sugar food stimuli. We used the facial expression method to assess changes in the consummatory behaviour relating to a single, specific food item after VSG surgery. We found that VSG resulted in increased negative (dislike) facial expressions and decreased positive (liking) facial expressions for a chocolate milkshake stimulus. In addition, facial expressions remained unchanged across a similar test-retest interval in non-surgical control subjects (148).

In summery, the available literature suggests a shift from liking to disliking of sweet and fatty food post VSG. However, more studies are required to confirm those findings.

1.6.2.4 Appetitive reward value of taste

Very little work has been performed in humans and animals to determine whether there are any changes in the appetitive hedonic sub-domain of taste function after VSG.

In his study, Wilson-Pérez *et al.* (2013) showed that rats not only had a conditioned taste aversion to intra-gastric oil administration but also reduced motivation to consume high fatty/high sugary food after VSG (426). Using a Progressive Ratio Task (PRT) they assessed the motivation for VSG rats to earn sucrose and peanut-oil reinforcers compared to Naïve and Sham rats. In this study, VSG rats earned significantly fewer sucrose and peanut-oil reinforcers than Naïve or Sham rats (426).

Using the modified version of PRT for the use in human studies, our research group have shown that the appetitive reward value of a tastant high in sugar and fat decreased after VSG surgery in adolescents (148). Our data is consistent with the changes shown in rodents after VSG (426) and in adult patients after RYGB (146) , but not RYGB animals (439). This does raise the question of whether, despite best efforts, patients may still behave in a specific way to “please” the investigator, a problem that is not seen in rats.

In summary, despite the small number, the above studies suggest a possibility for VSG and RYGB to function in the same manner in reducing the appetitive behaviour towards sweet and fatty food.

To summarise the evidence of the effect of VSG on changes in eating behaviour, I conclude that similar to RYGB, the available studies show a trend towards reduced total food and healthier shift in food preferences explicable by positive changes in different domains of taste. However, this is based on very limited studies and therefore it does not represent strong and solid scientific conclusion. More studies are required in this area.

1.7 Endoluminal Duodeno-Jejunal Bypass Liner (DJBL)

Despite the impressive weight loss and improvement in T2DM, obesity surgery procedures still carry a high risk of complications of which some can be serious and 1 in 1000 are fatal (440). In addition, not all obese patients are eligible for obesity surgery due to preoperative high risks. Therefore, the need for an effective and safer strategy for the treatment of obesity is very high.

The Endoluminal Duodeno-jejunal Bypass Liner or EndoBarrier® (DJBL) (GI Dynamics, Lexington, Massachusetts, USA) is a thin, flexible, sleeve-like device, made of a single use 60cm fluoropolymer. The DJBL is inserted endoscopically through the mouth and anchored to the proximal small intestine to acts as a physical barrier between the walls of the duodenal and the food ingested (441).

The DJBL aims to mimic the intestinal bypass and possibly components of the restrictive effects of Roux-en-y gastric bypass surgery without the need for stapling or anastomosis. Hormones that control appetite and blood sugar level are normally released when food comes in contact with the walls of the duodenal. By eliminating this mechanism, bile and pancreatic secretions are only mixing with chyme at the jejunum (442), resulting in changes in the levels of hormones, and a lower blood sugar levels in a similar manner to that seen after RYGB ((443), (444)).

Unlike procedures such as RYGB, the DJBL does not permanently alter the anatomy of the GI tract. It is designed to be removed at the end of the treatment period, which is 12 months or sooner. Therefore, the DJBS may represent a novel, easy to perform, economic, and reversible endoscopic application for the treatment of obesity and T2DM. Potential mechanisms of action could include duodenal bypass with alteration of incretin pathways such as GLP-1 or other undefined signals, delayed gastric emptying, partial duodenal mechanical obstruction, or enhanced delivery of undigested nutrients to the more distal bowel with augmentation of incretin secretion (441).

1.7.1 Weight loss

The DJBL is a new procedure and, like any novel technique, information on long-term weight loss outcomes is limited. Most studies in the literature have used the excess weight loss and/or total body weight at 12 weeks as a main outcome measure. Those studies showed encouraging results with a reduction of 8.2%-11.2% in total body weight (445). However, a longer follow-up period is required to assess the effectiveness of any weight loss intervention/procedure.

In a review carried out by Neff *et al.* (2013) on the outcome of glycaemic control and weight following DJBL, it was shown that treatment with DJBL for up to 12 months could result in a reduction of total body weight ranging between 8.0%-19.0% (446).

Another study carried out by Koehestanie *et al.* (2014) on 31 DJBL patients and 39 controls on a dietary intervention, showed that treatment with DJBL for 6 months resulted in a reduction of 10% total body weight compared to 4.7% in the control group. Patients were followed up for another 6 months and although by the end of the 6 months post-DJBL removal, follow-up patients had regained some of their weight, the reduction of total body weight remained higher in the DJBL patients compared to the controls, 5.8% compared to 3.5%, respectively (447).

Betzel *et al.* (2014) carried out a study to assess the safety of the DJBL in the Netherlands. Though this study was not intended to assess the rate of weight loss, they presented weight loss data for 26 patients completing a 6-months treatment and 61 patients completing a 12-months treatment. Those patients had a significant weight loss of 9.5% and 9.2%, respectively (448). This study shows that significant weight loss, maintained at least for the duration of the device treatment, is achievable regardless of the specific standardized calorie controlled diet of most weight loss intended clinical trials.

In summary, DJBL can result in at least 9% weight loss over 12 months treatment. More weight loss may be achievable with stricter dietary guidelines.

1.7.2 Glycaemic control

Obesity surgery is currently considered the gold standard treatment for obesity and T2DM. The mechanisms behind its substantial metabolic benefits need to be further elucidated. Similar to other obesity surgeries (423), DJBL also results in an improved glycaemic control within days of device implant despite of any weight loss (449).

According to Neff *et al.* (2013) who concluded the findings from four randomised clinical trials ((450), (451), (452), (449)), at 12-months DJBL resulted in reduced HbA1c levels by 1.7% and a reduction in the pharmacotherapy dosage used during the trial (446).

Koehestanie *et al.* (2014) demonstrated that HbA1c was also lowered from 8.3% in both groups to 7.0% in the DJBL group and 7.9% in the controls at 6 months ($P<0.05$ between groups). After the removal of DJBL, levels of HbA1c were elevated but were still lower than the baseline results and lower in the DJBL compared to controls, 7.3% versus 8.0%, respectively, albeit not significant different ($P = 0.95$ between groups) (447). However, when compared to baseline levels, 6-months after DJBL removal, HbA1c levels remain significantly decreased (453).

In summary, DJBL results in a significant reduction of HbA1c maintainable throughout the treatment period. Longer follow-up studies are required to determine post-device removal glycaemic levels.

No current information regarding changes in food preferences and eating behaviour following DJBL are available. However, clinical observations suggest a shift in food preferences similar to that seen in RYGB. As a novel technique, more research is required to understand the mechanism behind the DJBL on weight loss and changes in food choices and eating behaviour. The elucidation of the mediators underlying any changes in eating behaviour may yield new pharmacological targets, weight loss procedures, or personalised treatments of obesity and its associated comorbidities.

1.7.3 Gut hormones

Limited evidence is currently available on the effect of DJBL on gut hormones as a potential mechanism for weight loss and improvement in T2DM.

In 2013, De Jonge et al. was the first to investigate changes in gut hormones in patients with DJBL. They carried out a meal tolerance test before, 1-week, and 24-weeks post device insertion and measured fasting and postprandial GLP and GIP levels. Their results demonstrated a significant increase in postprandial GLP-1 response as early as 1-week, which remained elevated throughout the device implant duration. In contrast, postprandial GIP levels showed an immediate trend towards decreased levels but only reached statical significance at 24-weeks post implant. Fasting GLP-1 and GIP were not affected by DJBL in this study (449). Moving forward with measurements of gut hormones, De Jonge et al. (2016) also demonstrated a significant increase in fasting and postprandial PYY, a significant decrease in postprandial CCK, and a significant increase in fasting ghrelin. Though the increased level of fasting ghrelin was accompanied by a more rapid and pronounced decline in its postprandial levels (454).

Most recently, Vilarrasa *et al.* (2017) assessed the changes in gut hormones in patients with grade 1 obesity and long-lasting T2DM (455). Contrary to de Jonge's *et al.* (2013) findings (449) they reported no change in GLP-1 AUC at any time point during a 12-months follow-up period (455). However, their results of fasting ghrelin and PYY levels did support the previous finding of de Jonge (2016) (454).

These studies are well designed studies but miss a control group and are not randomised. Large randomised controlled studies are still required.

1.8 Hypothesis

Obese diabetic patients have a greater weight loss, and better diabetes control after DJBL implant than fellow patients who will have the best conventional medical care for the treatment of obesity and diabetes. This may be a result of a reduction in food intake and changes in the macronutrient composition of total food intake. DJBL patients may have a conditional avoidance to high GI carbohydrates and fatty food so they may shift towards consuming more protein and lower GI carbohydrates and more fruits and vegetables.

The weight loss and improvement in diabetes may be explicable by low levels of postprandial hunger and high postprandial fullness but not with baseline (fasting) hunger levels or psychological traits.

DJBL patients may not have a change in sweet taste detection thresholds but they will have a reduced appetitive and consummatory taste reward value as a result of changes in the hedonic pathway of taste.

1.9 Aims

To assess whether the DJBL affects eating behaviour 6-months post intervention compared to Best Medical Practice for the treatment of obesity and Type 2 Diabetes.

1.10 Objectives:

To test the hypothesis of this thesis my objectives were:

1. To assess eating behaviour and dietary macronutrients choices of obese T2DM patients who had a DJBL implant vs. obese diabetic patients who had the standard

medical therapy for the treatment of obesity and diabetes, using 3-Day Food Diaries, 24-Hour Diet Recalls, and Food Frequency Questionnaires.

2. To assess hunger levels, and psychological traits of eating behaviour in obese diabetic patients who had a DJBL implant to obese diabetic patients who had the standard medical therapy for the treatment of obesity and diabetes, using Visual Analogue Scales and Eating Behaviour Questionnaires.

3. To assess the taste detection domain in obese diabetic patients who have an EndoBarrier device implant vs. obese diabetic patients who have standard medical therapy for the treatment of obesity and diabetes, using the taste detection method.

4. To assess the appetitive reward value of sweet/fat taste in obese diabetic patients who had a DJBL implant vs. obese diabetic patients who had the standard medical therapy for the treatment of obesity and diabetes, using a Progressive Ratio Task (PRT).

5. To assess the consummatory reward value of sweet taste in obese diabetic patients who had a DJBL implant vs. obese diabetic patients who had the standard medical therapy for the treatment of obesity and diabetes, using Visual Analogue Scales.

CHAPTER 2 METHODS

2 Methods

2.1 Study design

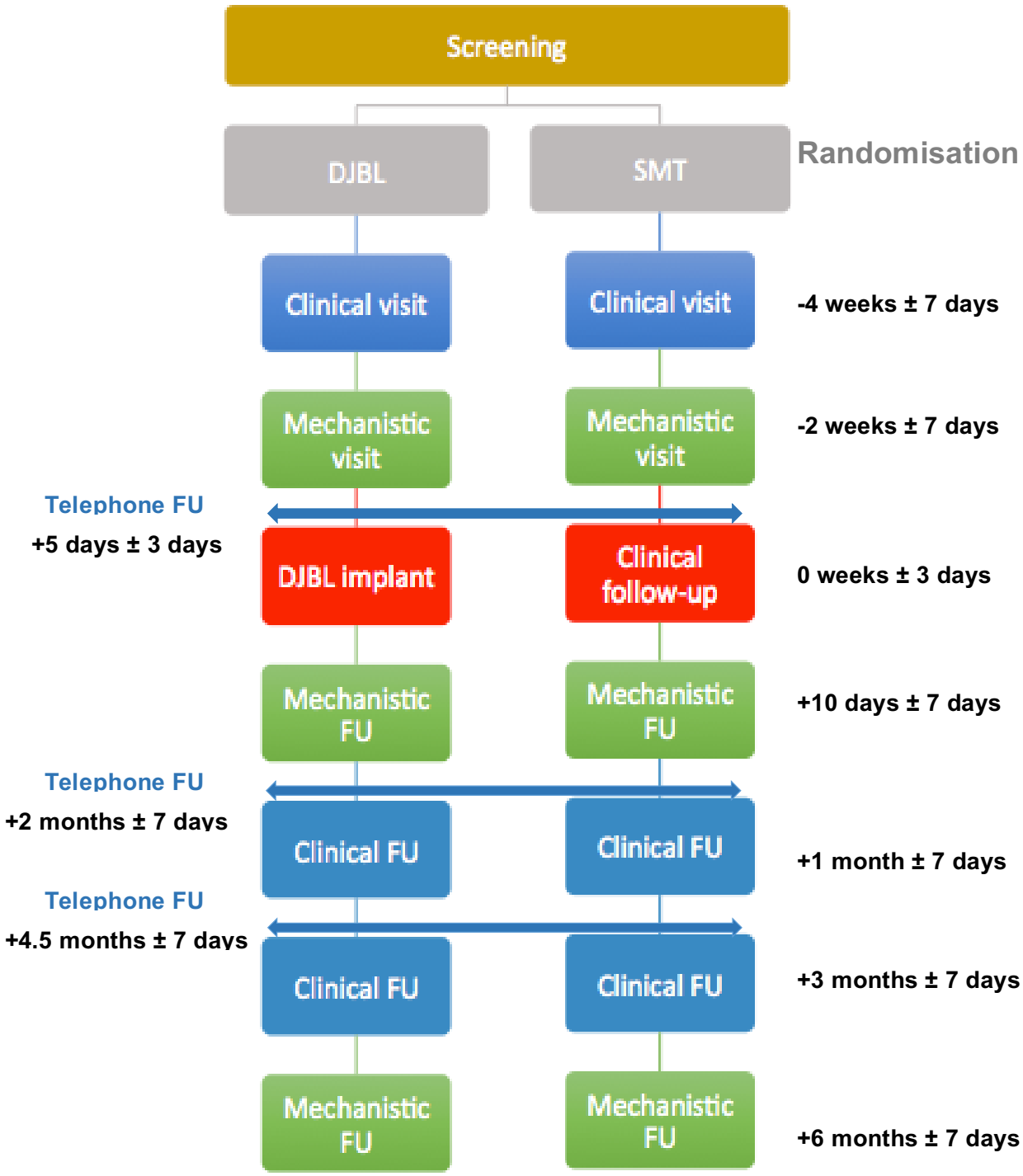
This was a randomized controlled study of the DJBL device compared with standard medical therapy (SMT) for the management of obese subjects with T2DM. Over 6 months, the study was performed at two investigational sites, Imperial College Healthcare NHS Trust and University Hospital Southampton NHS Foundation Trust.

The study was part of a large (n=160), ongoing, 2-years follow-up clinical trial, where individuals in both trial arms were invited for regular medical check-ups including measurement of weight, blood pressure, blood parameters (HbA1c, cholesterol, triglycerides, fasting blood glucose, insulin), quality of life (EQ-5D) and use of health services, as well as to record any adverse events and medications. As part of the main trial, all individuals were followed-up by the study diabetologists, endocrinologists, and a specialist dietitian/nutritionist for 24 months.

The investigations discussed in this thesis were conducted during the first 6 months of the main trial timelines. However, the duration of the device implant in the main trial is for 12 months. After the end of the 12 months, the device is removed and both arms are to be followed up for an additional 12 months.

2.1.1 Study flow chart

Figure 7 Flow chart for the first 6 months of the main trial



note 6 Mechanistic visit refers to the study days where all investigational procedures related to this thesis are carried out. Clinical visits refer to the visits where clinical assessments are carried out by the main trials Physicians and Dietitian. Boxes in red represent the intervention start day i.e. device implant in the treatment arm vs. a clinical visit for the control arm.

2.2 Methods common to all investigations

2.2.1 Ethical approval

The study was approved by the Fulham Research Ethics Committee (REC) (14/LO/0871) and the Imperial College Healthcare NHS Trust Joint Research Office.

2.2.2 Recruitment

Obese diabetic subjects were identified from a number of areas including:

1. Registers of patients with diabetes who have consented to be contacted about future research including DARE (Diabetes Alliance for Research in England REC 2002/7/118)
2. Hospital or GP patient databases/notes review (Research Site or Participant Identification Centre)
3. Face to face approach during routine clinic visits (Research Site or Participant Identification Centre)
4. Posters and leaflets in GP surgeries and hospital clinic areas
5. Newspaper/Web adverts
6. Diabetes and Obesity Support groups
7. Study websites
8. Social media websites

2.2.3 Inclusion Criteria

1. Age 18-65 years (male or female)
2. T2DM for at least 1 year (HbA1c 7.5-10.0% = 58-86 mmol/mol)
3. On oral T2DM medications (metformin is allowed, but not required)
4. BMI 30-50 kg/m2 with adequate insulin reserve as indicated with insulin C-peptide levels > 0.5 ng/mL

2.2.4 Exclusion criteria

1. Language barrier, mental incapacity, unwillingness or inability to understand and be able to complete questionnaires
2. Non-compliance with eligibility criteria
3. Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using adequate contraceptive methods
4. Current use of insulin
5. Previous diagnosis with Type 1 DM or a history of ketoacidosis
6. Requirement of NSAIDs (non-steroidal anti-inflammatory drugs) or prescription of anticoagulation therapy during the implant period
7. History of iron deficiency and/or iron deficiency anaemia
8. Symptomatic gallstones or kidney stones at the time of screening
9. History of coagulopathy, upper gastro-intestinal bleeding conditions such as oesophageal or gastric varices, congenital or acquired intestinal telangiectasia
10. Previous GI surgery that could affect the ability to place the device or the function of the implant
11. Presence of active H. pylori using C13 urea breath test (if subjects have active H. pylori at baseline, they can receive appropriate treatment and then subsequently enroll into the study)
12. Family history of a known diagnosis or pre-existing symptoms of systemic lupus erythematosus, scleroderma or other autoimmune connective tissue disorder
13. Severe liver (AST, ALT or gGT >4 times upper limit) or kidney failure (serum creatinine >180mmol/l), estimated Glomerular Filtration Rate (GFR) cut-off is 60
14. Severe depression, unstable emotional or psychological characteristics (indicated by Beck Depression Inventory II score >28)
15. Poor dentition and inability to adequately chew food
16. Planned holidays up to three months following the DJBL Implant
17. Previous DJBL implantation

2.2.5 Estimation of drop-out rate

When designing this study, particularly the number of patients used, I used my experience in the global trial of NovoNordisk, the SCALE™–Obesity and Pre-diabetes study (456). In this study, 3731 patients underwent randomization: 2487 to lifestyle intervention plus liraglutide,

at a dose of 3.0 mg once daily, and 1244 to intensive lifestyle intervention plus placebo. In the placebo group, a drop out rate of approximately 50% was observed in our site (Imperial College London). The intensive lifestyle treatment in the SCALE study is very similar to the standard medical therapy in this thesis. Therefore, I used a 50% drop-out rate to estimate the final number of participants in my study

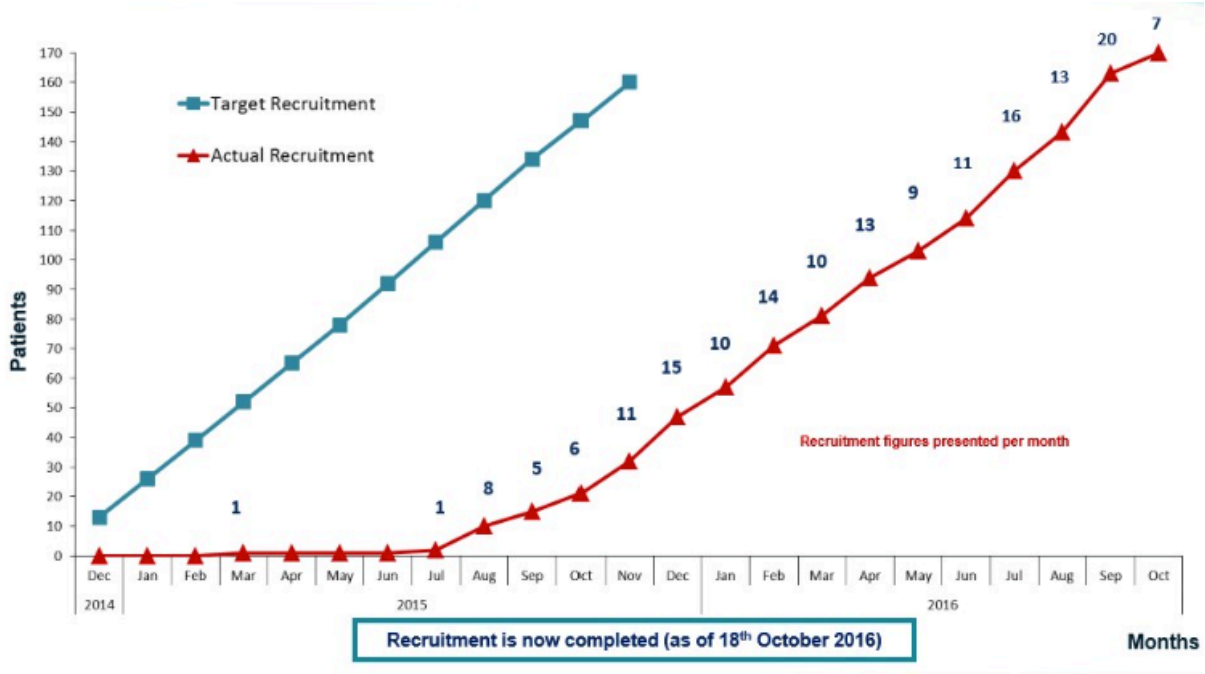
2.2.6 Power-calculations

The effects of DJBL on sweet taste detection have never been examined before. Therefore, the sample size was calculated based on the sweet taste detection results of a previous RYGB study (111) that found a mean decrease in taste detection threshold (expressed as EC50 – Half Maximal Effective Concentration) of 0.16±0.08. A conservative estimation was made that, as the DJBL is only one of the components of RYGB, its effect size would be half that of RYGB. Therefore assuming that the DJBL would reduce the sweet taste EC50 by 0.08±0.08, Ten patients in the DJBL group was predicted to permit greater than 80% power to detect significant differences at the $p<0.05$ level, using two-tailed tests. Longitudinal assessments in a group of standard medical therapy patients (minimum n=10) will be conducted in parallel to control for temporal stability of the end-point.

2.2.7 Recruitment challenges and patients number

Recruitment for this study was part of the main clinical trial, where three sub-studies were being conducted at the same time. Patients recruited for the main trial were given the choice of participating in ‘one’ or ‘none’ of those sub-studies. Therefore, recruitment for this sub-study was slow to reach the total number required for this sub-study. In addition, the study was paused for recruiting new patients between March 2015-June 2015 to update the recruitment documents with the risk of Hepatic abscess as per the American ENDO trial (Figure 8). Despite all the challenges faced, a total of 180 patients were recruited into the main trial, of which 42 subjects participated in the Food Preferences sub-study. However, patients recruited in the last quarter of 2016 had their devices inserted/intervention started after the completion deadline of my PhD and were therefor not due for their 6-months follow-up visit within my PhD timelines.

Figure 8 Patients recruitment over the study time



The figure shows the pause in recruitment between March and June 2015 and patients' accrual overtime against the target recruitment. It also shows how it conflicted with my PhD completion deadline (Oct 2016).

2.2.8 Randomisation

After the screening visit, all eligible patients for the study were randomised into one of the two arms of the study via the InForm system (the eCRF database for the study), which was programmed with a randomization schedule provided by an independent statistician. This was protected against bias in the randomization process as patients were allocated automatically.

2.2.9 Dietetic Input

At the baseline clinical visit, all patients diet history and current eating behaviour were assessed by a specialist dietitian/nutritionist. On the subsequent clinical follow-up visits, all patients received diet and physical activity counselling according to the local standards. The dietary counselling programme intended to provide each subject with lifestyle and behavioural modification information, and good eating practices.

In the DJBL arm, all subjects received written information on how their diet would change after DJBL insertion. They also received written information on the liquid diet pre- and post-DJBL insertion and on how to follow a low-calorie diet after the liquid diet ends (described below).

Subjects in the SMT arm were required to follow the same liquid diet as the DJBL arm in order to standardise the diet in both groups. They received written information on how to follow the liquid diet and how to follow a low-calorie diet after the liquid diet ends (described below).

2.2.9.1 Liquid diet

All subjects followed a liquid diet for a total of 21 days. This is inline with the dietary recommendations provided to patients receiving a DJBL implant globally. The liquid diet was based on 1200kcal for women and 1500kcal for men and consisted of:

- Fortisips compact meal replacements: 4 bottles (125ml each) for women and 5 bottles for men. Product nutrient composition is presented in table 2.1
- Smooth/ clear soups (1 medium bowl/day)
- Water
- No added-sugar squashes
- Tea or coffee without sugar

Table 2-1 Fortisip compact nutrient composition

Average contents	Per 100ml	Per 125ml
Energy (kcal)	240	300
Protein (g)	9.6	12
Protein (%)	16	16
Carbohydrate (g)	29.7	37.1
Carbohydrate (%)	49	49
Fat (g)	9.3	11.6
Fat (%)	35	35

Subjects started the liquid diet 7 days before the intervention visit (coloured with red in figure 7) and continued it for 14 days thereafter. Subjects in the DJBL arm also received information on the use of vitamin and mineral supplements, long-term dietary considerations and certain food exclusions including fibrous vegetables, popcorn, fizzy drinks, and fried food.

After the liquid diet, subjects in both study arms were advised to follow a low-calorie diet, based on the guidelines below.

2.2.9.2 Low-calorie diet

All subjects were recommended to consume 600 calories less every day, depending on their age, gender, activity levels and body weight. Guidelines for daily amounts were between 1200 and 1500 calories for women and between 1500 and 1800 calories for men.

According to local standards (Diabetes UK), subjects were advised to eat regularly every day (5 times/day), to control their portion sizes, and intake of carbohydrates/ starchy foods, to increase their intake of low glycaemic index (GI) and high protein foods, as well as vegetables, and to reduce their intake of foods high in fat, sugar, and alcohol.

2.2.9.3 Exercise advice

All subjects were advised to include more physical activity in their daily routine and were also encouraged to do more activity in their leisure time. They were asked to start with short periods of low-intensity exercise and increase the intensity and duration slowly. The goal was to include 150 minutes/week of moderate intensity and 75 minutes/week of vigorous intensity aerobic activity and muscle strengthening activities.

2.3 Description of Interventions

2.3.1 DJBL

The DJBL is a single use, minimally invasive device, consisting of 3 components: the implant, the delivery system, and the removal system. Each component was provided sterile to the end user. A brief description of each component is presented below.

On the intervention day, subjects arrived to the pre-assessment unit, as part of the theatres at St. Mary's Hospital or Southampton Hospital, after eight hours fast. Subjects were instructed to take a proton pump inhibitor (PPIs) (omeprazole 40 mg BID) 3-days prior to their device implant procedure and to continue with the medication throughout the study and for 2 weeks after the explant.

2.3.1.1 Implant

The implant component of the system is comprised of a nitinol anchor, which is used to reversibly affix the device to the wall of the duodenum and an impermeable fluoropolymer EndoBarrier Gastrointestinal Liner extending approximately 2 feet into the small bowel. The anchor materials are commonly used in implants and have a long history of biocompatibility.

The implant is open at both ends to allow for passage of chyme (a semi-fluid mixture of partially digested food) from the stomach to the lower jejunum. The anchor portion of the device is located in the duodenal bulb, proximal to the bile duct. The EndoBarrier Gastrointestinal Liner portion resides in the duodenum and a portion of the jejunum. While the chyme passes through the inside of the EndoBarrier Gastrointestinal Liner, the bile and pancreatic enzymes pass outside the Liner. The bile and pancreatic enzymes will mix with the chyme at the end of the EndoBarrier Gastrointestinal Liner.

2.3.1.2 Implantation

The implant is delivered on a custom catheter fabricated from materials with a long history of biocompatibility (medical grade PEBAX and high density polyethylene tubing and PTFE-coated stainless steel wire). The sterile catheter is approximately 3 meters long to facilitate delivery of the implant through the mouth into the jejunum. The catheter is designed to be sufficiently flexible to track through the intestine without kinking. Implantation and removal of the EndoBarrier device requires fluoroscopic x-ray guidance to determine the position of the device. Mean fluoroscopic x-ray time for insertion is 7 minutes (range 1-20 minutes). The constraint (maximum effective dose) for the whole procedure (implant and explant) is 9 mSv, which is equivalent to 3.3 years natural background radiation in the UK (2.7mSv/year background) and results in a cancer risk of 1 in 2200 for a healthy 40 year old (5% per Sv risk factor).

2.3.1.3 Explanation

The removal components did not happen during this study timelines as it occurs 12 months after the intervention day. Nevertheless, the EndoBarrier Gastrointestinal is removed with a custom grasper that passes through the working channel of a standard gastroscope. The gastroscope which is fitted with a foreign body retrieval hood is used to locate the implant. The grasper is passed through the working channel of the gastroscope and used to grab the polypropylene tether located on the proximal portion of the anchor. The proximal end of the anchor is collapsed by pulling on the tether and the anchor is then pulled into the foreign body hood. Once the collapsed anchor is in the hood, the implant is removed by withdrawing the gastroscope through subject's mouth.

2.3.2 Standard medical therapy (SMT)

The standard medical therapy (SMT) arm was used as a control arm. It was carried out in accordance with the guidelines of the American Diabetes Association/European Association for the Study of Diabetes. These guidelines are applicable to an International audience and thus would adhere to the current best worldwide practice that would still be likely to be relevant when the results are published following study completion.

2.4 Study day procedures

2.4.1 Study day flow chart

8.00	Arrival
8.10	Body measurements
8.30	Fasting Visual Analogue Scale (VAS)
9.00	Sweet taste detection sensitivity test
10.00	Eating behaviour and psychological questionnaires
11.00	Sweet taste consummatory reward value test
11.30	24-hr dietary recall + Food Frequency Questionnaire
11.55	Fasting Visual Analogue Scale (VAS)
12.00	Standardised meal
12.15	
12.30	
13.00	Postprandial Visual Analogue Scale (VAS)
14.00	
15.00	
15.15	Sweet appetitive reward value test
15.30	Subject leave

2.4.2 Body Measurements

2.4.2.1 Anthropometric measurements

Weight was measured at all visits using the same pair of scales on both sites. Height without shoes was recorded at the screening visit and used for the measurement of BMI throughout the study. BMI was calculated as follows: BMI = weight (kg)/height^2 (m^2).

Waist circumference was measured using non-stretchable measuring tape in the horizontal plane midway between the uppermost border of the iliac crest and the lower border of the costal margin (rib cage). In some cases it was difficult to palpate those bony landmarks, in those cases, the tape was placed at the level of the belly button. Readings were recorded to the nearest 0.5 cm.

2.4.2.2 Bio-electrical impedance

As well as baseline anthropometric measurements, all subjects had their percentage body fat determined by bioelectrical impedance analysis. This is a painless, safe procedure to measure total body fat involves standing on a metal platform for 1 minute so that the body's electrical resistance can be measured.

2.4.3 Assessment of food intake and food preferences

2.4.3.1 Food diaries

Subjects were asked to keep a food diary for up to three days at baseline (2 weeks before), 10-days post and 6-months post intervention. This is in order to determine their total calorie intake and macronutrient composition (Appendix 1).

Information gathered in the food diaries and its respective portions were then analysed using Dietplan 6.3.

2.4.3.2 24-hour dietary intake

A 24-hour dietary recall assessment was performed 2 weeks before, 10-days post and 6-months post intervention using the multiple-pass method. This validated method refers to the steps involved during a dietary interview. It allows the revisiting and reviewing of nutritional data.

- First pass- To obtain a quick list of foods consumed
- Second pass- To prompt for food items that may have been forgotten
- Third pass- To record information about the meals and snacks consumed, including the time and place
- Fourth pass- To collect detailed description of foods eaten and portion sizes
- Finally, the record is reviewed and additional details of foods eaten and portion sizes are completed

A Nutritionist or a trained Research Nurse carried out the diet recall interviews by following a detailed Standard Operational Procedure (SOP) (Appendix 2). Information gathered in the dietary recall and its respective portions were then analysed using Dietplan 6.3.

2.4.3.3 Food frequency questionnaire

Habitual food choices i.e. food preferences were estimated using the European Prospective Investigation of Cancer Food Frequency Questionnaire (EPIC FFQ) 2-weeks before and 6-months post intervention. The EPIC FFQ questionnaire was developed as part of the EPIC-Norfolk Study. The questionnaire is a 10 page A4 document, divided into 2 parts (Appendix 3):

- Part 1, contains a list of 130 foods. For each item on the list, participants were asked to indicate their usual rate of consumption choosing from nine frequency categories. The categories range from "never or less than once/month" to "6 times per day". The

servings are specified in terms of units or common portions (e.g. one apple, one slice of bread) or household measures (e.g. glass, cup, spoon). An average portion size was assigned to each questionnaire item.

- Part 2 includes a set of additional questions on type and brand of breakfast cereal; type of fat used in frying, roasting, grilling or baking; and the amount of visible fat on meat. These questions are linked to relevant items on the list and used to help categorise breakfast cereals and total fat and fatty acid consumption respectively. A further question on milk is also found in part 2, requesting information on the type and quantity of milk consumed.

The FFQ data were processed using the FETA system, which converts the frequency category for each of the 130 food categories into an amount for each nutrient profile and from that calculates average daily nutrient intake. During the processing of the FFQ, the free text from part 2 of the FFQ were matched and converted into the appropriate nutrient database codes. In the cases where participants did not put a tick on each line or made multiple ticks on a single line, responses were given specific codes during entry and treated as missing data. Individuals with more than 10 missing lines of data were excluded (457).

2.4.4 Assessment of eating behavior

All subjects completed a set of eating behaviour and psychological questionnaires 2-weeks before and 6-months post intervention, using an online version created by our department. Subjects used an IPad to complete the questionnaires on site. In some cases subjects were not able to complete the full set of questionnaires on the day, in such cases, a website link was emailed to them to complete the questionnaires at home. Scores were automatically calculated and presented on an excel spreadsheet for the use in the statistical analysis.

Psychological characteristics questionnaires:

- **Barratt Impulsivity Scale (BIS)** is a self-report measure of impulsivity (a personality trait) (458). The questionnaire consists of 30-items cumulating a total impulsiveness score. A higher score represents higher impulsivity rate.
- **Hospital Anxiety and Depression Scale (HADS)** assesses depression and anxiety. The cut-off values for anxiety and depression levels are 0–7 “normal”, 8–10 “borderline abnormal”, and 11–21 “abnormal” (459).
- **Beck Depression Inventory (BDI−II)** assesses the severity of depression. The cut-off values for depression levels are 0–13 “minimal”, 14–19 “mild” 20–28 “moderate”, and 29-63 “sever” (460).
- **Behavioural Inhibition and Activation System (BIS / BAS)** measures appetitive motives, that is, to move toward something desired. It consists of three subscales: Reward Responsivity (RR) measures positive responses to the anticipation of reward; Drive (DR) measures the persistent pursuit of desired goals; Fun-Seeking (FS) measures a willingness to approach a new event on the spur of the moment. In contrast, the BIS measures aversive motivation, that is, to move away from something unpleasant, such as punishment or negative events (461). Higher scores in both scales mean a higher tendency toward the measured factor.

Eating styles

- **Dutch Eating Behaviour Questionnaire (DEBQ)** measures three types of overeating styles: restraint eating refers to overeating after a period of strict cognitive control; emotional eating is eating in response to emotional arousal states such as fear, anger, or anxiety; and external eating which refers to eating in response to

external food cues such as sight and smell of food (44). A higher score in each eating style means more tendency toward the measured factor.

- **Three Factor Eating Questionnaire (TFEQ)** assess eating behaviour from three dimensions: cognitive restraint, which is consciously trying to resist eating in order to control body weight; disinhibition referring to a loss of control over eating; and the susceptibility to hunger (50). Higher scores indicate greater cognitive restraint, uncontrolled eating, and food intake, in response to feelings of hunger.
- **The Power of Food Scale (PoF)** assesses the psychological impact of living in food-abundant environments. It measures the appetitive drive, rather than consumption of palatable foods, at three levels of food proximity: food available; food present; and food tasted (462). A higher score reflects the control or power of food has over an individual.
- **Alcohol Use Disorders Identification Test (AUDIT)** assesses alcohol use and alcohol-related consequences. It consists of 3 domains: hazardous alcohol use; dependence symptoms, and harmful alcohol use (463). Higher scores reflect greater severity of alcohol problems and dependence.

Hunger

Assessment of hunger was carried out using Visual analogue scale (VAS) at 2-weekd before, 10-days after, and 6-months after the intervention. VAS is a 100mm scale anchored with “Not at all” on one end and with “Extremely” on the other end to provide a quantifiable objective measure, translated from subjective sensations (Figure 8).

Figure 9 Visual Analogue Scale (VAS)

The scale is rated based on different questions. In this study, the following questions were asked:

- How hungry do you feel right now?
- How full do you feel right now?

Subjects attended the clinical research facility on those occasions after an over-night fast and were asked to rate the VAS at the following time points: upon arrival at 8am (fasting), before a standardised meal at 11am (fasting), at 15mins, 30min, 60min, 120min, and 240min (postprandial). The standardised meal consisted of 250ml of Fortisips (vanilla flavour), total macronutrient composition: Energy 600kcal, Protein 24g, Carbohydrates 74.2g, Fat 23.2g. Patients were given 10 minutes to consume the meal.

The VASs used in this study were in an electronic version and completed by the subjects using an IPad. Scores were automatically calculated and presented in an excel spreadsheet for the use in the statistical analysis.

2.4.5 Assessment of taste sensitivity for sweet taste

2.4.5.1 Procedure for sweet detection sensitivity

All subjects were investigated for sucrose sensitivity 2-weeks before, 10-days post, and 6-months post intervention. Detection test for sucrose was performed following the same method of constant stimuli previously described by Bueter *et al.* (2011) (111).

Subjects arrived at 8.00 to the clinical research facility in the morning after an overnight fast starting at 23:00. All solutions were prepared daily using the same still natural mineral water (Caledonian Still Natural Mineral Water, Sainsbury's Supermarkets Ltd., London, UK: pH 7.4, calcium 27mg/l, chloride 6.4mg/l, bicarbonate 103 mg/l, magnesium 6.9 mg/l, sodium 6.6 mg/l, sulphate 10.6 mg/l) and presented at room temperature. As per our previous validated protocol (111), seven sucrose (Sigma-Aldrich, Dorset, UK) concentrations were used in this study: 2.1, 6.25, 12.5, 25, 50, 100 and 300 mM. Concentrations were tested in eight blocks, each block consisting of seven sucrose and seven water stimuli. Sucrose and water stimuli were presented in random order without replacement. Thus, each of the seven sucrose concentrations was presented once within a block. The random arrangement of solutions changed on each study visit to eliminate learning, expectation and habituation. Fifteen millilitres of water or sucrose stimuli were offered in polystyrene cups and subjects were given a period of 5sec to sample the stimulus in the mouth. Subjects then expectorated the

sample and were given additional 5sec to indicate whether the stimulus was water or not. Each stimulus was followed by a thorough 10sec water rinse, which was expelled before the next stimulus was offered. After the completion of the first four blocks, the test was interrupted with a 10 min rest period. To maintain attention to the task, the correct answer for each cup of a tastant solution was provided immediately after the patient's response.

2.4.5.2 Data analysis for sucrose detection sensitivity

The data collected from the sucrose detection test allows for the derivation of a psychometric function, which is a mathematical equation that plots the performance of subjects against the physical aspect of the stimulus i.e. concentration of stimulus. Performance is measured as a percentage of correct responses (responses where the subject was able to correctly detect the stimulus).

To do this, a "hit" was defined as when the subject correctly reported that the stimulus was different from water when sucrose was presented. A "false alarm" (FA) was defined when the subject incorrectly reported that the stimulus was different from water when water was presented. The hit rate for a given sucrose concentration was adjusted for the false alarm rate to derive a "corrected hit rate" using the following equation:

$$Corrected\ hit\ rate = \frac{P(hit) - P(FA)}{1.0 - P(FA)}$$

Where P(hit) = the proportion of sucrose trials of a given concentration that were hit, and P(FA) = the proportion of water trials that were false alarms. Thus, when the uncorrected hit rate is equal to the false alarm rate, the corrected hit rate=0.

Concentration-response curves were fit to the corrected hit rate values for each subject for the three tested occasions (2-weeks before, 10-days after, and 6-months post intervention) to derive a family of individual psychometric functions using the following logistic equation:

$$f(x) = \frac{a}{1 + 10^{((log10(x) - c) * b)}}$$

where log10(x) = log10 concentration, a = the upper asymptote of performance, b = slope, and c = the log10 concentration at 1/2a performance (i.e. EC50). We defined the c parameter as the threshold because it represents the inflection point of the psychometric function and thus optimally represents lateral shifts in sensitivity.

2.4.6 Assessment of the appetitive reward value for sweet taste

2.4.6.1 Procedure for sweet appetitive reward value assessment

This test was carried out 2-weeks before and 6-months post intervention only. Testing occurred 3 hours after the subjects consumed a standardised meal consisting of 250ml of Fortisips (vanilla flavour), total macronutrient composition: Energy 600kcal, Protein 24g, Carbohydrates 74.2g, Fat 23.2g, in a quiet room within the clinical research facility. Before testing, subjects rated their hunger, fullness and desire to eat using a horizontal 100 mm Visual Analogue Scale (VAS) with the anchors “not at all” and “extremely” on either end.

Assessment of appetitive sweet reward value was performed following the same method of Progressive Ratio Task (PRT) previously described by Miras *et al.* (2012) (146). Subjects were placed in front of a computer screen and a plate of 20 chocolate candies (M&M® crispy candies, Mars UK Limited, Slough UK), each one containing approximately 4 kcal (energy contribution: 43.7% sugars, 44.1% fat). The following prompt appeared on the screen: “You can earn food by clicking on the mouse button. Click as much or as little as you like. When you no longer want to continue, press the spacebar to stop the session”. Upon completion of each ratio, a message box appeared on the screen: “You have earned food. Enjoy your reward and after you have swallowed it completely you may click on OK to continue with the programme.” After ingesting the reward, the subjects then pressed the OK button in the message box only if they wished to progress to the next ratio in order to obtain another chocolate candy.

The starting ratio was 10 clicks with a geometric increment of 2 (i.e. 10, 20, 40, 80 etc.). This progression schedule was chosen based on pilot experiments in both obese and normal-weight volunteers carried out by Miras *et al.* (2012) (146). The instructor ensured that all participants understood the experiment then left the room and subjects were left on their own to complete the task. When the effort of repeatedly pressing the mouse button was perceived to be greater than the reward value of the chocolate candy, subjects pressed on the space bar to terminate the session indicating the breakpoint was reached.

2.4.6.2 Data analysis of the sweet appetitive reward value

The number of candies left after completion of the experiment was subtracted from 20 to give the total number consumed. This was correlated with the number of completed ratios from the computer software to ensure participants followed the instructions reliably.

The point when subjects stopped responding to obtain a reinforcer i.e. stopped clicking was defined as the breakpoint. Whereas, the number of responses in the last completed ratio indicates the reward value of the reinforcer.

2.4.7 Assessment of the consummatory reward value for sweet taste

2.4.7.1 Procedure for sweet consummatory taste reward value assessment

This test was carried out 2-weeks before, 10-days after, and 6-months post intervention. Consummatory taste reward value test for sucrose was performed following the same methodology previously described by Bueter *et al.* (2011) (111).

Subjects arrived at 8.00 to the clinical research facility after an overnight fast starting at 23:00. All solutions were prepared daily using the same still natural mineral water (Caledonian Still Natural Mineral Water, Sainsbury's Supermarkets Ltd., London, UK: pH 7.4, calcium 27mg/l, chloride 6.4mg/l, bicarbonate 103 mg/l, magnesium 6.9 mg/l, sodium 6.6 mg/l, sulphate 10.6 mg/l) and presented at 4C°. A modified version of the originally validated protocol (111) was used. Five sucrose (Sigma-Aldrich, Dorset, UK) concentrations were used in this study: 0, 50, 100, 200, 400 mM. Concentrations were tested in three blocks with each block consisting of five sucrose samples presented in random order without replacement and five refrigerated water rinse (15ml). Participants were asked to put the solutions into their mouths, swirl it, and rate its intensity and pleasantness using hedonic scales (explained below). After each cup of sucrose solution, they were asked to use the water rinse to cleanse their mouths for the next tastant.

Before the commencement of this test, patients were given detailed explanations on how to rate the following 3 scales: Intensity generalised Labelled Magnitude Scale (gLMS), and the "just about right" scale, Hedonic generalised Labelled Magnitude Scale (gLMS) (Appendix).

- The Intensity generalised labelled magnitude scale (gLMS)

  The patient was asked to rate the intensity of the solution relative to the intensity of any sensations they have ever experienced. This scale was uni-directional, with a lower extreme end rating of 'barely detectable' to the higher extreme end rating of 'strongest intensity of any kind'. The length of the scale was further divided into 4 other ratings, ranging from 'weak' to 'very strong' intensity.

- The "Just About Right" (JAR) scale

  This scale was used to rate the sweetness and preference of the taste solution as compared to the sweetness of their ideal soft drink. This scale was divided equally in the middle where the ideal rating was situated ('Just right: My ideal sweetness in a drink') while measurements of the most positive ('Far too sweet: I would never drink it) and most negative rating ('Far too little sweetness: I would never drink it') were depicted at either extreme end.

- The Hedonic gLMS

  The patient needed to rate their "liking" of the solution relative to any liking feeling they have ever experienced. This scale was divided equally in the middle where the ideal rating was situated ('Neutral) while measurements of the most positive ('Strongest liking of any kind') and most negative rating ('Strongest disliking of any kind') were depicted at either extreme end. The scale is further divided into 4 categories each direction into ratings ranging from 'weak liking/disliking' and 'very strong liking/disliking'.

2.4.7.2 Data analysis of the sweet consummatory taste reward value scales

The ratings on the scales were analysed using a ruler.

- The Intensity (gLMS): the scale was rated with 0mm at the lower end (barely detectable) to 200mm at the highest end (strongest intensity of any kind).
- The “Just About Right” (JAR) scale

  The scale was rated with 0mm at the middle (just about right), -100mm at the lowest end (far too little sweet), and +100mm at the highest end (far too sweet).
- The Hedonic gLMS: This scale was rated with 0mm at the lower end (Strongest disliking of any kind) to 200mm at the highest end (Strongest liking of any kind).

2.5 Statistical analysis

Parametric tests were used. All data were normally distributed and data were expressed as mean ± standard error of the mean (SEM). One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures. Two-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to study the effect and interaction of Group and Time on different variables. Linear regression models were used to examine associations. Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

CHAPTER 3 ANTHROPOMETRIC DATA

3 Anthropometric data

3.1 Introduction

Obesity and its related comorbidities including T2DM are reaching dangerous levels in the UK and around the globe. Currently, the most effective treatment is bariatric surgery and particularly the RYGB. However, despite the impressive weight loss and improvement in T2DM, bariatric surgery procedures still carry a high risk of complications of which some can be serious and 1 in 1000 are fatal (440). In addition, not all obese patients are eligible for bariatric surgery due to preoperative high risks. Therefore, the need for an effective and safer strategy for the treatment of obesity and T2DM is very high.

The DJBL is a new procedure and, like any novel technique, information on long-term weight loss outcomes is limited. Most studies in the literature have used the excess weight loss and/or total body weight at 12 weeks as a main outcome measure. Those studies showed encouraging results with a reduction of 8.2%-11.2% in total body weight (445). However, a longer follow-up period is required to assess the effectiveness of any weight loss intervention/procedure.

In a review carried out by Neff *et al.* (2013) on the outcome of glycaemic control and weight following DJBL, it was shown that treatment with DJBL for up to 12 months could result in a reduction of total body weight ranging between 8.0%-19.0% (446).

Another study carried out by Koehestanie *et al.* (2014) on 31 DJBL patients and 39 controls on a dietary intervention, showed that treatment with DJBL for 6 months resulted in a reduction of 10% total body weight compared to 4.7% in the control group. Patients were followed up for another 6 months and although by the end of the 6 months post-DJBL removal, follow-up patients had regained some of their weight, the reduction of total body weight remained higher in the DJBL patients compared to the controls, 5.8% compared to 3.5%, respectively (447).

Betzel *et al.* (2014) carried out a study to assess the safety of the DJBL in the Netherlands. Though this study was not intended to assess the rate of weight loss, they presented weight loss data for 26 patients completing a 6-months treatment and 61 patients completing a 12-months treatment. Those patients had a significant weight loss of 9.5% and 9.2%, respectively (448). This study shows that significant weight loss, maintained at least for the duration of the device treatment, is achievable regardless of the specific standardized calorie controlled diet of most weight loss intended clinical trials.

In addition, the most recent review and meta-analysis on the effect of DJBL included five RCTs with 235 subjects and 10 observational studies with 211 subjects. [9]. The Meta analysis showed that weight loss was in favour of the DJBL, relative to diet-controlled patients (464).

In summery, DJBL can result in at least 9% weight loss over 12 months treatment. More weight loss may be achievable with stricter dietary guidelines.

3.2 Materials and method

3.2.1 Subjects

Forty-Two subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. SMT via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Anthropometric measurements was carried out 2-weeks before intervention (Baseline), 10-day post intervention and while on the liquid diet, and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

3.2.2 Body Measurements

Detailed description of the methods used for body measurements are described in chapter two: Materials and Methods (2.4.2).

3.2.3 Statistical methods

The data were normally distributed as assessed by D'Agostino & Pearson normality test and are therefore expressed as mean ± standard error of the mean (SEM).

The data were compared 'between' groups at baseline and when the data is presented as a delta of the measurements in the 10-days analysis. A parametric paired t-test was performed to compare two time-points within each group and a parametric unpaired t-test was performed to compare time-points between groups. One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were performed to test for significant differences between pre- and post-operative repeated measures. Two-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were performed to test for significant differences between groups during repeated measures.

Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

3.3 Results

3.3.1 Attrition

All 42 recruited subjects (23 DJBL, 19 SMT) completed their 10-days post intervention visits and they were included in the 10-days data analysis as 'intention-to-treat'.

However, due to the timelines of this thesis, only 25 subjects (12 DJBL, 13 SMT) were due for the long-term follow-up (6-months post intervention) by the time data had to be locked for analysis. In the DJBL group, two patients had the device removed prior to the 6-months follow-up visit, and in the SMT groups two subjects were lost to follow-up and 1 subject withdrew consent. Therefore, a total of 20 subjects (10 DJBL, 10 SMT) were included in the 6-months follow-up data analysis. Those participants are referred to as 'Completers as per protocol'.

3.3.2 Baseline assessment

Baseline characteristics of subjects who participated in the study are shown in Table 3.1 (A and B).

The 'intention-to-treat' DJBL participants were heavier at baseline than the SMT ($p=0.03$) and had a larger waist circumference ($p=0.048$), and fat-free mass ($p=0.004$) (Table 3-1 A).

The baseline characteristics of the 'completers' differed significantly in age only with the DJBL participants being significantly younger than the SMT participants 48.1±2.6 and 55.3±1.3 ($p= 0.02$), respectively (Table 3-1 B).

Table 3-1 (A and B) Baseline characteristics of study participants

A) Intention-to-treat participants (DJBL n=23, SMT n=19)

	DJBL (n=23)	**SMT (n= 19)**	**P value**
Age (y)	51.0±1.6	54.2±1.4	0.16
Women (%)	26	57	
Weight (kg)	112.4±3.9	100.6±3.3	0.03
BMI (kg/m^2)	36.5±1.1	35.8±0.9	0.67
Waist circumference (cm)	119.8±2.8	112.0±2.6	0.048
Fat (%)	37.9±1.4	41.2±1.8	0.15
Fat mass (kg)	42.8±2.4	41.3±2.1	0.66
Fat-free mass (kg)	69.6±2.6	56.6±3.5	0.004

B) Completers analysis as per protocol (DJBL n=10, SMT n=10)

	DJBL (n=10)	**SMT (n= 10)**	**P value**
Age (y)	48.1±2.6	55.3±1.3	0.02
Women (%)	50	60	
Weight (kg)	106.7±6.9	98.66±4.7	0.35
BMI (kg/m^2)	35.8±1.7	35.6±1.4	0.91
Waist circumference (cm)	115.6±4.1	112.0±3.8	0.53
Fat (%)	40.6±2.3	40.7±2.4	0.97
Fat mass (kg)	43.3±3.9	40.4±3.5	0.59
Fat-free mass (kg)	63.4±4.7	58.2±3.3	0.39

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; BMI: Body Mass Index. All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data are presented as mean ± standard error of the mean (SEM). Between groups analyses were performed with unpaired *t*-tests.

3.3.3 10-days post-interventions

All anthropometric measurements decreased significantly at 10-days post intervention, except % fat (p=0.67) in the 'Intention-to-treat' DJBL participants and fat-free mass (p=0.63) in the SMT participants (Table 3-2 A).

The 10-days follow up measurements of the 'Completers' was inline with the anthropometric changes of the 'Intention-to-treat' (Table 3-2 B).

Participants in the 'Intention-to-treat' (n=23) DJBL arm lost an average of 5.4±0.4%, equating to 6.0±0.6kg which was significantly higher (p=0.02) than the SMT arm (n=9) who lost an average of 4.4±0.2 kg, equating to 4.5±0.3kg from baseline (p<0.0001) as seen in Figure 10-A. The 10-days post intervention body weight for the 'study completers' (n=10) was 4.3±0.5% equating to -4.5±0.5kg in the DJBL group and 4.6±0.2% equating to also 4.5±0.3kg in the SMT (n=10). The difference between the two groups was not statistically different (Figure 10-B).

Table 3-2 (A and B) Anthropometric measurements at 10-days post intervention.

A) Intention-to-treat participants (DJBL n=23, SMT n=19)

	DJBL (n=23)			SMT (n= 19)		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Weight (kg)	112.4±3.9	106.4±3.8	<0.0001	100.6±3.3	96.2±3.2	<0.0001
BMI (kg/m^2)	36.5±1.1	34.6±1.1	<0.0001	35.8±0.9	34.3±1.0	<0.0001
Waist circumference (cm)	119.8±2.8	115.2±2.6	<0.0001	112.0±2.6	109.1±2.5	0.0006
Fat (%)	37.9±1.4	37.4±1.6	0.67	41.2±1.8	40.1±2.0	0.0005
Fat mass (kg)	42.8±2.4	39.7±2.2	0.0002	41.3±2.1	39.3±2.2	<0.0001
Fat-free mass (kg)	69.6±2.6	66.4±3.0	<0.0001	56.6±3.5	58.9±2.7	0.63

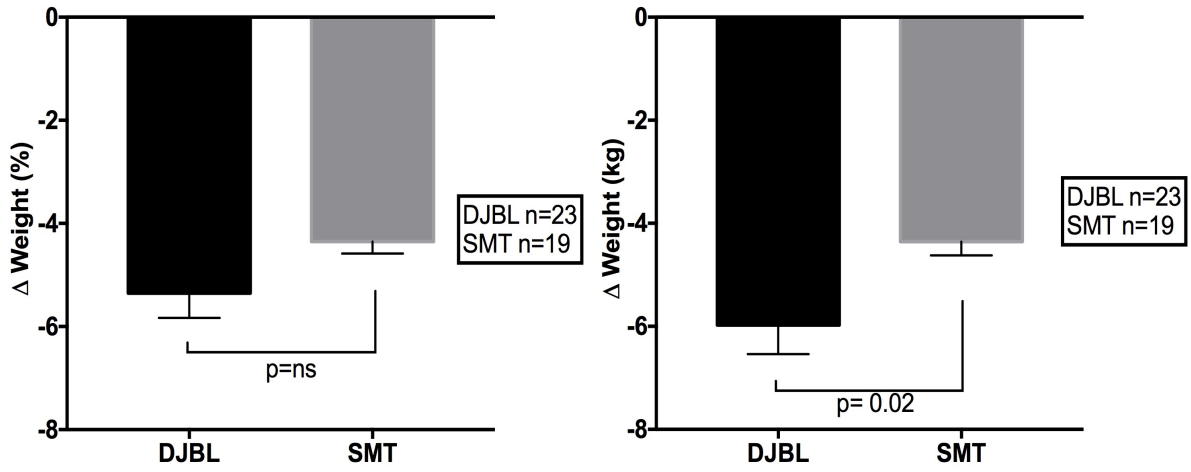
B) Completers analysis as per protocol (DJBL n=10, SMT n=10)

	DJBL (n=10)			SMT (n= 10)		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Weight (kg)	106.7±6.9	102.2±6.8	<0.0001	98.66±4.7	94.2±4.5	<0.0001
BMI (kg/m^2)	35.8±1.7	34.3±1.6	<0.0001	35.6±1.4	34.0±1.4	<0.0001
Waist circumference (cm)	115.6±4.1	112.3±3.6	0.0497	112.0±3.8	108.8±3.6	0.02
Fat (%)	40.6±2.3	39.4±2.8	0.76	40.7±2.4	39.6±3.0	0.03
Fat mass (kg)	43.3±3.9	39.0±3.2	0.043	40.4±3.5	39.1±3.7	<0.0001
Fat-free mass (kg)	63.4±4.7	61.5±6.5	0.02	58.2±3.3	58.7±3.0	0.004

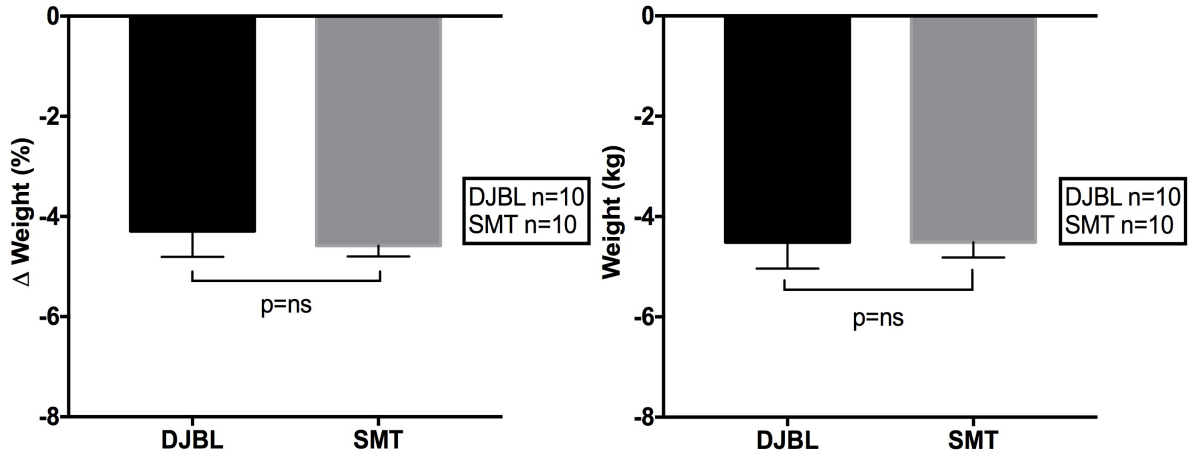
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; BMI: Body Mass Index. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Within groups analyses were performed with paired *t*-tests.

Figure 10 (A and B) Absolute and percentage delta weight loss at 10-days post intervention

A) Intention-to-treat participants (DJBL n=23, SMT n=19) at 10-days



B) Completers analysis as per protocol (DJBL n=10, SMT n=10) at 10-days



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between groups analyses were performed with unpaired *t*-tests.

3.3.4 6-months post-interventions

3.3.4.1 One-way ANOVA

Changes in anthropometric measurements for the 'Completers' of both treatment groups are presented in Table 3-3.

Both groups continued to lose weight over the 6-months study period (Figure 11 and Figure 12). The DJBL participants lost an average of -4.3±0.5% equating to -4.5±0.5kg at 10-days which significantly increased to -8.6±0.8% at 6-months post intervention. Data were significantly different between all 3 visits (Table 3-3).

Subjects in the SMT lost 4.6±0.2% equating to -4.5±0.3kg and -9.1±2.4kg at 10-days post intervention, which significantly increased to -9.1±2.1% at 6-months post intervention (Figure 11 and Figure 12). Data was only significantly different between baseline and 10-days post, and between baseline and 6-months post intervention (Table 3-3).

Reduction in BMI measurements corresponded with the measurements in weight (Table 3.3).

Waist circumference was the lowest at 6-months post intervention in both groups. The overall ANOVA of waist circumference in the DJBL group was significant but a Tukey post hoc test did not show significant differences between any of the study visits (Table 3-3). In the SMT, waist circumference was statistically different between all visits (Table 3.3).

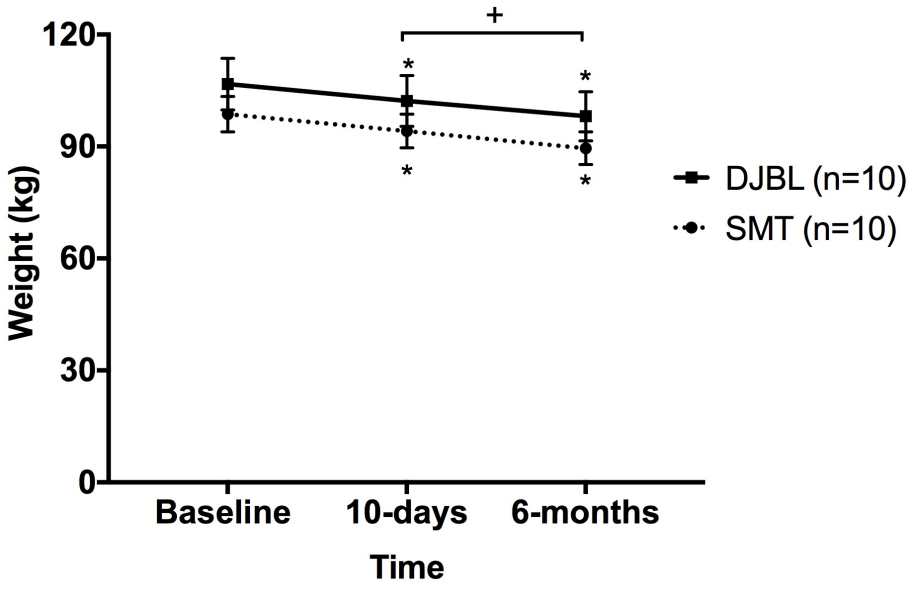
Percentage of fat loss was only significantly different between baseline and 6-months in both groups (Table 3.3). The SMT group lost more fat mass whereas the DJBL group lost more fat-free mass at 6 months post-intervention (Table 3.3).

Table 3-3 Changes in anthropometric measurements at 10-days and 6-months post intervention for completers in both treatment groups

	DJBL					SMT				
	Baseline	**10-days**	**6-months**	**Overall ANOVA P value**	***Post hoc* pair-wise comparison, P value**	**Baseline**	**10-days**	**6-months**	**Overall ANOVA P value**	***Post hoc* pair-wise comparison, P value**
Age (years)	48.1±2.6	N/A	N/A			56.3±1.5	N/A	N/A		
Women (%)	50	N/A	N/A			60	N/A	N/A		
Height (cm)	172.1±3.7	N/A	N/A			168.6±2.3	N/A	N/A		
Weight (kg)	106.7±6.9	102.2±6.8	98.11±6.6	<0.0001	BL>10D,<0.05 BL>6M,<0.05 10D>6M,<0.05	98.66±4.7	94.2±4.5	89.5±4.4	0.008	BL>10D,<0.05 BL>6M, <0.05
BMI (kg/m^2)	35.8±1.7	34.3±1.6	32.9±1.7	<0.0001	BL>10D,<0.05 BL>6M,<0.05 10D>6M,<0.05	35.6±1.4	34.0±1.4	32.2±1.1	0.01	BL>10D,<0.05 BL>6M,<0.05
Waist circumference (cm)	115.6±4.1	112.3±3.6	111.9±3.7	0.03	NS	112.0±3.8	108.8±3.6	104.1±4.2	0.004	BL>10D,<0.05 BL>6M,<0.05 10D>6M,<0.05
Fat (%)	40.6±2.3	39.4±2.8	37.6±2.6	0.009	BL>6M,<0.05	40.7±2.4	39.6±3.0	35.8±2.4	0.01	BL>6M,<0.05
Fat mass (kg)	43.3±3.9	39.0±3.2	37.3±4.0	<0.0001	BL>6M,<0.05 10D>6M,<0.05	40.4±3.5	39.1±3.7	32.2±2.9	0.01	BL>10D,<0.05 BL>6M,<0.05
Fat-free mass (kg)	63.4±4.7	61.5±6.5	61.0±4.5	0.054		58.2±3.3	58.7±3.0	58.4±4.0		

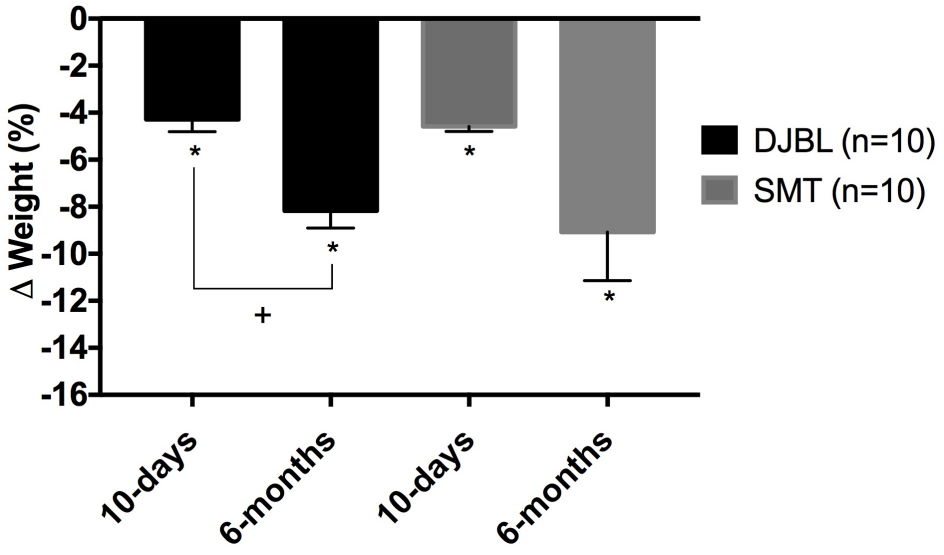
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; within groups analyses were performed with One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures.

Figure 11 Body weights throughout the study for completers as per protocol



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; within groups analyses were performed with One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures.

Figure 12 Delta weight loss at 10-days and 6-months post intervention for completers as per protocol



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; within groups analyses were performed with One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures.

* As compared to baseline / + between visits

3.3.4.2 Two-way ANOVA

Two-way repeated measures ANOVA was used to compare between DJBL and SMT at multiple time-points. As an extension, within group comparisons are also presented in this section as assess with two-way ANOVA (Table 3.4).

Time had a significant impact on all anthropometric parameters except on the fat free mass (p=0.1). There was no 'type of treatment' effect or 'time x treatment interaction' effect on any parameter (Table 3.4).

Post hoc analysis revealed a significant difference in weight between DJBL and SMT at baseline (p=0.0001), which remained significantly different between the two groups throughout the study. Nevertheless, both groups had a significant reduction in weight at 10-days and 6-months post intervention. At 6-months post intervention the DJBL group lost a total of 8.6kg compared to the SMT groups which lost a total of 9.1kg (p=<0.0001). It is tricky to interpret this change as the baseline values were also statistically different. BMI values reveal no significant difference between groups at any time-point, but a statistical significance within groups (Table 3.5).

The waist circumference was not significantly different between groups at baseline. Both groups had a significant reduction in waist circumference at 6-months post intervention compared to baseline. However, the SMT group had a significantly higher reduction in waist circumference at 6-months compared to the DJBL group (p=0.01) (Table 3.5).

Percentage fat loss was only significantly lower at 6-months post intervention compared to baseline in the SMT group (p=0.01) (Table 3.5).

Table 3-4 Two-way ANOVA results for anthropometric measurements at baseline, 10-days and 6-months post interventions

	DJBL (n=10)			SMT (n= 10)			Treatment F; P [a]	Time F; P [b]	Treatment X Time F; P[c]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**			
Age (years)	48.1±2.6	N/A	N/A	56.3±1.5	N/A	N/A			
Women (%)	50	N/A	N/A	60	N/A	N/A			
Height (cm)	172.1±3.7	N/A	N/A	168.6±2.3	N/A	N/A			
Weight (kg)	106.7±6.9	102.2±6.8	98.1±6.6	98.66±4.7	94.2±4.5	89.5±4.4	0.9; p=0.4	33.6;p<0.0001	0.1;p=0.9
BMI (kg/m^2)	35.8±1.7	34.3±1.6	32.9±1.7	35.6±1.4	34.0±1.4	32.2±1.1	0.03; p=0.9	37.6;p<0.0001	0.3; p=0.8
Waist circumference (cm)	115.6±4.1	112.3±3.6	111.9±3.7	112.0±3.8	108.8±3.6	104.1±4.2	0.8; p=0.4	21.0;p<0.0001	0.7; p=0.5
Fat (%)	40.6±2.3	39.4±2.8	37.6±2.6	40.7±2.4	39.6±3.0	35.8±2.4	0.1; p=0.7	17.0;p=0.0002	0.6; p=0.5
Fat mass (kg)	43.3±3.9	39.0±3.2	37.3±4.0	40.4±3.5	39.1±3.7	32.2±2.9	0.01; p=0.9	21.5;p<0.0001	1.0; p=0.4
Fat-free mass (kg)	63.4±4.7	61.5±6.5	61.0±4.5	58.2±3.3	58.7±3.0	58.4±4.0	0.2; p=0.7	3.5; p=0.1	1.0; p=0.4

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA)

a F(2,18) for all parameters

b F(1,9) for all parameters

c F(2,18) for all parameters

Table 3-5 Two-way ANOVA Post hoc multiple comparisons of repeated measure for anthropometric measurements

	DJBL (n=10)			SMT (n= 10)			*Post hoc* pair-wise comparison, P value [a]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**	
Age (years)	48.1±2.6	N/A	N/A	56.3±1.5	N/A	N/A	
Women (%)	50	N/A	N/A	60	N/A	N/A	
Height (cm)	172.1±3.7	N/A	N/A	168.6±2.3	N/A	N/A	
Weight (kg)	106.7±6.9	102.2±6.8	98.1±6.6	98.66±4.7	94.2±4.5	89.5±4.4	ENDO BL > SMT BL, p=0.0001 ENDO 10-days > SMT 10-days, p=0.0001 ENDO 6-months > SMT 6-months, p=<0.0001 ENDO BL > ENDO 10-days, p=0.03 ENDO BL > ENDO 6-months, p<0.0001 SMT BL > SMT 10-day, p=0.03 SMT 10-days > SMT 6-months, p=0.02
BMI (kg/m^2)	35.8±1.7	34.3±1.6	32.9±1.7	35.6±1.4	34.0±1.4	32.2±1.1	ENDO BL > ENDO 6-months, p=0.0002 SMT BL > SMT 6-months, p<0.0001 SMT 10-days > SMT 6-months, p=0.02
Waist circumference (cm)	115.6±4.1	112.3±3.6	111.9±3.7	112.0±3.8	108.8±3.6	104.1±4.2	ENDO BL > ENDO 6-months, p=0.04 SMT BL > SMT 6-months, p=0.004 ENDO 6-months > SMT 6-months, p=0.01
Fat (%)	40.6±2.3	39.4±2.8	37.6±2.6	40.7±2.4	39.6±3.0	35.8±2.4	SMT BL > SMT 6-months, p=0.01
Fat mass (kg)	43.3±3.9	39.0±3.2	37.3±4.0	40.4±3.5	39.1±3.7	32.2±2.9	ENDO BL > ENDO 6-months, p=0.01 SMT BL > SMT 6-months, p=0.0004 SMT 10-days > SMT 6-months, p=0.01
Fat-free mass (kg)	63.4±4.7	61.5±6.5	61.0±4.5	58.2±3.3	58.7±3.0	58.4±4.0	ENDO BL > SMT BL, p=0.01 ENDO 10 days > SMT 10-days, p=0.03

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA) with Tuky post hoc multiple comparisons.

a Only the significant findings are presented

3.4 Discussion

In this chapter, I found that both types of treatments resulted in similar changes in anthropometric measurements during a 6-months treatment period. This study is unique in that it is the first to compare the DJBL device to another group that also has an excellent medical and dietary intervention, identical to the one received by the treatment group, in a randomised controlled trial.

The purpose of collecting the body measurements data on the 10-days post-intervention visit was to reflect on the adherence to the liquid diet phase of the study more than a measurement of the acute effect of the device. The higher absolute weight loss in the DJBL group (in the 'intention-to-treat') at this time point can be a result of the higher baseline weight the DJBL group started with in the first instance. This was corrected for when the data were presented in percentage weight loss and the difference then became insignificant. In addition, one of the main side effects of the DJBL device is acute pain and nausea, which settle after about 2 weeks of the device insertion (465). As a result, participants in the DJBL group may have consumed less liquid food, intentionally or unintentionally.

Both groups continued to lose weight over the 6-months period and achieved very similar and satisfactory end results. The amount of weight loss in the DJBL group was comparable to that reported in other studies of 6-months outcome (447, 448). However, the novelty in our findings is that our data is suggesting that the weight loss is perhaps due to calorie restriction only, and the bypass of the proximal small bowel having a minimal affect, at least in the first 6-months. It has been previously suggested that one aspect of weight loss post Roux-en-Y Gastric Bypass is attributed to the bypass of the proximal small bowel that alters bile flow. Bile induces the release of appetite suppressant hormone GLP-1 (466, 467), causing reduced food intake and thus additional weight loss occurs. The DJBL device follows the same concept but its impact on food intake will be discussed in the next chapter.

This is the first study to report that the control group achieve similar results to the DJBL group. However, this study is also the first randomised controlled study investigating the DJBL device and therefore it is the first unbiased study. Rohde *et al.* (2016) described the majority of the DJBL studies fulfilling at least one 'high risk of bias' parameter (464).

In this study, all study participants were given the same intensive counselling on diet and exercise, however, It is worth mentioning that anecdotal reports from the clinical visits may suggest that it is possible that the SMT participants felt more under pressure to control their weight with lifestyle interventions and adhered better to the physical component of the intervention as oppose to the DJBL device participants which relied more on the presumed benefits of the device. This type of data was not collected in any quantitative method so it is difficult to know whether it is of a significant importance but verbal repots add to the benefits of carrying out human clinical studies. It has been previously suggested that DJBL produces it's effects on weight loss and diabetes improvements regardless of patient's conscious efforts to control their food intake or lifestyle, suggesting a role of physiological and neurological factors similar to that seen post RYGB. In support of this hypothesis, the only sham randomized controlled humans trial has shown that device patients lost 11.9% excess weight loss (EWL) compared to 2.7% in the sham group at 12 weeks, despite both groups having identical nutritional counseling (465).

The 6-months results of this chapter are not conclusive and can be considered preliminary analysis due to the small size number included. The findings need to be confirmed with further analysis including the entire recruited cohort 'intention-to-treat-participants'.

In summary, this chapter has explored the effect of the DJBL device and SMT on weight loss and other body characteristics during a 6-months period. The results of this chapter suggest that weight loss is predominantly due to calorie restriction and that there is no additional benefit on weight loss by the endoscopic bypass of the proximal small bowel in the first 6-months. The subsequent chapters will investigate whether the DJBL device has an effect on different eating behaviour entities that reflect the physiological change caused by the bypass of the proximal small bowel.

CHAPTER 4 AIM ONE: THE EFFECT OF DJBL ON FOOD INTAKE AND FOOD PREFERENCES

4 Food intake and food preferences

4.1 Introduction

Food intake (ingestion of food) is an innate behaviour predominantly regulated by signals of hunger and satiety to initiate and stop an eating episode or a meal in response to peripheral signals.

The DJBL aims to mimic the intestinal bypass and possibly components of the restrictive effects of Roux-en-y gastric bypass surgery without the need for stapling or anastomosis. Hormones that control appetite and blood sugar level are normally released when food comes in contact with the walls of the duodenum. By eliminating this mechanism, bile and pancreatic secretions are only mixing with chyme at the jejunum (442), resulting in changes in the levels of hormones, and a lower blood sugar levels in a similar manner to that seen after RYGB ((443), (444)). Potential mechanisms of action could include duodenal bypass with alteration of incretin pathways such as GLP-1 or other undefined signals, delayed gastric emptying, partial duodenal mechanical obstruction, or enhanced delivery of undigested nutrients to the more distal bowel with augmentation of incretin secretion (441).

It has been hypothesized that changes in eating behavior elicited by RYGB is a mainly a result of the nutrient exclusion from duodenum along with early delivery of partially digested nutrient into the mid-jejunum small bowel. Endoscopic placement of the DJBL reproduces in isolation, these two RYGB anatomical components and in theory should produce the same powerful neuroendocrine response to the food ingested, characterized by increased levels of several gut derived peptides involved in blood glucose homeostasis and energy balance regulation.

Clinical observations form our obesity clinic suggested possible selective food preferences post DJBL insertion away from fatty food, in some patients but not all. Possible mechanisms for the effect of DJBL on food choices may be related to the adverse events related to GI symptoms that occur in some patients. Nausea is the most common adverse event reported and may be diet related, however, and in most instances it did not prompt any action or

treatment and disappeared within 2 weeks (443, 468). Nausea caused by selective macronutrients or types of food can elicit food aversion to certain foods as seen in RYGB and VSG patients.

As a novel technique, more research is required to understand the mechanism behind the reported benefits of DJBL on weight loss and blood sugar. The elucidation of the mediators underlying any changes in eating behaviour may yield new pharmacological targets, weight loss procedures, or personalised treatments of obesity and its associated comorbidities.

4.2 Materials and methods

4.2.1 Subjects

Forty-Two subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. SMT via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Anthropometric measurements was carried out 2-weeks before intervention (Baseline), 10-day post intervention while on the liquid diet, and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

4.2.2 Assessment of total food intake

Food intake was assessed using food diaries and 24-hour dietary recalls. Details of the assessment method are described in chapter two: Materials and Methods, section (2.4.3.1) and (2.4.3.2).

4.2.3 Assessment of food preferences

Habitual food choices i.e. food preferences, were estimated using the European Prospective Investigation of Cancer Food Frequency Questionnaire (EPIC FFQ). Details of the assessment method are described in chapter two: Materials and Methods, section (2.4.3.3).

4.2.4 Outcome measures

The data collected from the food diaries and 24-hr dietary recall were grouped together and averaged to estimate the total food intake and macronutrient composition at baseline, 10-days post intervention and 6-months post intervention.

Whereas the data collected from the FFQ was used to estimate changes in food preferences at baseline and 6-months post intervention only.

4.2.5 Statistical methods

The data were normally distributed as assessed by D'Agostino & Pearson normality test and are therefore expressed as mean ± standard error of the mean (SEM).

The data were compared 'between' groups at baseline and when the data is presented as a delta of the measurements in the 10-days analysis. A parametric paired t-test was performed to compare two time-points within each group and a parametric unpaired t-test was performed to compare time-points between groups. One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were performed to test for significant differences between pre- and post-operative repeated measures.

Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

4.3 Results

4.3.1 24-hours Diet Recalls

4.3.1.1 Attrition

At baseline, data for 21 DJBL and 18 SMT patients were available for analysis. Due to non-compliance, withdrawal or not yet due for a follow-up visit, the numbers of completed participants at the 6-months visit were 6 DJBL and 9 SMT.

4.3.1.2 Baseline assessment

At Baseline, there were no significant differences in the total food intake and macronutrients composition between the two treatment groups in the 'intention-to-treat-participants (Table 4-1 A). The study completers group, had a significant difference in their protein intake relative to their total energy intake with the SMT groups consuming more protein than the DJBL group at baseline ($p=0.01$) (Table 4-1 B). The study completers analyses also showed a significant difference in the grams of carbohydrates consumed at baseline between the DJBL group and the SMT group; with the DJBL group consuming more carbohydrates ($p=0.02$) (Table 4-1 B). Fibre intake was also significantly different at baseline between the two groups ($p=0.045$) (Table 4-1 B).

Table 4-1 (A and B) Baseline total calorie intake and macronutrient composition as assessed with 24-hr diet recalls

A) Intention-to-treat (DJBL n=21, SMT n=18)

	DJBL (n=21)	SMT (n=18)	P value
Total energy intake			
Calorie intake (Kcal/day)	2112±197	1955±180	0.57
Calorie intake (KJ/day)	8836	8179	
Macronutrient composition			
Protein (g)	83±7.6	91±8.7	0.46
Protein (%)	16±1.0	19±1.2	0.06
Carbohydrate (g)	241±23	198±19	0.17
Carbohydrate (%)	42±1.7	39±2.6	0.32
Fat (g)	90±9	86±10	0.73
Fat (%)	38±1.6	38±1.9	0.97
Other sources of energy			
Alcohol (%)	2±1.0	3±1.7	0.71
Fiber (%)	2±0.2	1.6±0.2	0.26

B) Completers analysis as per protocol (DJBL n=6, SMT n=9)

	DJBL (n=6)	SMT (n=9)	P value
Total energy intake (Kcal/day)			
Calorie intake (Kcal/day)	2641±485	1733±186	0.07
Calorie intake (KJ/day)	11049	7250	
Macronutrient composition			
Protein (g)	91±22	92±11	0.94
Protein (%)	14±1.7	22±1.9	0.01
Carbohydrate (g)	290±53	164±14	0.02
Carbohydrate (%)	43±3	39±4.8	0.50
Fat (g)	114±23	70±11	0.08
Fat (%)	38±3	35±2.8	0.40
Other sources of energy			
Alcohol (%)	3.4±2.5	3.7±2.7	0.94
Fiber (%)	2.1±0.3	1.3±0.2	0.045

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

4.3.1.3 10-days post-intervention

Intention-to-treat analysis (DJBL n=21, SMT n=18)

The DJBL and SMT groups reduced their food intake close to 1200kcal (Table 4-2 A). The DJBL group reduced their energy intake from 2112±197 to 1142±102 (p=0.0003) and the SMT group reduced their energy intake from 1955±180 to 1182±94 (p=0.0008) (Table 4-2 A).

The reduction in total calories was a result of a reduction in the grams of all the macronutrients (CHO, protein and fat). Due to the type of diet (liquid meal replacements) both groups were consuming at the phase of the trial, fibre intake was significantly lower in both groups (p=0.04 in both groups) (Table 4-2 A).

There were no significant changes in the percentage macronutrient intake relative to the total energy intake (Table 4-2 A).

Completers analysis as per protocol (DJBL n=6, SMT n=9)

The change in total energy intake of the study completers (Table 4-2 B) was inline with data of the 'intention-to-treat' that are presented in table 4-2 A and outlined above, except the change in energy intake in the DJBL did not reach statistical significance (p=0.07). In addition, the trend of change in the macronutrients composition was also inline with the change in the 'intention-to-treat-participants and study completers combined' that are presented in table 4-2 A. However, the data did not reach statistical difference in most of the parameters except for percentage intake of protein and fibre in the DJBL group, and the grams of protein in the SMT group (Table 4-2 B).

Table 4-2 (A and B) Change in total calorie intake and macronutrient composition at 10-days post-intervention as assessed with 24-hr diet recalls

A) Intention-to-treat analysis (DJBL n=21, SMT n=18)

	DJBL (n=21)			SMT (n= 18)		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Total energy intake (Kcal/day)						
Calorie intake (Kcal/day)	2112±197	1142±102	0.0003	1955±180	1182±94	0.0008
Calorie intake (KJ/day)	8836	4778		8179	4945	
Macronutrient composition						
Protein (g)	83±7.6	55±5.6	0.0003	91±8.7	48±4.1	0.003
Protein (%)	16±1.0	20±1.3	0.11	19±1.2	17±1	0.14
Carbohydrate (g)	241±23	135±12	0.001	198±19	137±12	0.03
Carbohydrate (%)	42±1.7	46±2.1	0.09	39±2.6	44±1.9	0.18
Fat (g)	90±9	45±5.5	0.0003	86±10	49±4.6	0.02
Fat (%)	38±1.6	33±1.9	0.13	38±1.9	38±1.6	0.94
Other sources of energy						
Alcohol (%)	2±1.0	Nil	0.06	3±1.7	Nil	0.15
Fiber (%)	2±0.2	1.2±0.24	0.04	1.6±0.2	0.65±0.24	0.04

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

B) Completers analysis as per protocol (DJBL n=6, SMT n=9)

	DJBL			SMT		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Total energy intake (Kcal/day)						
Calorie intake (Kcal/day)	2641±485	1348±196	0.07	1733±186	1160±121	0.01
Calorie intake (KJ/day)	11049	5640		7250	4853	
Macronutrient composition						
Protein (g)	91±22	60±9.2	0.20	92±11	50±6.6	0.003
Protein (%)	14±1.7	18±0.6	0.03	22±1.9	18±2.0	0.09
Carbohydrate (g)	290±53	150±17	0.08	164±14	137±15	0.29
Carbohydrate (%)	43±3	43±3.2	0.96	39±4.8	44±2.8	0.30
Fat (g)	114±23	59±12	0.09	70±11	48±6.9	0.47
Fat (%)	38±3	38±2.6	0.95	35±2.8	36±2.1	0.56
Other sources of energy						
Alcohol (g)	3.4±2.5	Nil	0.23	3.7±2.7	Nil	0.22
Fiber (%)	2.1±0.3	0.1±0.4	0.01	1.3±0.2	0.8±0.4	0.31

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

4.3.1.4 6-months post intervention

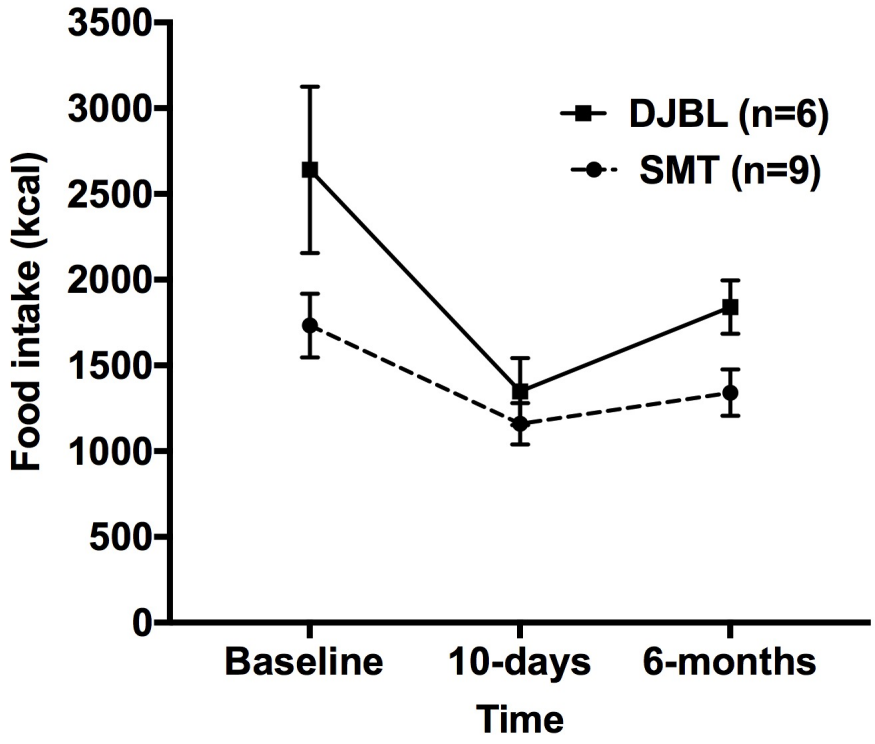
4.3.1.4.1 One-way ANOVA

As assessed with the 24-hr diet recalls, both groups showed a trend towards reduced total calorie intake at the 10-days post intervention visit, which was elevated at the 6-months post intervention visit but remained lower than baseline, albeit not significantly (Figure 13).

In the DJBL group, the energy intake went down from 1733±186 kcal/day at baseline to 1348±196 kcal/day at 10-days and then it rose up to 1841±156 kcal/day (overall ANOVA 0.09). Whereas the total calorie intake per day in the SMT went down from 1782±115.8 kcal/day at baseline to 1160±121 and rose up to 1342±136 (overall ANOVA p=0.05) (Table 4-3).

In the DJBL group, there were no significant differences in any of the macronutrients intake between baseline and 6-months or between 10-days and 6-months in the DJBL group (Table 4-3). Similar to the results from the paired T-Test described above, the fiber intake was significantly different between baseline and 10-days (p=0.03). In the SMT group, the grams of protein from baseline to 10-days was significantly reduced and the fibre intake at 6-months was significantly increased (Table 4-3).

Figure 13 Reduction in food intake over the 6-months period as assessed with 24-hour diet recalls



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with one-way ANOVA and Pair-wise post hoc ANOVA comparisons were performed using Tukey multiple comparison correction testing. Data defined significant at $p < 0.05$

Table 4-3 Total calorie intake and macronutrient composition at 10-days and 6-months follow-up for the DJBL and SMT completers as assessed with 24-hr diet recalls.

	Baseline	10-days	6-months	Overall ANOVA P value	*Post hoc* pair-wise comparison, P value
DJBL (n=6)					
Total energy intake					
Calorie intake (Kcal/day)	2641±485	1348±196	1841±156	0.09	
Calorie intake (KJ/day)	11049	5640	7702		
Macronutrient composition					
Protein (g)	91±22	60±9.2	77±12.0	0.31	
Protein (%)	14±1.7	18±0.6	17±2.9	0.32	
Carbohydrate (g)	290±53	150±17	193±32	0.11	
Carbohydrate (%)	43±3	43±3.2	38±3.8	0.42	
Fat (g)	114±23	59±12	87±6.9	0.10	
Fat (%)	38±3	38±2.6	42±2.5	0.39	
Other sources of energy					
Alcohol (%)	3.4±2.5	Nil	1.0±1.0	0.23	
Fiber (%)	2.1±0.3	0.1±0.4	2.2±0.4	0.02	Baseline >10-days; p=0.03

	Baseline	10-days	6-months	Overall ANOVA P value	*Post hoc* pair-wise comparison, P value
SMT (n=9)					
Total energy intake					
Calorie intake (Kcal/day)	1733±186	1160±121	1342±136	0.05	
Calorie intake (KJ/day)	7250	4853	5614		
Macronutrient composition					
Protein (g)	92±11	50±6.6	91±13	0.04	Baseline > 10-days; p=0.01
Protein (%)	22±1.9	18±2.0	27±3.2	0.07	
Carbohydrate (g)	164±14	137±15	118±14	0.18	
Carbohydrate (%)	39±4.8	44±2.8	33±3.1	0.13	
Fat (g)	70±11	48±6.9	58±9.3	0.20	
Fat (%)	35±2.8	36±2.1	38±3.9	0.57	
Other sources of energy					
Alcohol (%)	3.7±2.7	Nil	Nil	0.21	
Fiber (%)	1.3±0.2	0.8±0.4	2.6±0.45	0.01	6-months >10-days; p=0.02

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). Data within groups were compared with one-way ANOVA and Pair-wise post hoc ANOVA comparisons were performed using Tukey multiple comparison correction testing. Data defined significant at $p < 0.05$

4.3.1.4.2 Two-way ANOVA

Two-way repeated measures ANOVA was used to compare between DJBL and SMT at multiple time-points. As an extension, within group comparisons are also presented in this section as assess with two-way ANOVA (Table 4.4).

Treatment type had a significant impact on the calorie intake, grams of carbohydrates, and percentage protein intake. However, post hoc analysis revealed no significant difference between any parameters at any time point between and within groups (Table 4.5).

There was no impact of (Time) or (Time X Treatment) on any of the measured parameters (Table 4.4).

Table 4-4 Two-way ANOVA results for total calorie intake and macronutrient composition at 10-days and 6-months follow-up for the DJBL and SMT completers as assessed with 24-hr diet recalls.

	DJBL (n=6)			SMT (n= 9)			Treatment F; P [a]	Time F; P [b]	Treatment X Time F; P[c]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**			
Calorie intake (Kcal/day)	2641±485	1348±196	1841±156	1733±186	1160±121	1342±136	7.9; p=0.047	3.7; p=3.68	0.8; p=0.49
Calorie intake (KJ/day)	11049	5640	7702	7250	4853	5614			
Macronutrient composition									
Protein (g)	91±22	60±9.2	77±12.0	92±11	50±6.6	91±13	0.5; p=0.53	2.1, p=0.19	0.7; p=0.51
Protein (%)	14±1.7	18±0.6	17±2.9	22±1.9	18±2.0	27±3.2	9.1; p=0.04	1.3; p=0.33	1.2; p=0.35
Carbohydrate (g)	290±53	150±17	193±32	164±14	137±15	118±14	28.4; p=0.01	1.6; p=0.25	1.3; p=0.32
Carbohydrate (%)	43±3	43±3.2	38±3.8	39±4.8	44±2.8	33±3.1	4.6; p=0.09	2.6; p=0.12	0.4; p=0.69
Fat (g)	114±23	59±12	87±6.9	70±11	48±6.9	58±9.3	6.4; p=0.07	4.6; p=0.05	0.7; p=0.50
Fat (%)	38±3	38±2.6	42±2.5	35±2.8	36±2.1	38±3.9	1.4; p=0.30	1.5; p=0.29	0.4; p=0.69
Other sources of energy									
Alcohol (%)	3.4±2.5	Nil	1.0±1.0	3.7±2.7	Nil	Nil	0.3; p=0.59	2.3; p=0.17	0.9; p=0.42
Fiber (%)	2.1±0.3	0.1±0.4	2.2±0.4	1.3±0.2	0.8±0.4	2.6±0.45	0.4; p=0.57	16.5; p=0.001	1.0; p=0.41

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA)

a F(1,4) for all parameters

b F(2,8) for all parameters

c F(2,8) for all parameters

Table 4-5 Two-way ANOVA Post hoc multiple comparisons of repeated measure for total calorie intake and macronutrient composition as assessed with 24-hr diet recalls.

	DJBL (n=10)			SMT (n= 10)			*Post hoc* pair-wise comparison, P value [a]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**	
Average daily intake (Kcal/day)	2641±485	1348±196	1841±156	1733±186	1160±121	1342±136	
Calorie intake (KJ/day)	11049	5640	7702	7250	4853	5614	
Macronutrient composition							
Protein (g)	91±22	60±9.2	77±12.0	92±11	50±6.6	91±13	
Protein (%)	14±1.7	18±0.6	17±2.9	22±1.9	18±2.0	27±3.2	
Carbohydrate (g)	290±53	150±17	193±32	164±14	137±15	118±14	
Carbohydrate (%)	43±3	43±3.2	38±3.8	39±4.8	44±2.8	33±3.1	
Fat (g)	114±23	59±12	87±6.9	70±11	48±6.9	58±9.3	
Fat (%)	38±3	38±2.6	42±2.5	35±2.8	36±2.1	38±3.9	
Other sources of energy							
Alcohol (%)	3.4±2.5	Nil	1.0±1.0	3.7±2.7	Nil	Nil	
Fiber (%)	2.1±0.3	0.1±0.4	2.2±0.4	1.3±0.2	0.8±0.4	2.6±0.45	SMT 10-days > SMT 6-months; p=0.01

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA) with Tuky post hoc multiple comparisons; a Only the significant findings are presented

4.3.2 3-Day food diaries

4.3.2.1 Attrition

At baseline data for 21 DJBL and 18 SMT patients were available for analysis. Due to non-compliance, withdrawal or not yet due for a follow-up visit, the numbers we reduced to 6 DJBL and 9 SMT at the 6-months follow up.

4.3.2.2 Baseline assessment

At Baseline, there were no significant differences in the total food intake and macronutrients composition between the two treatment groups in both the 'intention-to-treat-participants and in the 'study completers' (Table 4-6 A and B).

Table 4-6 (A and B) Baseline total calorie intake and macronutrient composition as assessed with 3-day food diaries

A) Intention-to-treat (DJBL n=21, SMT n=18)

	DJBL (n=21)	SMT (n=18)	P value
Total energy intake			
Calorie intake (Kcal/day)	1899±120	1983±216	0.72
Calorie intake (KJ/day)	7945	8296	
Macronutrient composition			
Protein (g)	85±4.9	80±4	0.46
Protein (%)	18±1.2	18±1.1	0.93
Carbohydrate (g)	199±14	196±12	0.90
Carbohydrate (%)	38±1.3	41±1.7	0.24
Fat (g)	82±6.9	74±5.4	0.42
Fat (%)	39±1.2	37±1.6	0.25
Other sources of energy			
Alcohol (%)	3.2±1.1	2.7±1.1	0.73
Fiber (%)	1.7±0.1	2±0.2	0.23

B) Completers analysis as per protocol (DJBL n=6, SMT n=9)

	DJBL (n=6)	SMT (n=9)	P value
Total energy intake (Kcal/day)			
Calorie intake (Kcal/day)	1967±279	1751±87	0.40
Calorie intake (KJ/day)	8229	7326	
Macronutrient composition			
Protein (g)	99±12	84±6.3	0.26
Protein (%)	21±3.2	19±1.8	0.62
Carbohydrate (g)	199±34	185±14	0.67
Carbohydrate (%)	37±3	39±2.5	0.60
Fat (g)	83±13	72±7.8	0.42
Fat (%)	37±1.4	36±2.4	0.64
Other sources of energy			
Alcohol (%)	2.7±1.2	3.6±1.8	0.70
Fiber (%)	2±0.3	2.1±0.2	0.76

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

4.3.2.1 10-days post-intervention

Intention-to-treat analysis (DJBL n=21, SMT n=18)

As assessed with 3-day food diaries, both the DJBL and SMT groups reduced their food intake close to 1200kcal (Table 4-7 A). The DJBL group reduced their energy intake from 1899±120 to 1132±78 ($p<0.0001$) and the SMT group reduced their energy intake from 1983±216 to 1247±64 ($p=0.01$) (Table 4-5 7).

The reduction in total calories was a result of a significant reduction in the grams of all the macronutrients CHO, protein and fat (Table 4-7 A).

The percentage macronutrient composition in the DJBL groups shows that the liquid diet was providing significantly more CHO 46±1.4% compared to baseline 38±1.3% ($p=0.0001$) and less fat 35±0.9% compared to 39±1.2% at baseline ($p=0.0004$). The percentage protein intake did not differ significantly between the two time-points. Similar to the DJBL group, the SMT also had an increase in their CHO as a percentage of their total energy intake; it was increased from 41±1.7 to 46±0.69 ($p=0.001$). On the other hand, the liquid diet was providing significantly less protein compared to their baseline intake ($p=0.01$). The percentage of fat did not differ significantly between the two time-points (Table 4-7 A).

Percentage of alcohol intake was significantly reduced in the SMT but not in the DJBL group. Percentage of fibre intake was significantly reduced in both groups while at the liquid diet (Table 4-7 A).

Completers analysis as per protocol (DJBL n=6, SMT n=9)

The change in total energy intake of the study completers (Table 4-7 B) was inline with data of the 'intention-to-treat' that are presented in table 4-7 A and outlined above. In addition, the trend of change in the macronutrients composition was also inline with the change in

the ‘intention-to-treat-participants that are presented in table 4-7 A. However, the data did not reach statistical difference in most of the parameters except for grams of protein (p=0.01) and fat (p=0.02) in the DJBL group and grams of protein (p=0.001) in the SMT group. Also, similar to the ‘intention to treat participants’, the percentage carbohydrates intake was significantly increased in both groups.

Table 4-7 (A and B) Change in total calorie intake and macronutrient composition at 10-days post-intervention

A) Intention-to-treat analysis (DJBL n=21, SMT n=18)

	DJBL (n=21)			SMT (n= 18)		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Total energy intake						
Calorie intake (Kcal/day)	1899±120	1132±78	<0.0001	1983±216	1247±64	0.01
Calorie intake (KJ/day)	7945	4736		8296	5217	
Macronutrient composition						
Protein (g)	85±4.9	54±5	<0.0001	80±4	49±2.3	<0.0001
Protein (%)	18±1.2	19±1.5	0.61	18±1.1	16±0.24	0.01
Carbohydrate (g)	199±14	136±11	0.001	196±12	154±8.5	0.02
Carbohydrate (%)	38±1.3	46±1.4	0.0001	41±1.7	46±0.69	0.001
Fat (g)	82±6.9	43±3.5	<0.0001	74±5.4	52±2.8	0.001
Fat (%)	39±1.2	35±0.9	0.0004	37±1.6	38±0.58	0.74
Other sources of energy						
Alcohol (%)	3.2±1.1	0.5±0.45	0.06	2.7±1.1	Nil	0.03
Fiber (%)	1.7±0.1	0.8±0.19	0.001	2±0.2	0.3±0.09	<0.0001

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

B) Completers analysis as per protocol (DJBL n=6, SMT n=9)

	DJBL (n=6)			SMT (n= 9)		
	Baseline	**10-days**	**P value**	**Baseline**	**10-days**	**P value**
Total energy intake (Kcal/day)						
Calorie intake (Kcal/day)	1967±279	1228±87	0.02	1751±87	1304±102	0.01
Calorie intake (KJ/day)	8229	5137		7326	5455	
Macronutrient composition						
Protein (g)	99±12	62±9.4	0.01	84±6.3	51±3.3	0.001
Protein (%)	21±3.2	21±3.5	0.85	19±1.8	16±0.42	0.05
Carbohydrate (g)	199±34	144±15	0.07	185±14	164±13	0.25
Carbohydrate (%)	37±3	44±2.6	0.049	39±2.5	47±0.52	0.01
Fat (g)	83±13	44±2.5	0.02	72±7.8	53±4.5	0.07
Fat (%)	37±1.4	33±1.8	0.04	36±2.4	37±0.56	0.64
Other sources of energy						
Alcohol (g)	2.7±1.2	1.5±1.5	0.56	3.6±1.8	Nil	0.08
Fiber (%)	2.0±0.3	1.0±0.37	0.11	2.1±0.2	0.3±0.14	0.0003

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

4.3.2.2 6-months post intervention

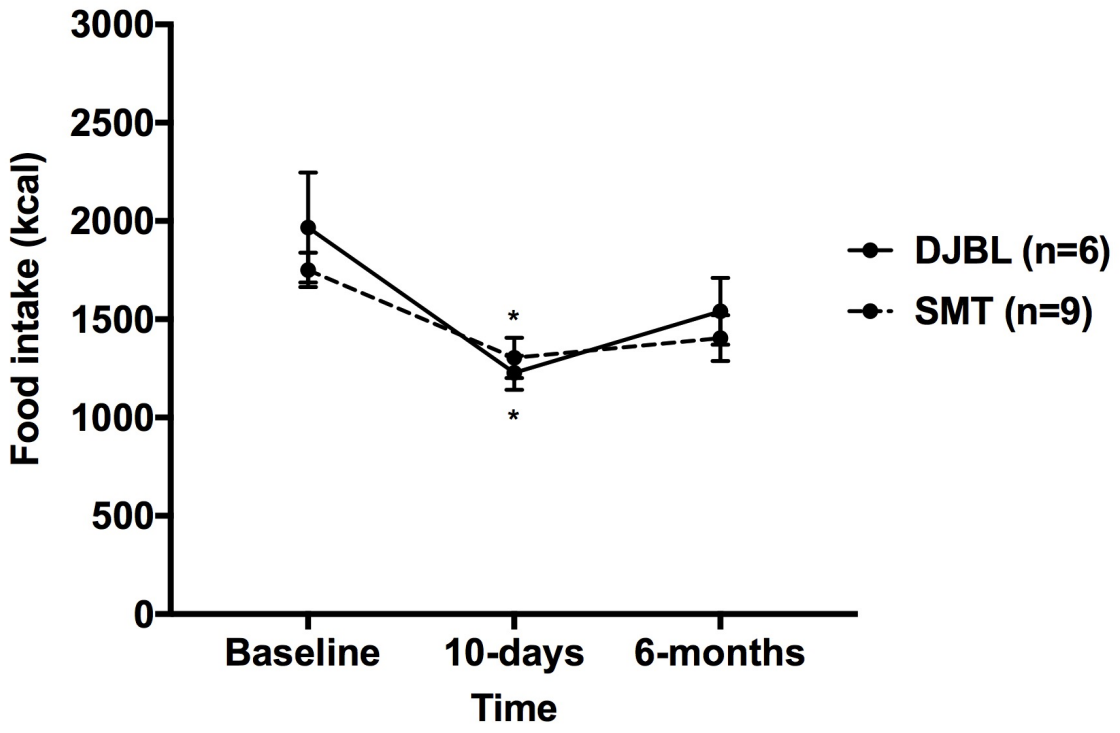
4.3.2.2.1 One-way ANOVA

As assessed with the 3-day food diaries, both groups significantly reduced their total calorie intake at the 10-days post intervention visit, which was then elevated at the 6-months post intervention visit but remained lower than baseline, albeit not significantly (Figure 14).

In the DJBL group, the energy intake went down from 1967±279 kcal/day at baseline to 1228±87 kcal/day at 10-days and then it rose up to 1540±170 kcal/day (overall ANOVA 0.014; Baseline > 10-days; p=0.03). Whereas the total calorie intake per day in the SMT went down from 1751±87 kcal/day at baseline to 1304±102 and rose up to 1405±117 (overall ANOVA p=0.013; Baseline > 10-days; p=0.013) (Table 4-8).

In the DJBL group, the consumption of protein was significantly higher at 6-months post intervention compared to 10-days post intervention but not to baseline (Baseline > 6-months; p=0.01). In the SMT group, the grams and percentage of protein intake increased from 10-days to 6-months post intervention (6-months > 10-days; p=0.04) but was not significantly different compared to baseline (Table 4-8).

Figure 14 Reduction in food intake over the 6-months period as assessed with 3-days food diaries



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with one-way ANOVA and Pair-wise post hoc ANOVA comparisons were performed using Tukey multiple comparison correction testing. Data defined significant at $p < 0.05$

Table 4-8 Total calorie intake and macronutrient composition at 10-days and 6-months follow-up for the DJBL and SMT completers as assessed with 3-days food diaries

	Baseline	10-days	6-months	Overall ANOVA P value	*Post hoc* pair-wise comparison, P value
DJBL (n=6)					
Total energy intake					
Calorie intake (Kcal/day)	1967±279	1228±87	1540±170	0.01	Baseline > 10-days; p=0.03
Calorie intake (KJ/day)	8229	5388	6443		
Macronutrient composition					
Protein (g)	99±12.0	62±9.4	84±13.0	0.01	Baseline > 10-days; p=0.02 Baseline > 6-months; p=0.01
Protein (%)	21±3.2	21±3.5	22±3.2	0.74	
Carbohydrate (g)	199±34.0	144±15.0	157±23.0	0.11	
Carbohydrate (%)	37±3.0	44±2.6	37±2.5	0.10	
Fat (g)	83±13.0	44±2.5	63±8.2	0.02	Baseline > 10-days; p=0.048
Fat (%)	37±1.4	33±1.8	36±2.2	0.12	
Other sources of energy					
Alcohol (%)	2.7±1.2	1.5±1.5	3.1±1.4	0.51	
Fiber (%)	2±0.3	1±0.37	2.2±0.2	0.06	
SMT (n=9)					
Total energy intake					

	Baseline	10-days	6-months	Overall ANOVA P value	*Post hoc* pair-wise comparison, P value
Calorie intake (Kcal/day)	1751±87	1304±102	1405±117	0.01	Baseline > 10-days; p=0.013
Calorie intake (KJ/day)	7326	5455	5878		
Macronutrient composition					
Protein (g)	84±6.3	51±3.3	89±12.0	0.03	Baseline > 10-days; p=0.002 6-months > 10-days; p=0.04
Protein (%)	19±1.8	16±0.4	25±3.1	0.04	6-months > 10-days; p=0.036
Carbohydrate (g)	185±14	164±13.0	145±21.0	1.71	
Carbohydrate (%)	39±2.5	47±0.5	37±4.5	0.07	
Fat (g)	72±7.8	53±4.5	53±8.2		
Fat (%)	36±2.4	37±0.6	34±4.3	0.60	
Other sources of energy					
Alcohol (%)	3.6±1.8	Nil	1.4±0.96	0.1	
Fiber (%)	2.1±0.2	0.3±0.1	2.3±0.2	<0.0001	Baseline > 10-days; p=0.001 6-months > 10-days; p=0.0001

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). Data within groups were compared with one-way ANOVA and Pair-wise post hoc ANOVA comparisons were performed using Tukey multiple comparison correction testing. Data defined significant at $p < 0.05$

4.3.2.2.1 Two-way ANOVA

Two-way repeated measures ANOVA was used to compare between DJBL and SMT at multiple time-points. As an extension, within group comparisons are also presented in this section as assess with two-way ANOVA (Table 4.9).

Treatment type only had a significant impact on the alcohol consumption. However, post hoc analysis revealed no significant difference between and within groups (Table 4.9).

Time had a significant impact on calorie intake, grams of protein, grams of fiber, percentage protein, and percentage fat (Table 4.9).

There was no impact of (Time X Treatment) on any of the measured parameters (Table 4.9).

Post hoc analysis revealed a significant difference between 10-days and 6-months percentage intake of protein in the SMT group (SMT 6-months > SMT 10-days; p=0.04), grams of fat intake in the SMT group (SMT Baseline > SMT 6-months; p=0.04); and fibre intake also in the SMT group (SMT 6-months > SMT 10-days; p=0.03). There were significant differences between groups at any time point for any parameter (Table 4.10).

Table 4-9 Two-way ANOVA results for total calorie intake and macronutrient composition at 10-days and 6-months follow-up for the DJBL and SMT completers as assessed with 3-day diet recall

	DJBL (n=6)			SMT (n= 9)			Treatment F; P [a]	Time F; P [b]	Treatment X Time F; P[c]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**			
Calorie intake (Kcal/day)	1967±279	1228±87	1540±170	1751±87	1304±102	1405±117	0.6; p=0.47	12.5; p=0.001	1.4; p=0.23
Calorie intake (KJ/day)	8229	5388	6443	7326	5455	5878			
Macronutrient composition									
Protein (g)	99±12.0	62±9.4	84±13.0	84±6.3	51±3.3	89±12.0	0.07; p=0.8	12.0; p=0.002	0.8; p=0.47
Protein (%)	21±3.2	21±3.5	22±3.2	19±1.8	16±0.4	25±3.1	0.04; p=0.84	4.9; p=0.03	2.8; p=0.10
Carbohydrate (g)	199±34.0	144±15.0	157±23.0	185±14	164±13.0	145±21.0	0.4; p=0.6	2.6; p=0.12	1.0; p=0.39
Carbohydrate (%)	37±3.0	44±2.6	37±2.5	39±2.5	47±0.5	37±4.5	0.01; p=0.9	6.9; p=0.01	0.3; p=0.74
Fat (g)	83±13.0	44±2.5	63±8.2	72±7.8	53±4.5	53±8.2	1.6; p=0.27	6.4; p=0.02	4.0; p=0.05
Fat (%)	37±1.4	33±1.8	36±2.2	36±2.4	37±0.6	34±4.3	0.1; p=0.74	0.2; p=0.79	1.6; p=0.24
Other sources of energy									
Alcohol (%)	2.7±1.2	1.5±1.5	3.1±1.4	3.6±1.8	Nil	1.4±0.96	0.003; p=0.96	3.0; p=0.10	1.8; p=0.20
Fiber (%)	2±0.3	1±0.37	2.2±0.2	2.1±0.2	0.3±0.1	2.3±0.2	2.7; p=0.16	22.7; p=0.0002	0.6; p=0.6

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA); a F(1,5) for all parameters; b F(2,10) for all parameters; c F(2,10) for all parameters

Table 4-10 Two-way ANOVA Post hoc multiple comparisons of repeated measure for total calorie intake and macronutrient composition as assessed with 3-day diet recall

	DJBL (n=10)			SMT (n= 10)			*Post hoc* pair-wise comparison, P value [a]
	Baseline	**10-days**	**6-months**	**Baseline**	**10-days**	**6-months**	
Calorie intake (Kcal/day)	1967±279	1228±87	1540±170	1751±87	1304±102	1405±117	DJBL Baseline > DJBL 10-days; p=0.007
Calorie intake (KJ/day)	8229	5388	6443	7326	5455	5878	
Macronutrient composition							
Protein (g)	99±12.0	62±9.4	84±13.0	84±6.3	51±3.3	89±12.0	
Protein (%)	21±3.2	21±3.5	22±3.2	19±1.8	16±0.4	25±3.1	SMT 6-months > SMT 10-days; p=0.04
Carbohydrate (g)	199±34.0	144±15.0	157±23.0	185±14	164±13.0	145±21.0	
Carbohydrate (%)	37±3.0	44±2.6	37±2.5	39±2.5	47±0.5	37±4.5	
Fat (g)	83±13.0	44±2.5	63±8.2	72±7.8	53±4.5	53±8.2	DJBL Baseline > 10-days; p=0.003 SMT Baseline > SMT 6-months; p=0.04
Fat (%)	37±1.4	33±1.8	36±2.2	36±2.4	37±0.6	34±4.3	
Other sources of energy							
Alcohol (%)	2.7±1.2	1.5±1.5	3.1±1.4	3.6±1.8	Nil	1.4±0.96	
Fiber (%)	2±0.3	1±0.37	2.2±0.2	2.1±0.2	0.3±0.1	2.3±0.2	SMT 6-months > SMT 10-days; p=0.03

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA) with Tuky post hoc multiple comparisons; a Only the significant findings are presented

4.3.3 Food preferences

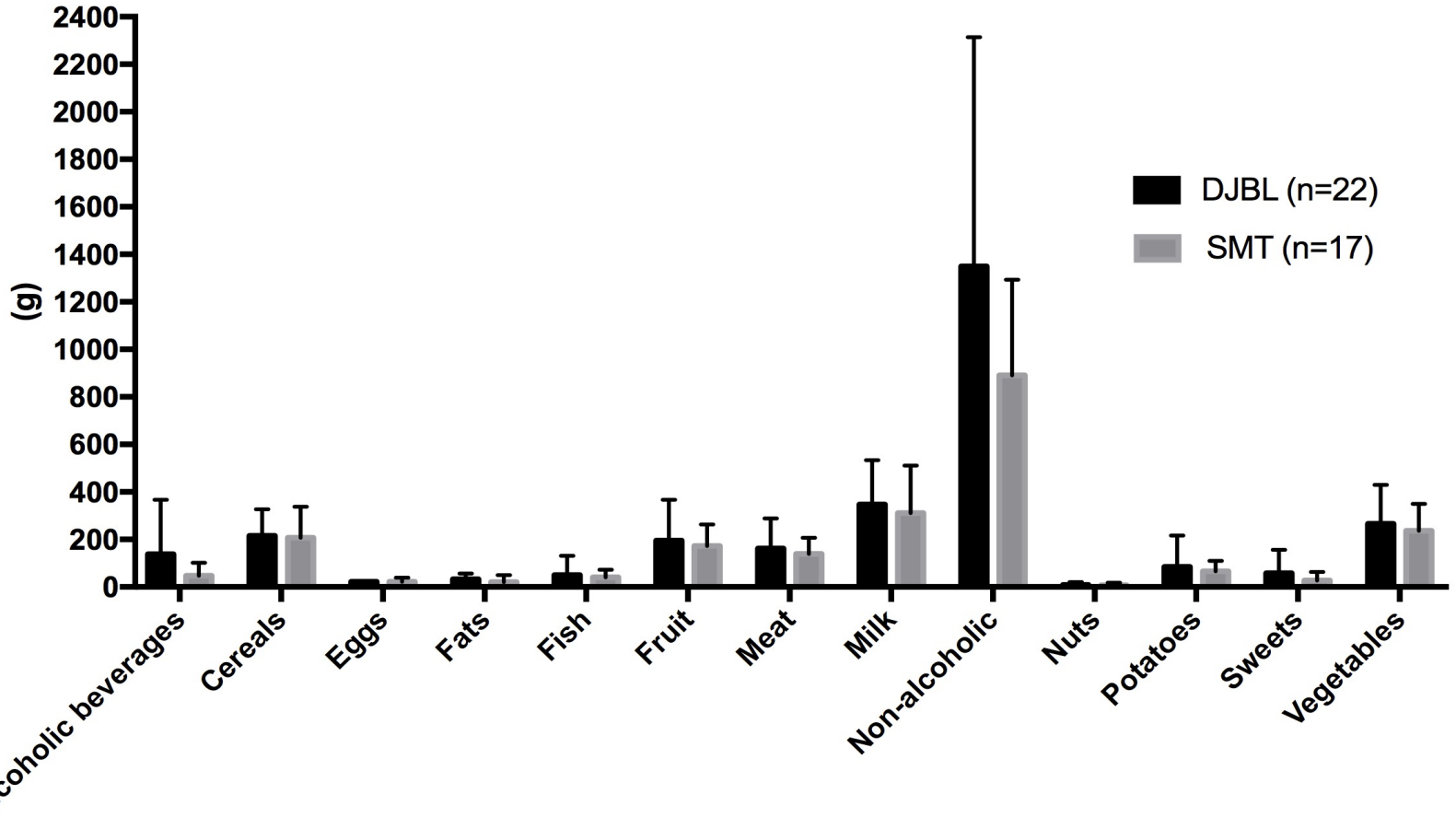
4.3.3.1 Baseline assessment

The baseline food preferences are shown in Figure 15 (A and B). There were no significant differences in the intake of any food categories between the intention-to-treat DJBL and SMT (Figure 15 A).

In the completers analysis as per protocol, fish intake at baseline was significantly higher in the SMT compared to the DJBL group (p=0.02) (Figure 15 B).

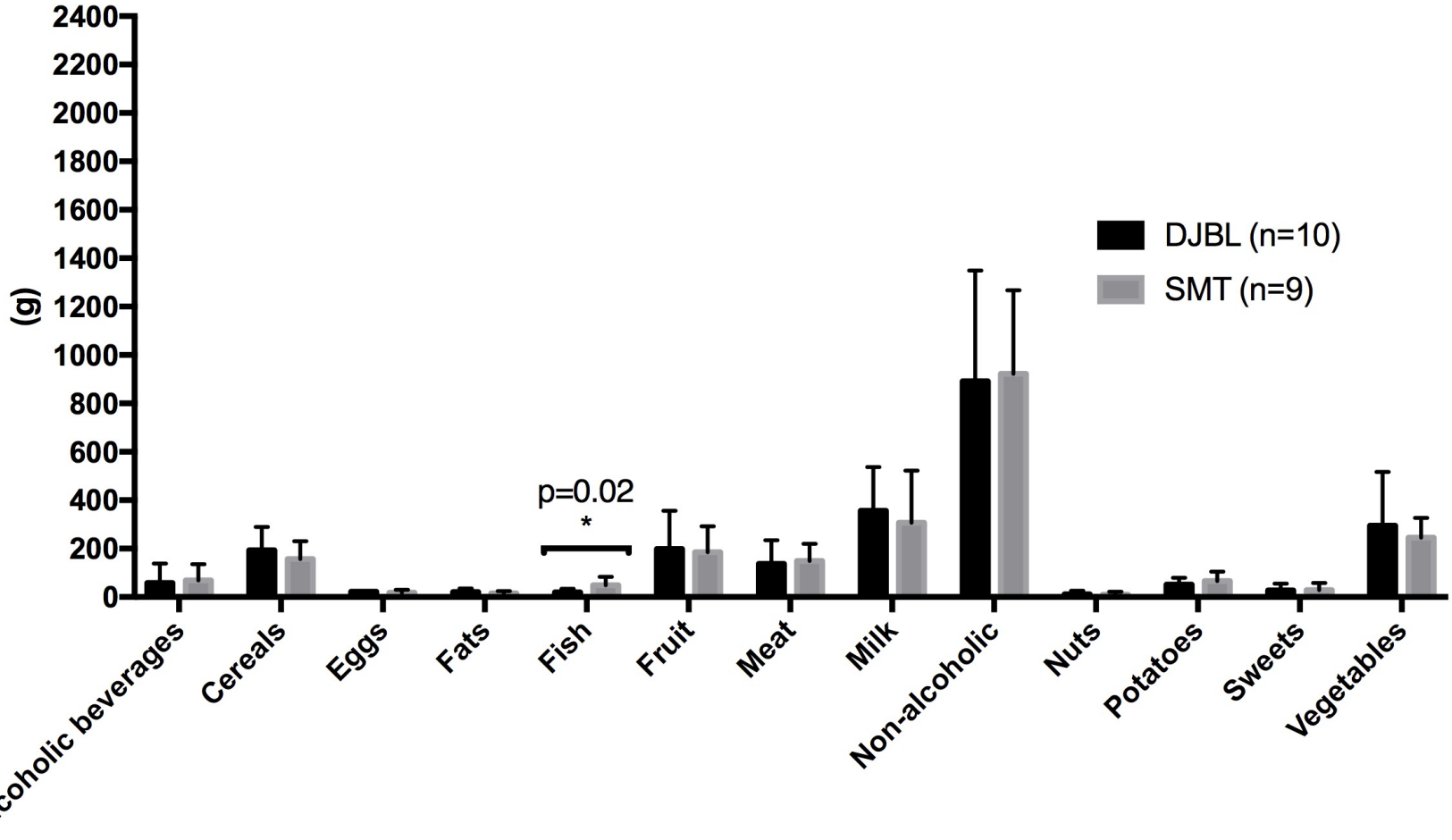
Figure 15 (A and B) Baseline food preferences

A) Intention-to-treat analysis (DJBL n=22, SMT n=17)



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

B) Completers analysis as per protocol (DJBL n=10, SMT n=9)



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

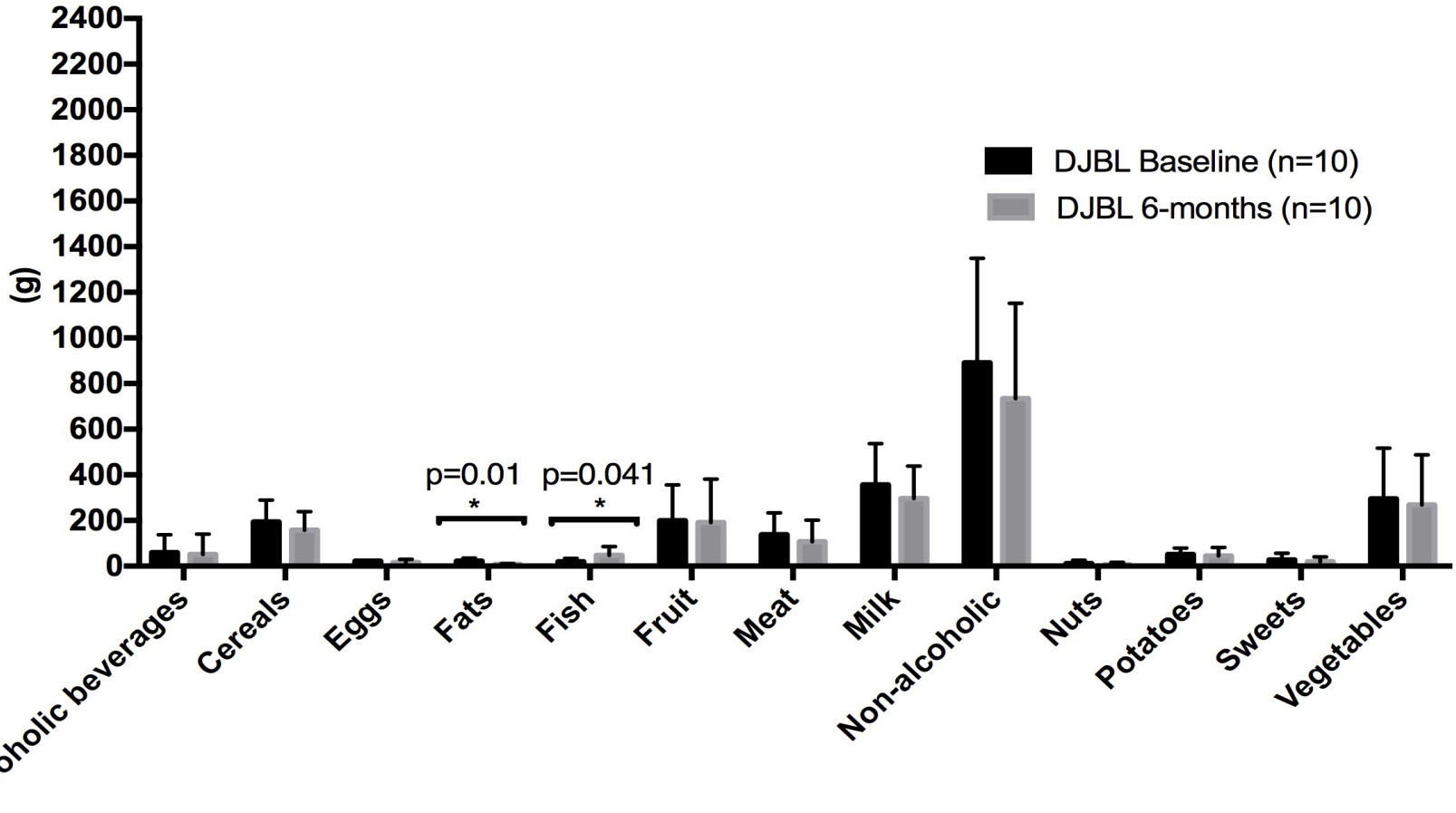
1.1.1.1 6-months post intervention

4.3.3.1.1 Paired T-test

The DJBL group reduced their intake of food high in fats and oils from 21.3±4.3g to 7.4±1.5g (p=0.01) and increased their fish intake from 19.0±4.7g to 46.7± 12.4g (p=0.041) (Figure 16 A). The SMT had no significant change in any of the food groups (Figure 16 B).

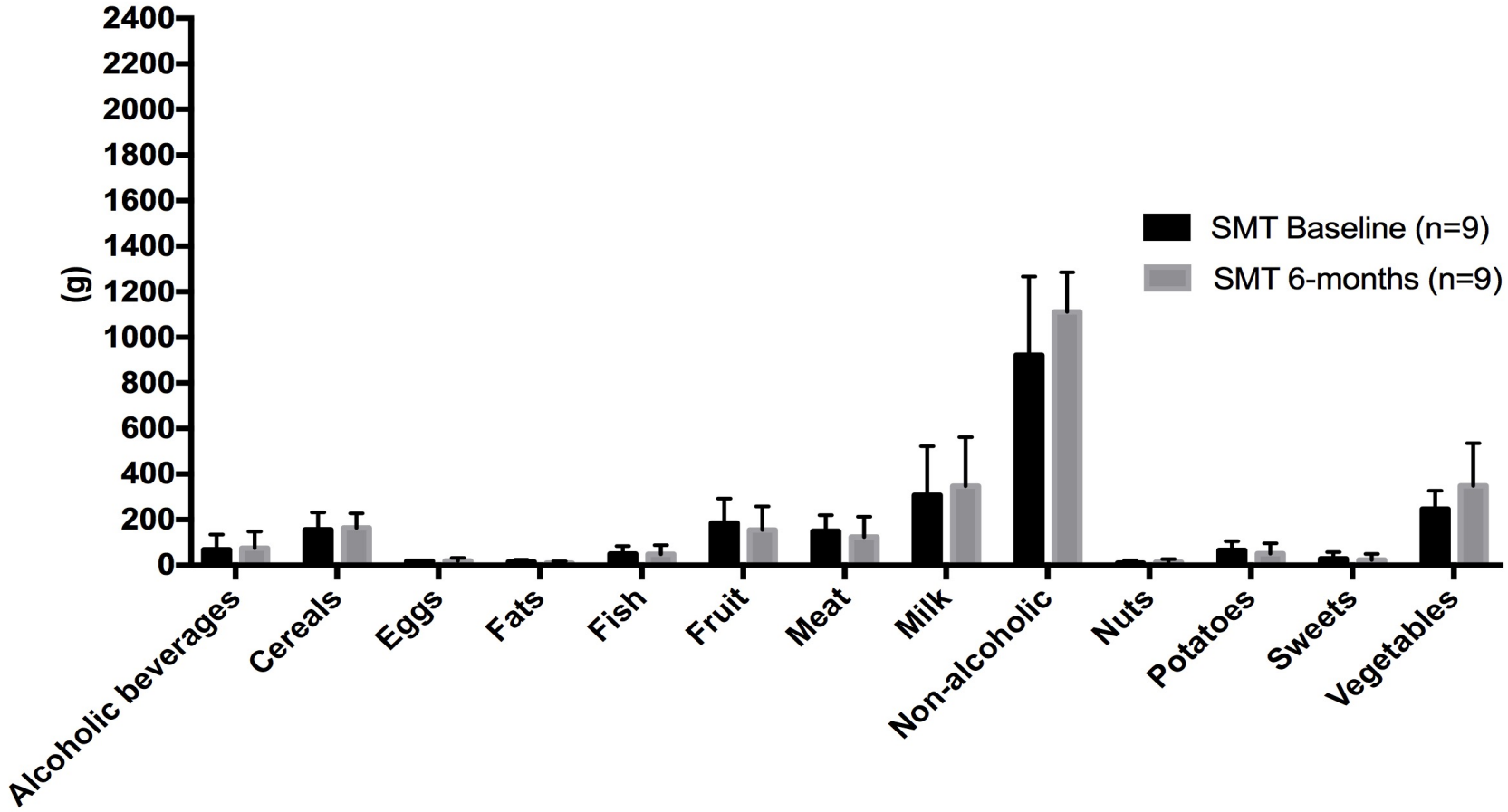
Figure 16 (A and B) Food preferences at baseline and 6-months post intervention

A) DJBL group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with paired *t*-tests. Data defined significant at $p<0.05$

B) SMT group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with paired *t*-tests. Data defined significant at $p<0.05$

4.3.3.1.2 Two-way ANOVA

Two-way repeated measures ANOVA was used to compare between DJBL and SMT at baseline and 6-months post intervention. As an extension, within group comparisons are also presented in this section as assess with two-way ANOVA (Table 4.11).

(Treatment) had no significant impact on any food item (Table 4.11).

There was a significant impact of (Time) on the intake of fats intake (p=0.02) (Table 4.11). Post hoc analysis revealed a significant difference between baseline intake and 6-months post intervention intake of fat in the DJBL group (p=0.045) (Table 4.12).

There was an impact of (Time X Treatment) on fish and non-alcoholic beverages. Post hoc analysis revealed a significant difference between the two groups at baseline for the consumption of fish with the SMT groups consuming significantly more. At 6-months post intervention the DJBL group significantly increased their intake of fish but there was significant difference between the two groups at 6-months post intervention (Table 4.12). In terms of the non-alcoholic beverages, the SMT groups consumed significantly more non-alcoholic beverages than the DJBL group at 6-months post intervention, but there were no other differences within groups or between groups at baseline (Table 4.12).

Table 4-11 Two-way ANOVA results for food preferences at baseline and 6-months post intervention

	DJBL (n=10)		SMT (n= 9)		Treatment F; P [a]	Time F; P [b]	Treatment X Time F; P[c]
	Baseline	6-months	Baseline	6-months			
Alcoholic beverage	59±25	52±28	69±22	76±24	0.10; p=0.76	0.0001; p=0.99	0.15; p=0.71
Cereal	194±30	158±26	157±25	164±21	0.05; p=0.82	0.18; p=0.68	1.11; p=0.32
Eggs	22±4.4	16±4.7	17±4.3	20±4.4	0.03; p=0.86	0.16; p=0.70	2.58; p=0.15
Fats	21±4.3	7.4±1.5	15±3.3	9.6±2.7	0.63; p=0.45	8.66; p=0.02	1.71; p=0.23
Fish	19±4.7	47±12	49±12	48±14	0.72; p=0.42	1.93; p=0.20	26.2; p=0.0009
Fruit	199±50	191±60	186±36	155±35	0.24; p=0.63	0.54; p=0.48	0.17; p=0.69
Meat	137±31	107±30	150±23	124±30	0.05; p=0.82	1.31; p=0.28	0.010; p=0.92
Milk	357±57	296±45	307±72	347±72	0.03; p=0.86	0.03; p=0.86	0.72; p=0.42
Non-Alcoholic beverage	892±145	734±132	922±115	1112±58	2.20; p=0.18	0.16; p=0.70	5.50; p=0.047
Nuts	11±4.7	6.1±3.3	10±4.1	14±4.4	0.16; p=0.70	0.05; p=0.83	2.28; p=0.17
Potatoes	51±9	44±12	66±13	51±15	0.34; p=0.58	0.87; p=0.38	0.47; p=0.51
Sweets	27±9.2	20±6.5	29±9.8	24±8.5	0.03; p=0.87	3.10; p=0.12	0.01; p=9.10
Vegetables	295±70	268±70	246±27	349±62	0.001; p=0.98	1.24; p=0.30	1.95; p=0.20

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA); a F(1,8) for all parameters; b F(1,8) for all parameters; c F(1,8) for all parameters

Table 4-12 Two-way ANOVA Post hoc multiple comparisons of repeated measure for anthropometric measurements

	DJBL (n=10)		SMT (n= 9)		*Post hoc* pair-wise comparison, P value [a]
	Baseline	**6-months**	**Baseline**	**6-months**	
Alcoholic beverage	59±25	52±28	69±22	76±24	
Cereal	194±30	158±26	157±25	164±21	
Eggs	22±4.4	16±4.7	17±4.3	20±4.4	
Fats	21±4.3	7.4±1.5	15±3.3	9.6±2.7	DJBL Baseline > DJBL 6-months; p=0.045
Fish	19±4.7	47±12	49±12	48±14	SMT Baseline > DJBL Baseline; p=0.0006 DJBL 6-months > DJBL Baseline; p=0.0005
Fruit	199±50	191±60	186±36	155±35	
Meat	137±31	107±30	150±23	124±30	
Milk	357±57	296±45	307±72	347±72	
Non-Alcoholic beverage	892±145	734±132	922±115	1112±58	SMT 6-months > DJBL 6-months; p=0.019
Nuts	11±4.7	6.1±3.3	10±4.1	14±4.4	
Potatoes	51±9	44±12	66±13	51±15	
Sweets	27±9.2	20±6.5	29±9.8	24±8.5	
Vegetables	295±70	268±70	246±27	349±62	

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; Between and within groups analysis were performed with Two-way (ANOVA) with Tuky post hoc multiple comparisons.

a Only the significant findings are presented

4.4 Discussion

In this chapter, I found that treatment with the DJBL did not have a superior affect on food intake or food preferences over a SMT during a 6-months treatment in obese, type 2 diabetic patients. This study is unique in that it is the first to compare the DJBL device to another group that also has an excellent medical and dietary intervention, identical to the one received by the treatment group, in a randomised controlled trial.

The short-term food intake data reflected on the adherence to the liquid diet phase of the study. Both groups consumed the recommended 1200-1500kcal/day from Fortisips liquid diet during the first 10-days post-intervention.

Both groups reported to consume less calories at 6-months post-intervention compared to baseline, although this was only significantly different in the SMT. The diet advice that was provided to both groups, equally, consisted of a calorie deficit of 600kcal/day. According to the reported food intake, the DJBL adhered better to this advice than did the SMT patients. However, verbal reporting of food intake is notoriously known to be an unreliable method of measuring food intake (469), particularly in the overweight and obese populations (470, 471). This is evidenced by the fact that there were no correlations between the reported change in food intake and weight loss in both groups.

One of the most challenging aspects of the science and practice of nutrition and dietetics is the measurement of energy and nutrient intakes, given the limitations of the methods to correctly measure food intake (472). Therefor, despite the unreliability of the indirect measurements of food intake, this study was an important step towards determining whether there is a need to take the investigation of the affect of DJBL on food intake further by the use of a buffet meal study (a direct measure). Buffet meal studies are more accurate and reliable but they are less efficient.

One of the benefits of running human clinical studies is grasping on information that may be missed and not collected with questionnaires or animal studies. Anecdotal reports of some, but not all, DJBL patients from the clinical visits of this study suggested that DJBL might

result in faster satiety during meal consumption resulting in an earlier termination of a meal and smaller portion sizes thus reduced food intake. DJBL leads to the bypass of the proximal small bowel, which as a result alters bile flow. Bile induces the release of appetite suppressant hormone GLP-1 (466, 467), causing reduced gastric emptying and reduced food intake. Whether the anecdotal reports are of a clinical significance or not, this can be determined by measuring postprandial gut hormones in future studies. In addition, as discussed in the previous chapter, it is possible that the SMT participants felt more under pressure to control their weight with lifestyle interventions and adhered very well to the diet component of the intervention as oppose to the DJBL device participants which relied more on the presumed benefits of the device resulting in equal changes in calorie intake. It has been previously suggested that DJBL produces it's effects on weight loss and diabetes improvements regardless of patient's conscious efforts to control their food intake or lifestyle (465).

It was hypothesised that DJBL patients may have a conditional avoidance to high GI carbohydrates and fatty food so they may shift towards consuming more protein and lower GI carbohydrates and more fruits and vegetables, similar to the changes observed post RYGB. The results of this chapter, particularly from that collected from the Food Frequency Questionnaire (FFQ), suggests a possible but not a definite change in food preferences. In this study, we found that DJBL patients consumed less food items containing fats and oils and more fish and fish products. However, even though the change was significantly different, it was not high enough to predict a change in food preferences. In addition, the percentage macronutrients composition of the total food intake was not consisting with the changes observed in the FFQ, suggesting a possible type-2-error.

The main limitations of this study include the use of unweighed, self-reported food intake measures which practically result in a biased, under-reporting of real energy intake (473). On the other hand, one of the strengths is the use of two methods, one-retrospective (24-hr diet recall) and one-prospective (3-days food diary), to estimate food intake.

To conclude, this is the first study looking at the affect of DJBL on food intake and food preferences in humans adding to the pool of evidence investigating the bypass of the proximal small bowel. We suggest that the bypass of the proximal small bowel does not result in changes in food intake and only modest changes in food preferences. The changes

that occur post RYGB may be a result of a different component of the operation or an additive effect of the profound changes of the GI tract.

CHAPTER 5 AIM TWO: THE EFFECT OF DJBL ON EATING BEHAVIOUR

5 Eating behaviour

5.1 Introduction

The term eating behaviour describes our relationship with food and it's characterised by physiological, psychological and social forces that are integrated in the brain and determine not only how much we eat, but also what, when, and how we eat (1). Psychological disorders such as depression and anxiety are very often prevalent amongst the obese population (474) and such disorders can potentially complicate the treatment of obesity (475).

Bariatric surgery and particularly RYGB has become an increasingly popular treatment option for individuals with obesity, as sustained post-operative weight loss and improvements in obesity-related comorbidities make it the most effective treatment for this population (476). The Endoluminal Duodeno-jejunal Bypass Liner or EndoBarrier® (DJBL) (GI Dynamics, Lexington, Massachusetts, USA) is a novel medical device currently being used for the treatment of T2DM and obesity (441). The DJBL aims to mimic the intestinal bypass and possibly components of the restrictive effects of Roux-en-y gastric bypass surgery without the need for stapling or anastomosis.

Only a limited number of studies have assessed eating behaviour in DJBL patients, and those have focused on verbally reported appetite and satiety (477), (478); and non have assessed the psychological or eating behaviour factors that determine those changes.

Tarnoff *et al.* (2009) were the first to report greater satiety after device implantation in a randomized controlled trial comparing low fat diet+EndoBarrier versus low fat diet only. Using satiety questionnaires, 17 out of 19 (90%) device subjects reported greater satiety at 12-weeks post-implant. Only one device subject reported less satiety than before the implantation, and one reported unchanged satiety (477). Similar results were seen in Lieberman *et al.* (2014) as they showed that VAS scores for feeding and hunger persistently reduced with greater weight loss over the 12 weeks of the study period (478). The increased level of satiety, however, is in contrast with the increased levels of ghrelin (447) and

unchanged (447) or reduced (479) levels of GLP-1 suggested to occur post EndoBarrier implantation.

The study of eating behaviour in humans, and the obese in particular, is challenging due to the effects of the social desirability bias (480), the variability of human nature itself and the behavioural experimental methodologies (83, 481, 482). A direct and comprehensive comparison of the effects of the DJBL and SMT, on eating behaviour has not been performed previously. Such a comparison is “ideal” from a scientific point of view, as patients in both groups lose weight and receive very similar dietary advice. Therefore any differences in eating behaviour between the groups would essentially exclude, or at the very least minimise, dietary advice and weight loss itself as confounders. Additionally, differential responses in neural and metabolic parameters between the two groups may provide clues as to the mechanisms underlying differences in eating behaviour.

5.2 Materials and method

5.2.1 Subjects

Forty-Two subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. SMT via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Psychological assessment was carried out 2-weeks before intervention (Baseline), and 6-months post intervention (long-term follow-up), whereas hunger and fullness ratings were carried out 2-weeks before intervention (Baseline), 10-days post intervention, and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

Subjects who completed the 6-months study period are referred to ‘study completers’, whereas those who have only finished their 10-days post intervention and are still to be due for their 6-months follow up visit are referred to as ‘intention-to-treat-participants’.

5.2.2 Psychological assessments

The following psychological questionnaires were used to assess for changes in psychological traits: Barratt Impulsivity Scale (BIS), Hospital Anxiety and Depression Scale (HADS), Beck Depression Inventory (BDI−II), Behavioural Inhibition and Activation System (BIS / BAS). Description of each questionnaire and their scoring ranges is described in detail in chapter two: Materials and Methods, section (2.4.4).

5.2.3 Eating behaviour assessments

The following eating behaviour questionnaires were used to assess for changes in eating styles and traits: Dutch Eating Behaviour Questionnaire (DEBQ), Three Factor Eating Questionnaire (TFEQ), The Power of Food Scale (PFS), Alcohol Use Disorders Identification Test (AUDIT). Description of each questionnaire is described in details in chapter two: Materials and Methods, section (2.4.4).

5.2.4 Hunger and appetite ratings

Assessment of hunger was carried out using Visual analogue scale (VAS). Description of the method used to apply the VAS is described in details in chapter two: Materials and Methods, section (2.4.4).

5.2.5 Statistical analysis

For the psychological and eating behaviour factors, data were compared 'between' groups at baseline using a parametric unpaired t-test. To compare baseline and 6-months follow-up data within each group a parametric paired t-test was performed. The data were normally distributed as assessed by D'Agostino & Pearson normality test and are therefore expressed as mean ± standard error of the mean (SEM).

Area under the curve (AUC) for hunger and fullness VAS ratings were calculated from T=0 to T=+180 minutes. The data were compared 'between' groups at baseline using a parametric unpaired t-test. To compare baseline and 10-days follow up data within each group a parametric paired t-test was performed. One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were performed to test for significant differences between pre- and post-operative repeated measures.

Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

5.3 Results

5.3.1 Attrition

All 42 recruited subjects (23 DJBL, 19 SMT) completed their baseline psychological assessment. However, only (21 DJBL and 19 SMT) were able to complete the hunger and fullness assessment as they were not suitable for the MMT study.

Due to the timelines of this thesis, only 25 subjects (12 DJBL, 13 SMT) were due for the 6-months post intervention visit by the time data had to be locked for analysis. In the DJBL group, two patients had the device removed prior to the 6-months follow-up visit, and in the SMT groups two subjects were lost to follow-up and 1 subject withdrew consent. Therefore, only a total of 20 subjects (10 DJBL, 10 SMT) were included in the 6-months follow-up data analysis.

5.3.2 Psychological and eating behaviour assessment

5.3.2.1 Baseline assessment

At Baseline, there were no significant differences in the psychological parameters and eating behaviour parameters between the two treatment groups neither in the ‘intention-to-treat analysis’ nor in the ‘completers analysis as per protocol’, as shown in table 5-1 (A and B, respectively).

Table 5-1 (A and B) Baseline psychological and eating behaviour characteristics of patients randomised to receive a DJBL or SMT

A) Intention-to-treat analysis (DJBL n=23, SMT n=19)

	DJBL (n=23)	SMT (n=19)	P value
Psychological parameters			
Impulsivity	57±4.3	59.5±4.1	0.68
HADS Anxiety	4.9±0.7	6.2±0.9	0.09
HADS Depression	3.8±0.6	5.4±0.9	0.14
BDI-II Severity of depression	8.5±1.4	10.4±1.8	0.39
BAS Drive	9.7±0.8	10.7±0.6	0.34
BAS Reward Responsiveness	14.5±1.0	16.0±0.6	0.35
BAS Fun-Seeking	10.3±0.8	11.3±0.5	0.23
BIS Aversive Motivation	17.5±1.4	20.4±0.7	0.08
Eating behaviour Parameters			
DEBQ Restraint	26.1±0.9	27.4±1.4	0.43
DEBQ Emotional	33.0±2.9	32.3±2.2	0.84
DEBQ External	31.9±1.1	31.3±0.7	0.67
TFEQ Hunger	6.9±0.9	5.8±0.7	0.36
TFEQ Cognitive Restraint	6.9±0.8	8.1±0.9	0.32
TFEQ Disinhibition	8.2±0.7	7.8±0.7	0.68
Power of food	3.3±0.3	3.1±0.2	0.55
Audit	4.4±0.7	3.2±0.7	0.25

B) Completers analysis as per protocol (DJBL n=10, SMT n=10)

	DJBL (n=10)	SMT (n=10)	P value
Psychological parameters			
Impulsivity	63.1±3.3	62.3±2.6	0.84
HADS Anxiety	4.5±0.9	6.4±3.2	0.17
HADS Depression	3.2±0.9	4.9±1.1	0.24
BDI-II Severity of depression	6.3±1.8	9.8±1.8	0.18
BAS Drive	10.6±0.6	10.4±0.6	0.79
BAS Reward Responsiveness	15.8±0.4	15.6±1.0	>0.99
BAS Fun-Seeking	11.0±0.7	11.0±0.7	0.88
BIS Aversive Motivation	19.5±0.8	19.8±0.8	0.79
Eating behaviour Parameters			
DEBQ Restraint	26.3±1.5	26.9±2.3	0.83
DEBQ Emotional	36.0±3.3	32.2±2.2	0.34
DEBQ External	32.3±1.5	31.0±1.0	0.46
TFEQ Hunger	6.2±1.3	6.3±0.8	0.96
TFEQ Cognitive Restraint	6.4±1.2	8.7±1.2	0.20
TFEQ Disinhibition	8.1±1.1	7.6±1.1	0.76
Power of food	3.6±0.4	3.2±0.4	0.43
Audit	4.9±0.9	3.9±1.0	0.45

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

1.1.1.1 6-months post-intervention

At 6-months post intervention, the SMT reported significantly lower depression levels as compared to baseline, 3.2±0.8 and 4.9±1.1, respectively (p=0.04), but this was not changed in the DJBL group. On the other hand, the reward responsiveness was significantly reduced from 15.8±0.4 to 15.1±0.3 (p=0.044) in the DJBL group but was not changed in the SMT (Table 5-2).

In terms of changes in eating behaviour, DEBQ restraint eating was increased in both groups from 26.3±1.5 to 32.8±0.9 (p= 0.01) in the DJBL group, and from 26.9±2.3 to 35.8±2.1 (p=0.004) in the SMT group. DEBQ emotion was lowered in the SMT but not DJBL group (p=0.02). DEBQ external was reduced in the DJBL group from 32.3±1.5 to 29.5±1.5 (p=0.02), similar trend of change occurred in the SMT but did not reach statistical difference (Table 5-2).

TFEQ cognitive restraint was increased in both groups but was only significantly higher in the DJBL group (p=0.003). On the other hand, disinhibition was lowered in both groups but only reached significance in the SMT group (p=0.01) (Table 5-2).

The power of food was lowered from 3.6±0.4 to 2.9±0.3 (p=0.03) in the DJBL. This was increased in the SMT from 3.2±0.4 to 3.5±0.4 but it just missed significance at (p=0.054) (table 5-2).

Table 5-2 Change in psychological and eating behaviour characteristics of patients randomised to receive a DJBL or SMT during a 6-months treatment period

	DJBL (n= 10)			SMT (n=10)		
	Baseline	**6-months**	**P-value**	**Baseline**	**6-months**	**P-value**
Psychological parameters						
Impulsivity	63.1±3.3	63.5±2.4	0.81	62.3±2.6	53.3±6.4	0.27
HADS Anxiety	4.5±0.9	5.2±0.8	0.19	6.4±3.2	4.3±0.9	0.10
HADS Depression	3.2±0.9	3.4±1.0	0.76	4.9±1.1	3.2±0.8	0.04
BDI-II Severity of depression	6.3±1.8	9.2±3.2	0.14	9.8±1.8	6.0±1.4	0.12
BAS Drive	10.6±0.6	9.7±0.6	0.07	10.4±0.6	9.0±1.4	0.26
BAS Reward Responsiveness	15.8±0.4	15.1±0.3	0.044	15.6±1.0	14.0±1.8	0.38
BAS Fun-Seeking	11.0±0.7	10.9±0.4	0.8	11.0±0.7	10.1±1.3	0.6
BIS Aversive Motivation	19.5±0.8	19.2±1.2	0.6	19.8±0.8	17.8±2.1	0.45
Eating behaviour Parameters						
DEBQ Restraint	26.3±1.5	32.8±0.9	0.01	26.9±2.3	35.8±2.1	0.004
DEBQ Emotional	36.0±3.3	37.8±4.6	0.65	32.2±2.2	27.8±2.4	0.02
DEBQ External	32.3±1.5	29.5±1.5	0.02	31.0±1.0	29.3±1	0.07
TFEQ Hunger	6.2±1.3	4.7±1.1	0.06	6.3±0.8	4.3±1.1	0.19
TFEQ Cognitive Restraint	6.4±1.2	13.1±0.8	0.003	8.7±1.2	11.5±1.7	0.22
TFEQ Disinhibition	8.1±1.1	7.1±1.3	0.29	7.6±1.1	5.0±0.7	0.01
Power of Food	3.6±0.4	2.9±0.3	0.03	3.2±0.4	3.5±0.4	0.054
Alcohol Audit	4.9±0.9	3.6±0.9	0.11	3.9±1.0	3.8±0.8	0.22

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

5.3.3 Appetite ratings

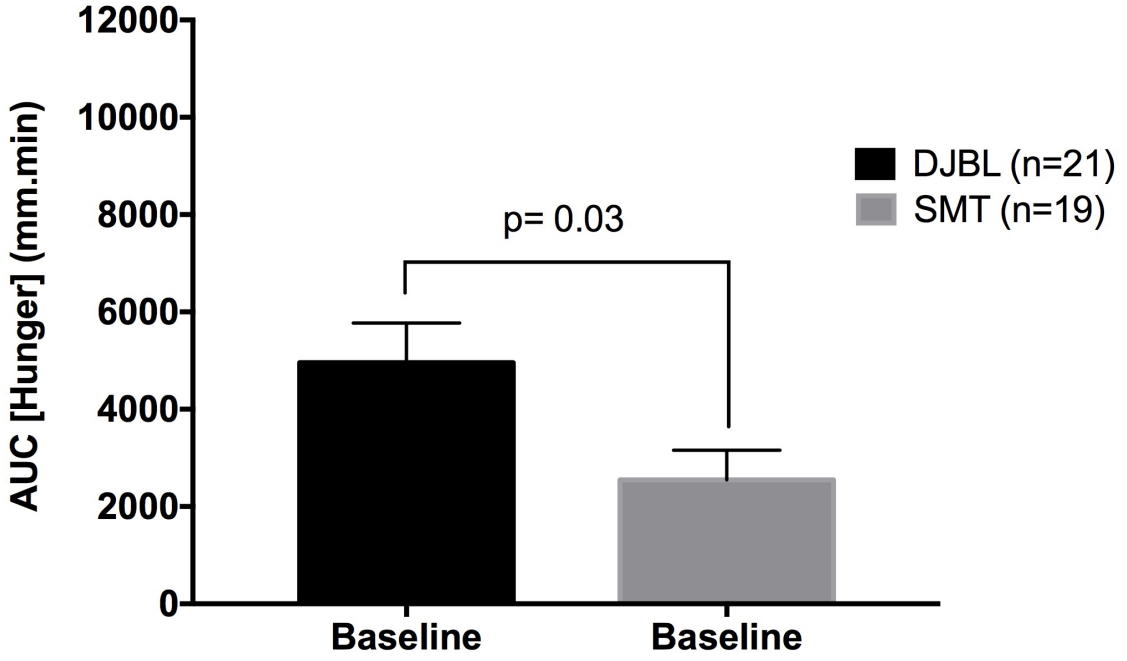
5.3.3.1 Baseline assessment

At baseline, the DJBL group reported that they were significantly hungrier than did the SMT group 4955±817.5mm.min compared to 2550±609.4mm.min, respectively (p=0.03) (Figure 17 A). However, this was not significantly different in the 'completers analysis as per protocol' with hunger level of 4920± 1116mm.min compared to 3221±1051mm.min in the DJBL and SMT groups, respectively (Figure 17 B).

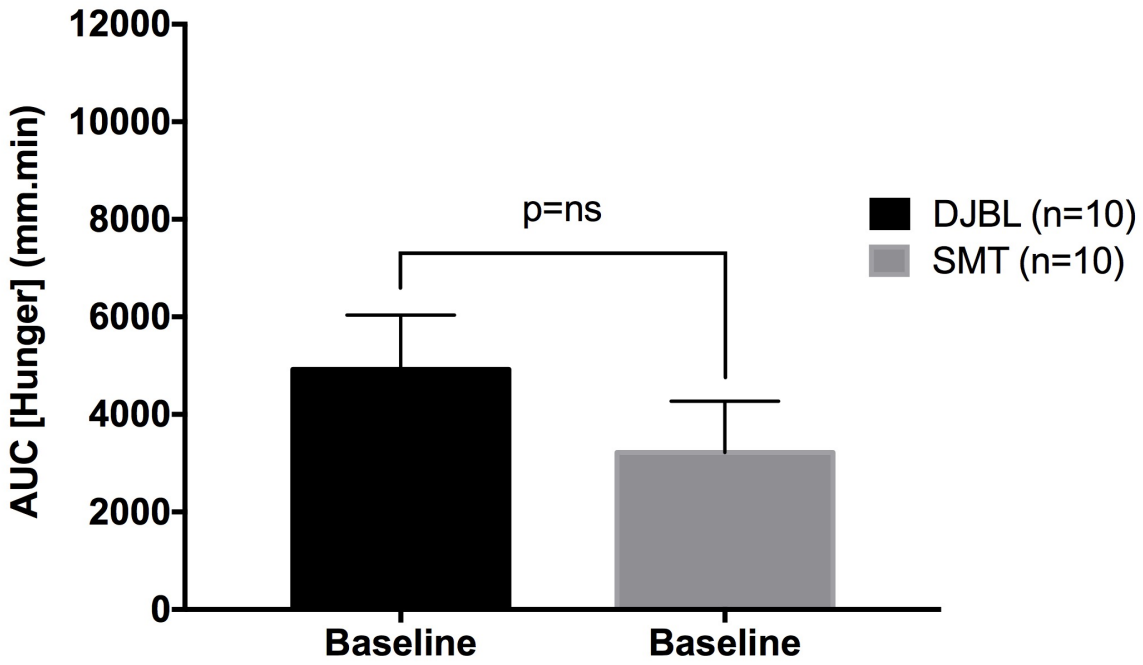
There were no significant differences in the reported fullness AUC levels in neither the 'intention to treat analysis' nor in the 'completers analysis as per protocol' (Figure 18 A and B).

Figure 17 (A and B) Baseline Area Under the Curve (AUC) for hunger ratings

A) Intention-to-treat analysis (DJBL n=21, SMT n=19)



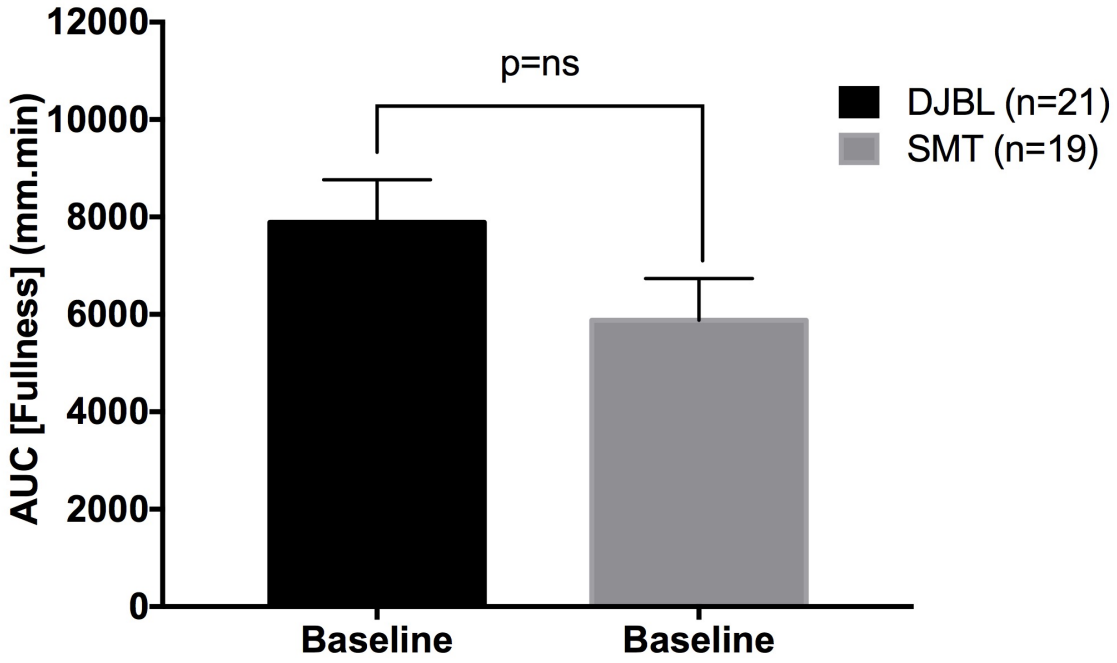
B) Completers analysis as per protocol (DJBL n=10, SMT n=10)



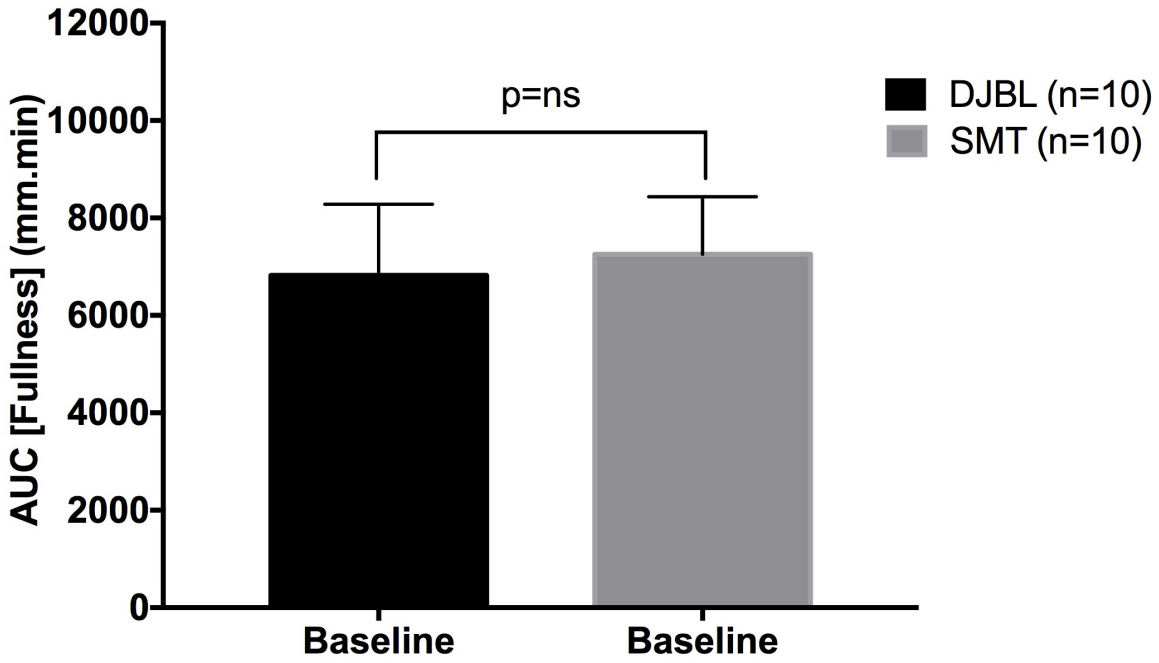
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

Figure 18 (A and B) Baseline Area Under the Curve (AUC) for fullness ratings

A) Intention-to-treat analysis (DJBL n=21, SMT n=19)



B) Completers analysis as per protocol (DJBL n=10, SMT n=10)



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

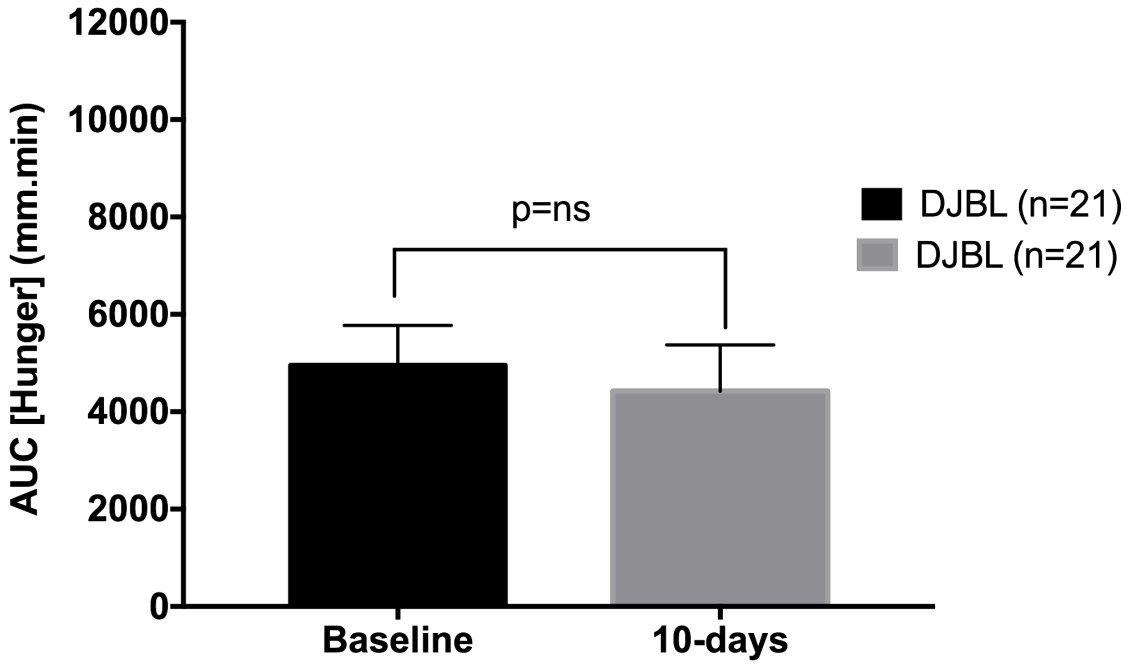
1.1.1.1 10-days post-intervention

During the liquid diet phase on the study (10-days post intervention) there was a trend towards a reduced hunger but this was not significantly different compared to baseline in neither the ‘intention to treat analysis’ nor in the ‘completers analysis as per protocol’ (Figure 19 A and B) and (Figure 20 A and B).

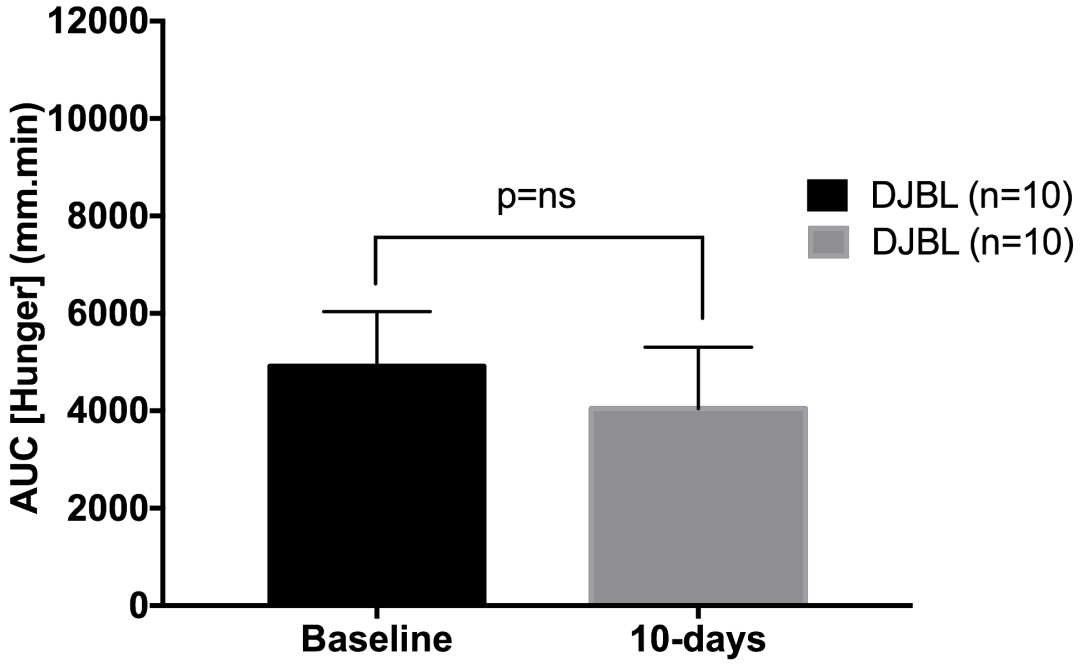
There was also a trend in increased reported fullness AUC in both DJBL and SMT therapy groups but this was not significantly different compared to baseline in neither the ‘intention to treat analysis’ nor in the ‘completers analysis as per protocol’ (Figure 21 A and B) and (Figure 22 A and B).

Figure 19 (A and B) Change in hunger ratings (AUC) at 10-days post intervention for DJBL patients

A) Intention-to-treat analysis (DJBL n=21)



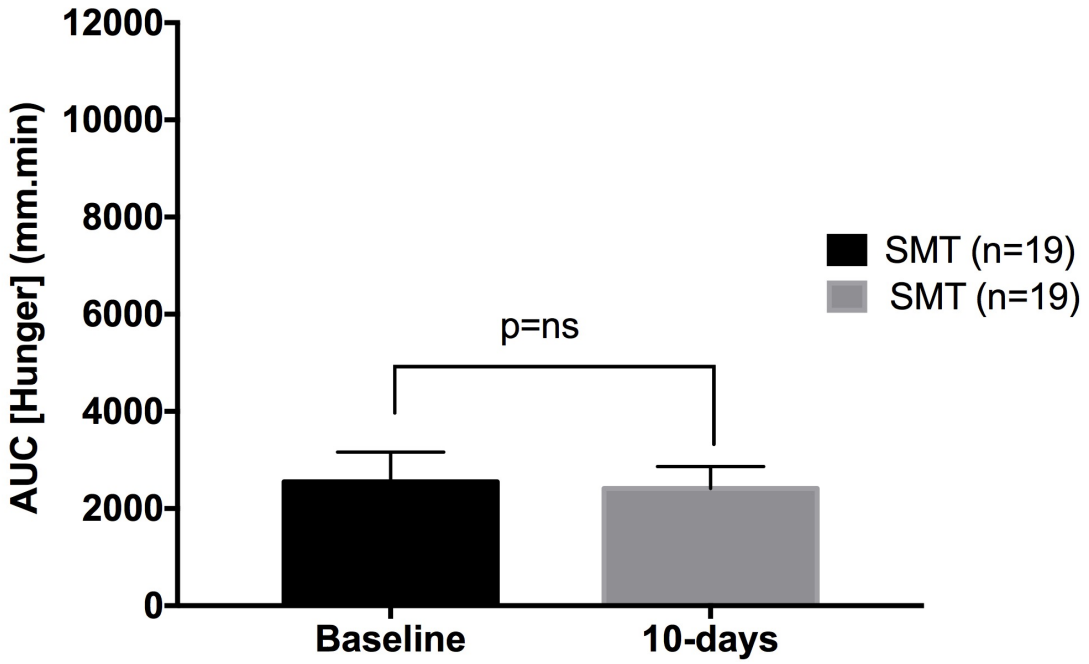
B) Completers analysis as per protocol (DJBL n=10)



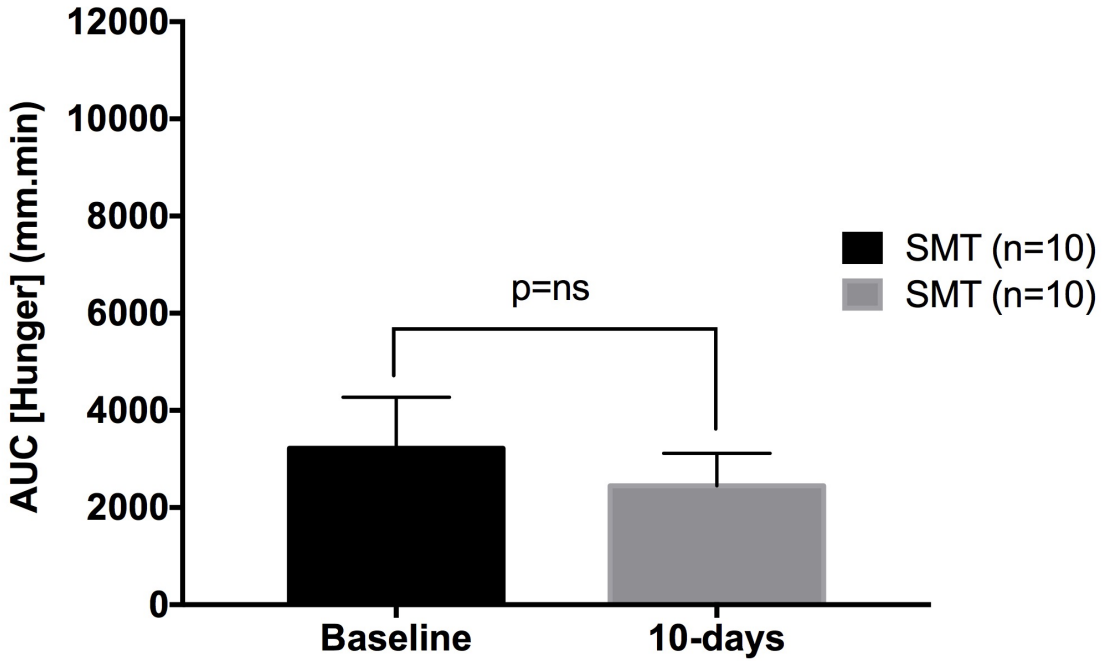
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

Figure 20 (A and B) Change in hunger ratings (AUC) at 10-days post intervention for SMT patients

A) Intention-to-treat analysis (SMT n=19)



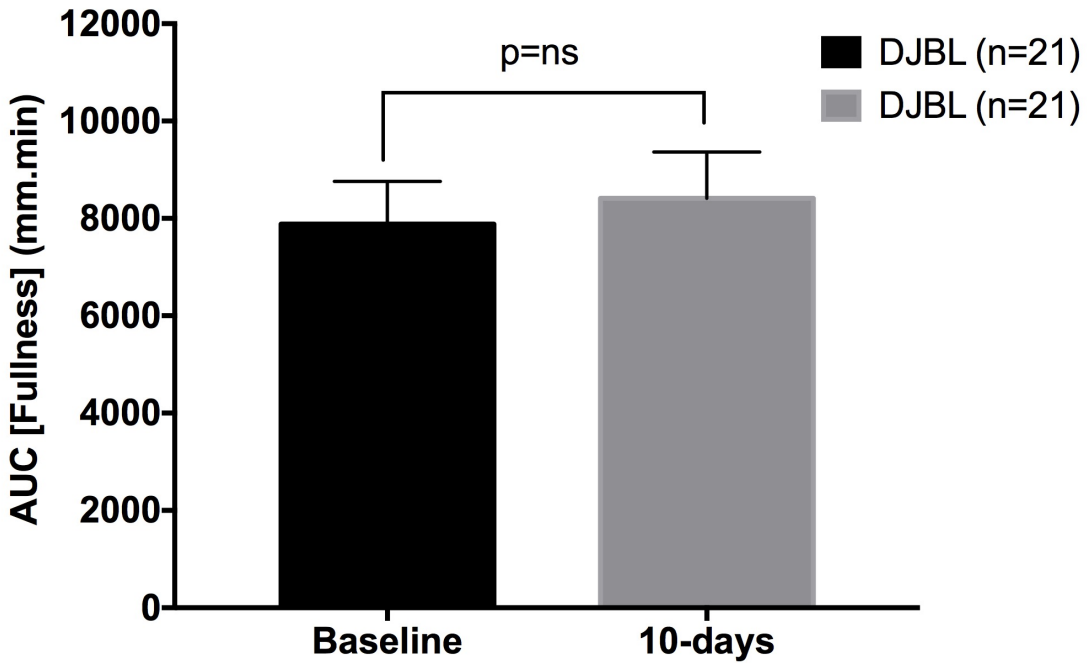
B) Completers analysis as per protocol (SMT n=10)



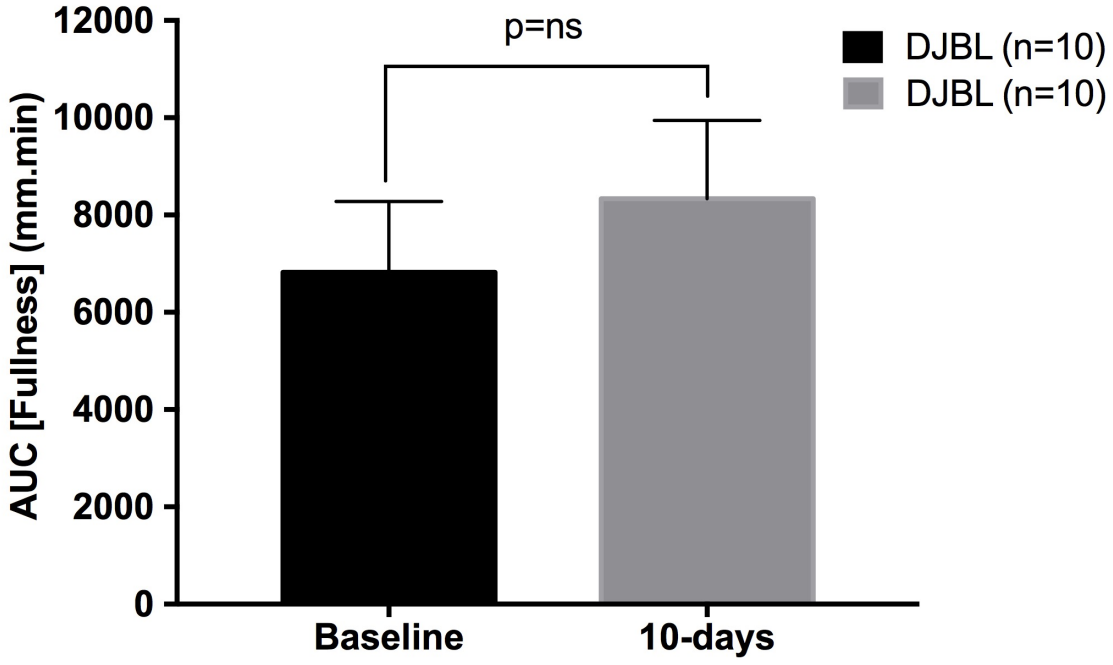
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

Figure 21 (A and B) Change in fullness ratings (AUC) at 10-days post intervention for DJBL patients

A) Intention-to-treat analysis (DJBL n=21)



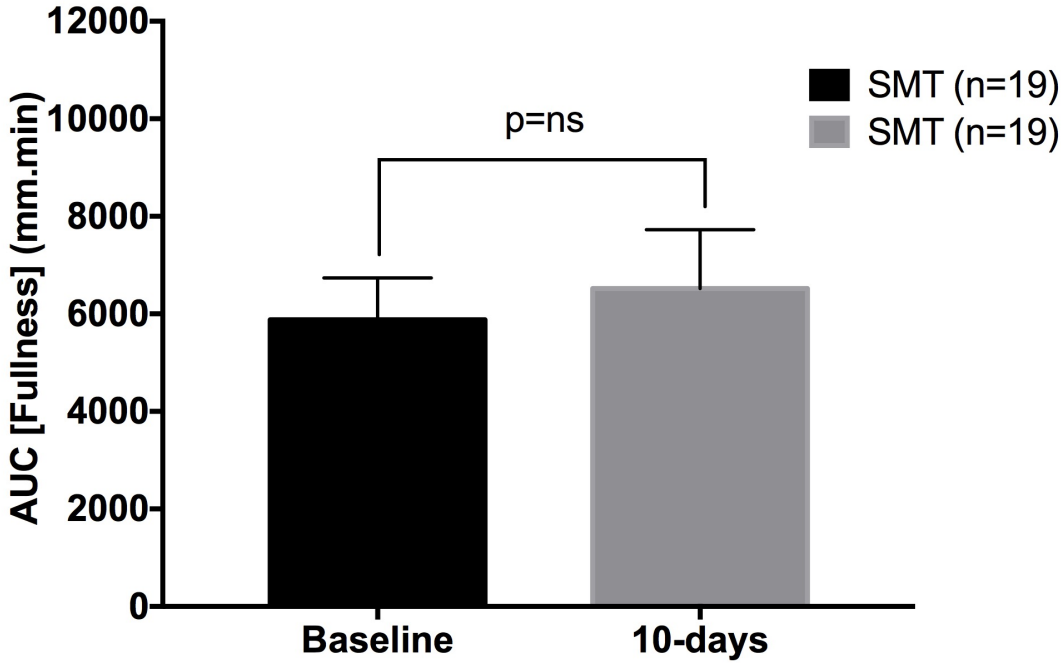
B) Completers analysis as per protocol (DJBL n=10)



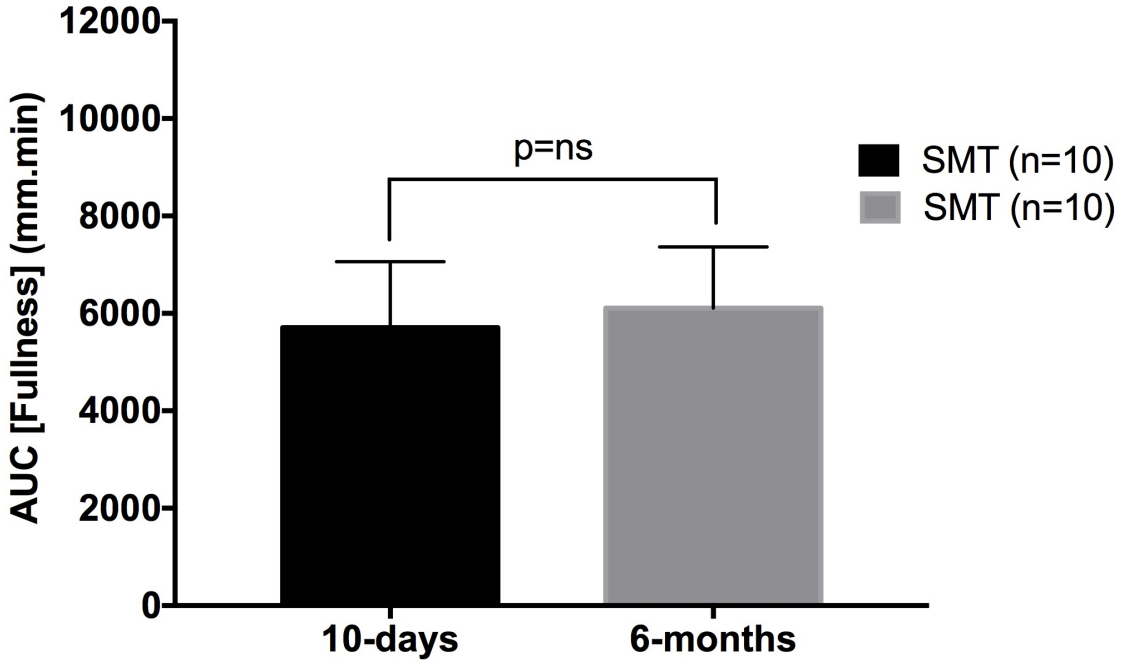
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

Figure 22 (A and B) Change in fullness ratings (AUC) at 10-days post intervention for SMT patients

A) Intention-to-treat analysis (SMT n=19)



B) Completers analysis as per protocol (SMT n=10)



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$

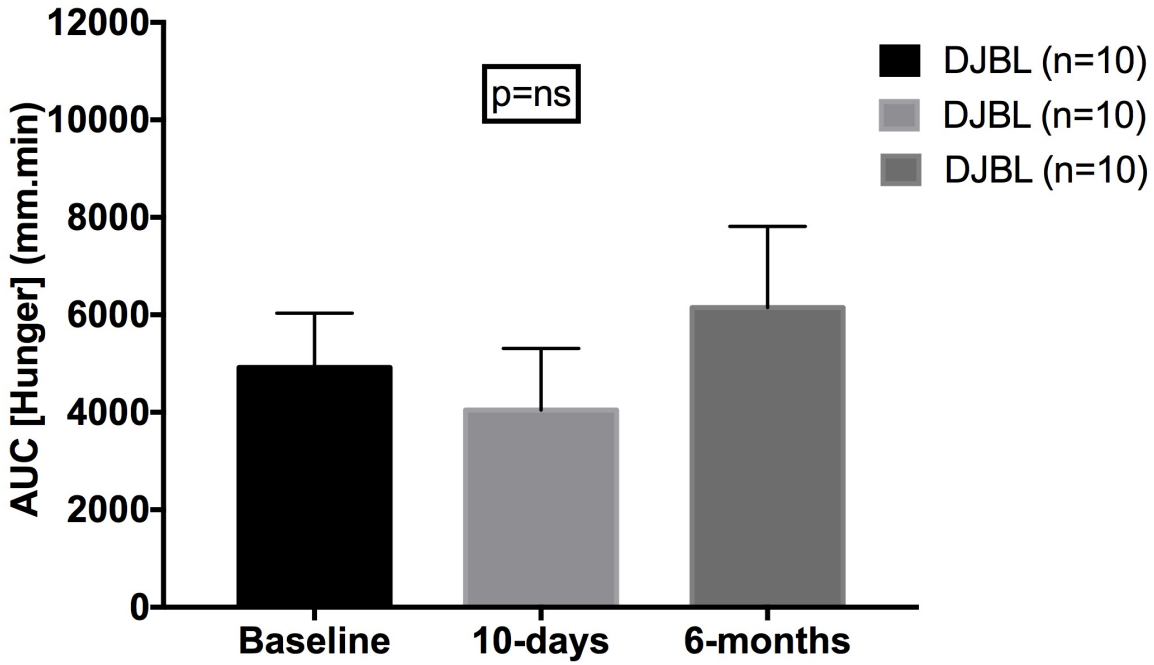
5.3.3.2 6-months post-intervention

At 6-months post intervention there was a trend towards a higher reported hunger levels AUC compared to baseline and 10-days post intervention in both the DJBL and SMT groups, but it did not reach statistical significance (Figure 23 A and B).

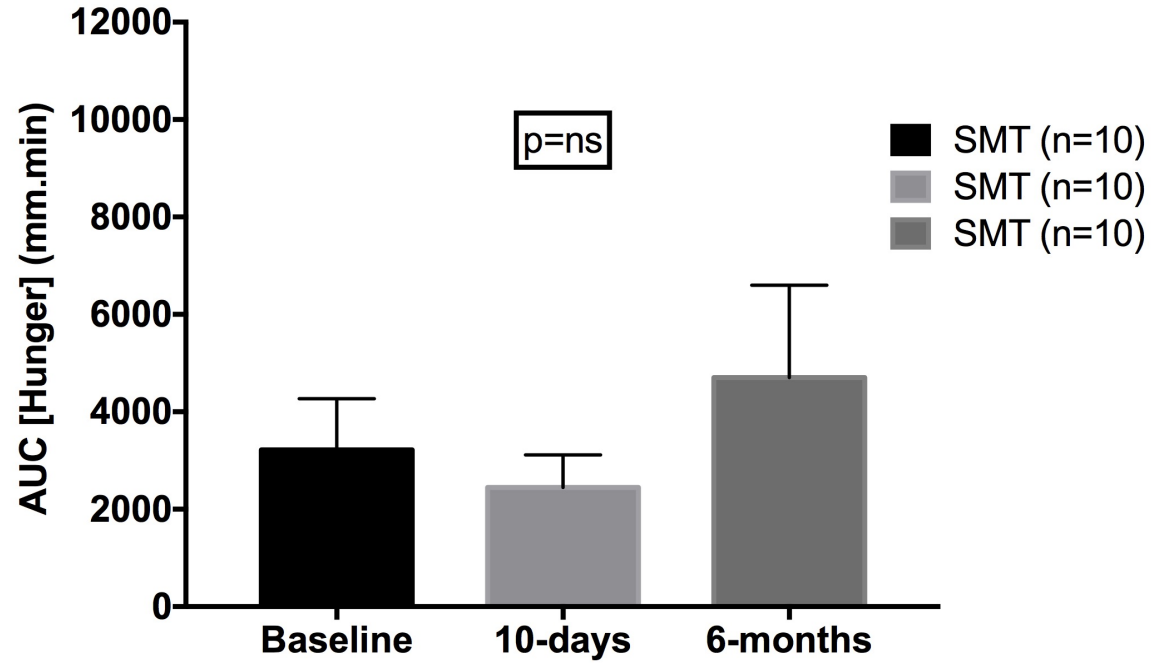
There was also no significant change in the fullness levels at 6-months post intervention compared to baseline and 10-days in either the DJBL or SMT groups (Figure 24 A and B).

Figure 23 (A and B) Change in hunger ratings (AUC) during the 6-months treatment period for both treatment groups

A) DJBL group



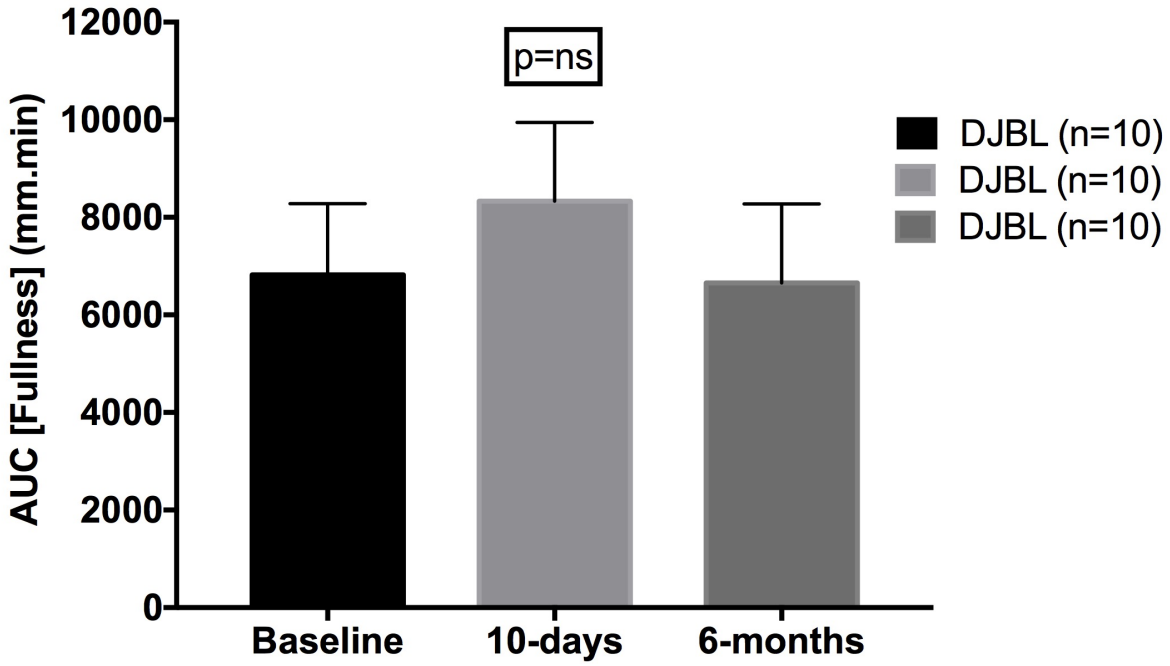
B) SMT group



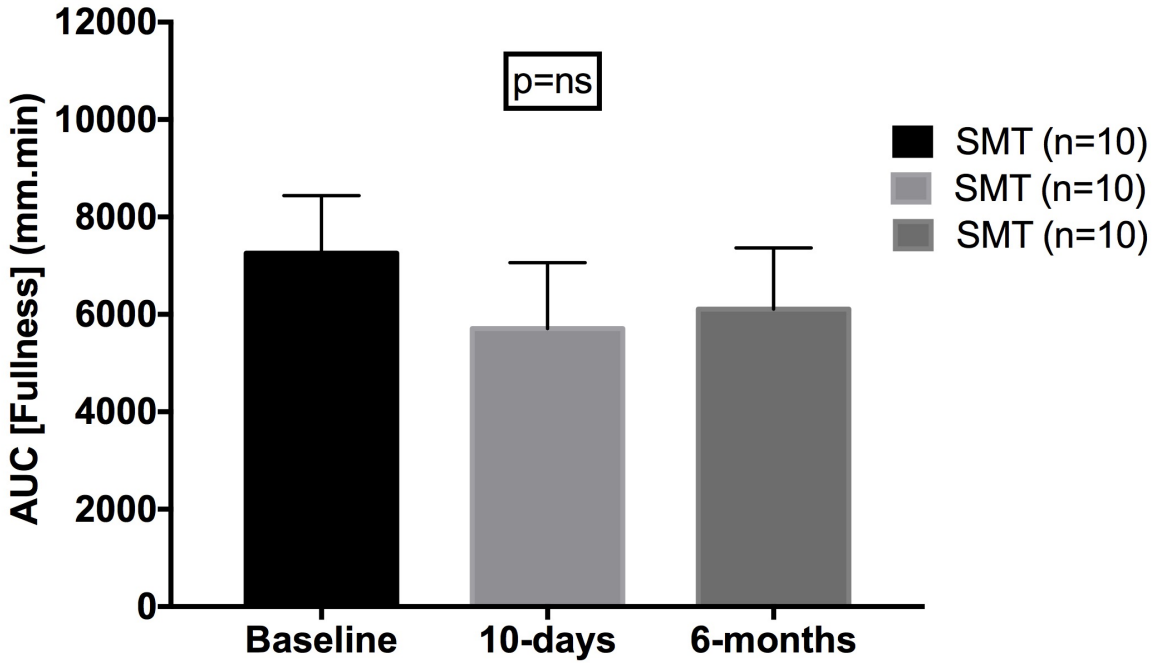
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; within groups analyses were performed with One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures.

Figure 24 (A and B) Change in fullness ratings (AUC) during the 6-months treatment period for both treatment groups

A) DJBL group



B) SMT group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy; within groups analyses were performed with One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were used to test for significant differences between pre- and post-operative measures.

5.4 Discussion

In this chapter, I found that neither the bypass of the proximal small bowel nor the standard medical therapy, change the vast majority of the psychological aspects of eating behaviour or appetite ratings. Both treatments lead to similar changes in eating behaviour that lead to similar weight loss results, as seen in chapter three.

Psychological factors

My comparison of the baseline and 6-months post intervention in the DJBL and SMT groups suggest that patients who lost a significant amount of weight through a non-invasive approach i.e standard medical therapy were more likely to be less depressed after they have lost weight, compared to those who lost their weight through the device implant, even though they were all within the normal depression range. It was interesting to find that both treatment groups in this study had 'normal' levels of depression and anxiety at baseline, as depression is very common in obese patients entering a weight loss treatment (483). Nevertheless, improvement in depression has been reported after significant weight loss after bariatric surgery (484-486) and behavioral and dietary interventions (487).

Reward responsivity reflects the degree to which a person experiences positive responses to rewards i.e. food. It has been linked to food craving, overeating, and preference for sweet and fatty food which, in turn leading to weight gain over the long term and increased BMI (488, 489). In obese individuals, CNS responses to visual food cues are high in areas involved in appetite and reward processing (insula, amygdala, orbitofrontal cortex, and striatum) (490-492). Multiple metabolic and hormonal factors can be involved in the activation of those areas including GLP-1 (493). It has been previously suggested that the bypass of the proximal small bowel alters bile flow. Bile induces the release of appetite suppressant hormone GLP-1 (466, 467), and hence may be affecting reward responsivity.

Eating behaviour factors

With regards to eating behaviour, dietary restraint was increased in both treatment groups and disinhibition was lowered in the SMT group. Dietary restraint is defined as a conscious

effort to resist eating with the aim of controlling body weight (494). Contradicting correlation with weight loss and weight loss maintenance was found in previous studies. In their study, Sarwer *et al.* (51) have found that higher baseline dietary restraint results in more weight loss following RYGB as a result of better adherence to the post-operative diet. However, based on the restraint theory, Polivy (46) argued that high dietary restraint can lead to increased periods of overeating resulting in higher consumption of calories following dieting. This theory was consistent with previous findings we published (52). Disinhibition is the opposite of restraint and is defined as the lack of control of certain behaviours. It results in erratic eating and unplanned meals and is associated with binge eating, a higher BMI and obesity (53). Although both treatment groups in this study had a lower disinhibition, it was only significantly reduced in the SMT, this may reflect that patients without the device had to work harder to control their eating. It has been previously suggested that DJBL produces it effects on weight loss and diabetes improvements regardless of patient's conscious efforts to control their food intake or lifestyle (465).

Emotional eating, overeating in response to negative emotions or stimuli, is associated with overweight and obesity (495-497). Koenders et al. (498) suggested that it is "emotional eating, rather than lifestyle behaviours, that drives weight gain" among people with overweight and obesity, but perhaps, this is an over exaggeration of the findings as an association is not causality. Our patients in the SMT group had lowered levels of emotional eating which can be attributed to the dietary and counselling therapy they have received during the intervention period.

External eating, eating in response to external food cues such as sight or smell of food, is considered a vulnerability factor in obese individuals leading to overeating and further weight gain (499). External eaters have an increased inclination to selectively obey food cues (500-502), this type of behaviour was significantly lowered in the DJBL group and as such it can be associated with the lowered levels of reward responsivity also found in this group.

Overall, both treatment groups had improved eating behaviour, this was expected from the excellent weight reduction results previously found and discussed in chapter three. However, this was attributed to different eating styles adopted during this 6-months.

Appetite ratings

Visual analogue scales (VAS) are commonly used in human behaviour studies. They provide a quantifiable objective measure translated from subjective sensations. The bypass of the proximal small bowel did not change the reported hunger and fullness ratings. Only a limited number of studies have reported outcomes of VAS in DJBL patients. Data presented in the ADA 2014 suggested that patients with DJBL have reduced appetite and a greater feeling of fullness at 3-months post device implant (478). However, our results are supported by the most recently published DJBL study, which found no acute or chronic change in food intake and appetite rating during a 6-months intervention (503).

One of the limitations in the use of VAS is the generality in interpreting the results. Some studies assess the raw data collected on certain time-points, mostly baseline or fasting (504), others use a delta of scales between different time points (505), and majority of studies use the area under the curve for a specific duration of time to assess satiety over a longer period of time (181, 504). The data presented in the ADA used a different approach by adding all the scores from the sub-scales i.e. how hungry do you feel, how much can you eat, how much do you think of food, how pleasant would be to eat right now, and how full do you feel, to create a total score reporting 'overall satiety level', which was to some extend similar to an approach used by (506). In addition, variability in appetite scores due to the type or size of meal consumed, add an extra burden when comparing different study results.

VAS may be a better indicator of the physiological state of hunger than as predictors of actual food intake. A number of studies have assessed the use of VAS as predictors of food intake (total daily food intake or at a subsequent meal). The findings are mixed but the majority of studies found that VAS can be used as predictor of energy intake in controlled laboratory conditions (180-182) but not with reported energy intake in a free-living context (183) or at least to a lower extent as suggested by Drapeau *et al.* (2007) (181). Mattes, 1990 pointed that the use of VAS to predict food intake in free-living individuals would not be accurate due to the natural setting people often eat when they are not hungry and sometimes do not eat when they do feel hungry (183). On the other hand, Heini *et al.* (1998) have noted that while no significant changes in hunger-satiety levels were found, remarkable correlations were found between postprandial changes in these variables with glucose and insulin (507). They also found that during energy restriction, changes in leptin are associated with changes in hunger-satiety ratings, reflecting the fact that leptin levels may predict palatability scores.

While providing interesting new findings, the present study has a number of limitations. The number of patients used in this study is very small compared to similar studies in this field and may have resulted in some type 2 errors. Further analysis on a larger sample size is necessary to confirm findings involving those two groups. In addition, the methods of this chapter were based on verbal reports only, direct measures of food intake together with measurements of physiological hormonal changes is required to confirm the results.

In summary, this study has explored some of the patient characteristics, which may influence eating behaviour and weight loss. Among patients treated with DJBL more patients had improved reward responsiveness and disinhibition, while more patients in the SMT had better improvement in depression scores, and emotional eating. Hunger and fullness ratings were not affected by either treatments. The results of this study generate a number of hypotheses that can be explored in future studies and add to the field of studies investigating the mechanisms of bariatric surgeries.

CHAPTER 6 AIM THREE: THE EFFECT OF DJBL ON SWEET TASTE DETECTION SENSITIVITY

6 Sweet taste sensitivity

6.1 Introduction

Taste is a decisive factor directly influencing eating behaviour by its effect on food preference and therefore on food intake. Many researchers believe that it can contribute to the development of obesity; however, it is challenging to know whether Hypogeusia (reduced taste sensation) causes hyperphagia and weight gain or vice versa. Bartoshuk et al. (2006) quoted “The obese live in different orosensory and orohedonic worlds than do the non-obese” (96).

Bariatric surgery, particularly the Roux-en-Y Gastric Bypass (RYGB) is the most effective treatment for obesity and its related comorbidities. It produces 20-30% weight loss maintained for at least 20 years (316, 317). It is generally accepted that bypass operations have more powerful effects on T2DM than non–bypass operations, but few studies have demonstrating this difference (383). Panunzi *et al.* (2016) found that by merging data from the SOS study and two other randomized controlled studies gastric diversion surgeries i.e. RYGB and BPD resulted in 76% of patients having excellent diabetes control compared with Gastric only surgeries i.e. VSG and BAND that resulted in 60% (384). However, a systematic review of 20 RCT comparing different types of obesity surgeries suggested that RYGB was more effective than VBG and BAND in weight loss but did not find any differences in diabetes control or other comorbidities (294).

Despite the impressive weight loss and improvement in T2DM, obesity surgery procedures still carry a high risk of complications of which some can be serious, and 1 in 1000 are fatal (440). Besides, not all obese patients are eligible for obesity surgery due to high preoperative risks. Therefore, the need for an effective and safer strategy for the treatment of obesity is very high.

The Endoluminal Duodeno-jejunal Bypass Liner or EndoBarrier® (DJBL) (GI Dynamics, Lexington, Massachusetts, USA) is inserted endoscopically through the mouth and anchored to the proximal small intestine to acts as a physical barrier between the walls of the duodenal and the food ingested (441). It aims to mimic the intestinal bypass and possibly components

of the restrictive effects of Roux-en-y gastric bypass surgery without the need for stapling or anastomosis. Hormones that control appetite and blood sugar level are typically released when food comes in contact with the walls of the duodenal. By eliminating this mechanism, bile and pancreatic secretions are only mixing with chyme at the jejunum (442), resulting in changes in the levels of hormones, and a lower blood sugar levels in a similar manner to that seen after RYGB ((443), (444)).

RYGB patients have a shift in their food choices from unhealthy fatty and sweet food to healthier options (206, 403), which may be a result if the increase sweet taste acuity observed very early on after the procedure (408). The mechanism behind this change is unknown, but different compartments of the surgical manipulations to the GI Tract can cause those health benefits.

The DJBL offers a novel and unique opportunity to apply a reductionist approach and interrogates the contribution of bypassing the proximal bowel in the change in taste. This study is the first to assess taste acuity and eating behaviour in DJBL patients.

6.2 Materials and method

6.2.1 Subjects

Forty subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. Best Medical Practice via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Taste detection was carried out 2-weeks before intervention (Baseline), 10-day post intervention and while on the liquid diet , and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

6.2.2 Taste detection test

Detection test for sucrose was performed following the same method of constant stimuli previously described by Bueter *et al.* (2011) (111). Details of the test description and its data analysis are described in chapter two: Materials and Methods, section (2.4.5).

6.2.3 Statistical analysis

The data were normally distributed as assessed by D'Agostino & Pearson normality test and are therefore expressed as mean ± standard error of the mean (SEM).

The data were compared 'between' groups at baseline and when the data is presented as a delta of the measurements. A parametric paired t-test was performed to compare two time-points within each group and a parametric unpaired t-test was performed to compare time-points between groups. One-way analysis of variance (ANOVA) with repeated measures and post-hoc Tukey tests were performed to test for significant differences between pre- and post-operative repeated measures. Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

6.3 Results

6.3.1 Attrition

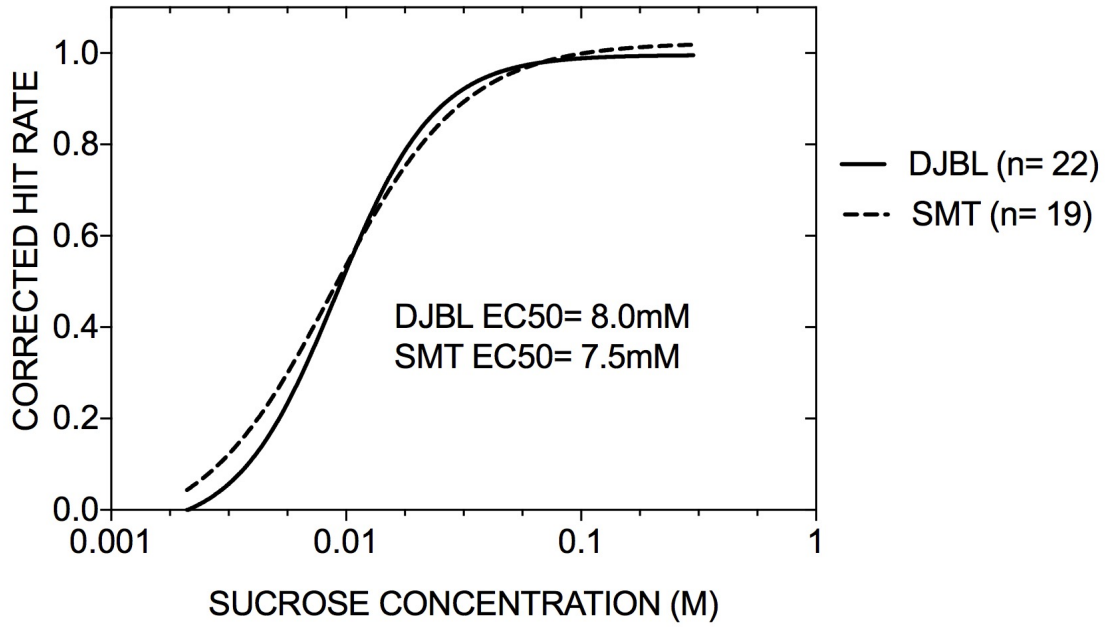
All subjects completed their 10-days post intervention visits. However, due to the timelines of this thesis, only 21 subjects (10 DJBL, 11 SMT) were due for the 6-months post intervention visit by the time data had to be locked for analysis, one of whom was lost to follow-up from the SMT group. Therefor, A total of 20 subjects (10 DJBL, 10 SMT) were included in the 6-months follow-up data analysis.

6.3.2 Baseline assessment

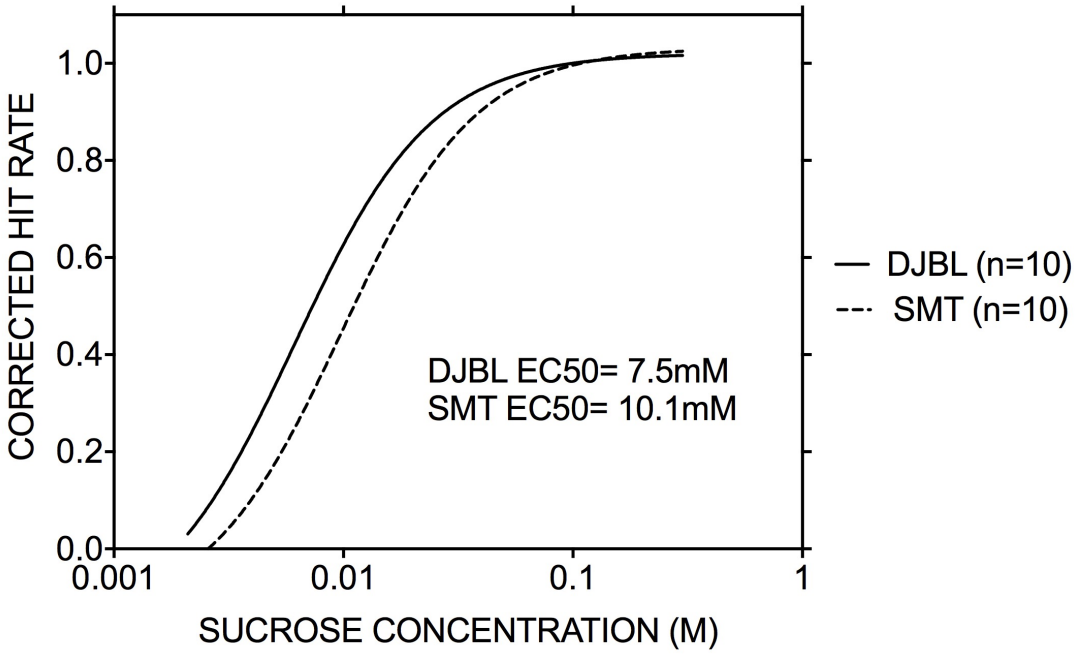
The baseline detection thresholds are shown in Figure 25 (A and B). There were no significant differences in the detection thresholds between the DJBL and SMT in the ‘intention-to-treat analysis’ (Figure 25 A), nor in the ‘completers analysis as per protocol’ (Figure 25 B).

Figure 25 (A and B) Baseline mean detectability functions

A) Intention-to-treat analysis (DJBL n=21, SMT n=19)



B) Completers analysis as per protocol (DJBL n=10, SMT n=10)



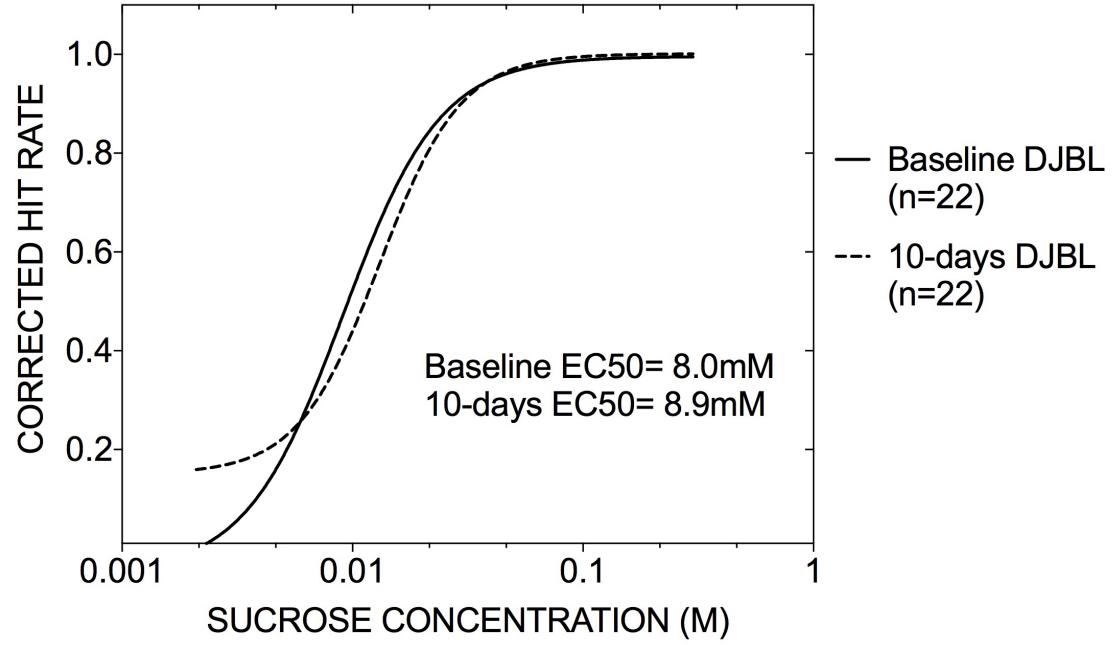
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with un-paired *t*-tests. Data defined significant at $p < 0.05$. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reached 50% of the maximum asymptote.

6.3.3 10-days post-intervention

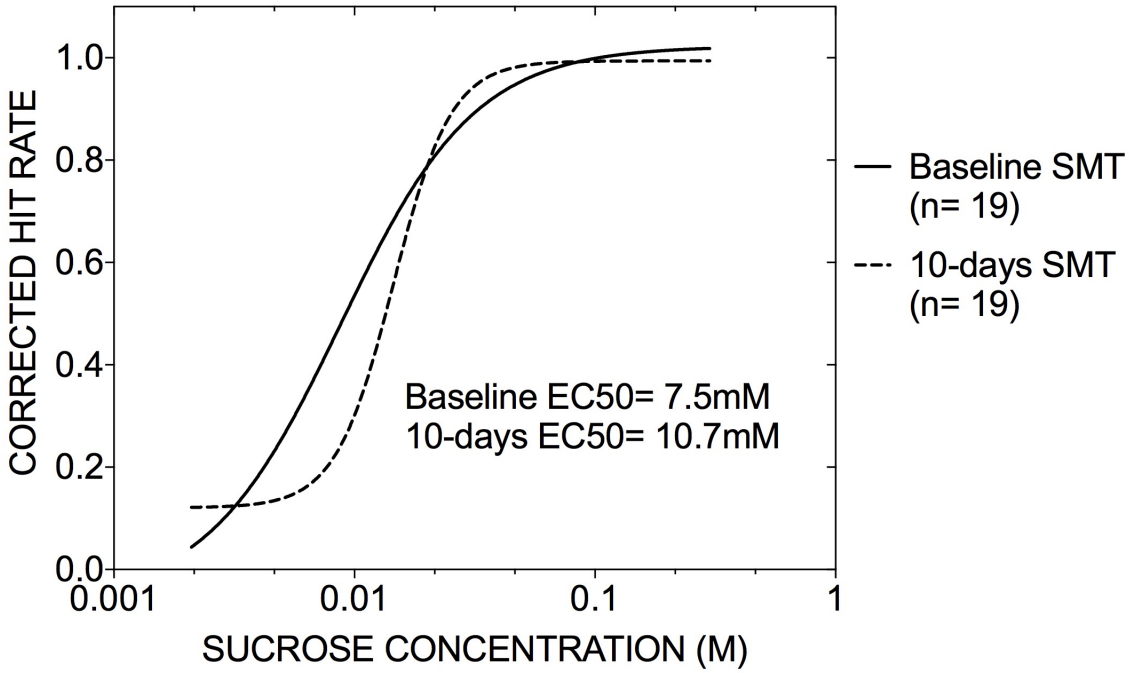
No significant difference was detected during the liquid diet phase on the study (10-days post intervention) compared to the baseline threshold in neither the ‘intention to treat analysis’ nor in the ‘completers analysis as per protocol’ (Figure 26 A and B) and (Figure 27 A and B).

Figure 26 (A and B) Change in mean detectability functions at 10-days follow up in the Intention-to-treat analysis (DJBL n=21, SMT n=19)

A) DJBL group



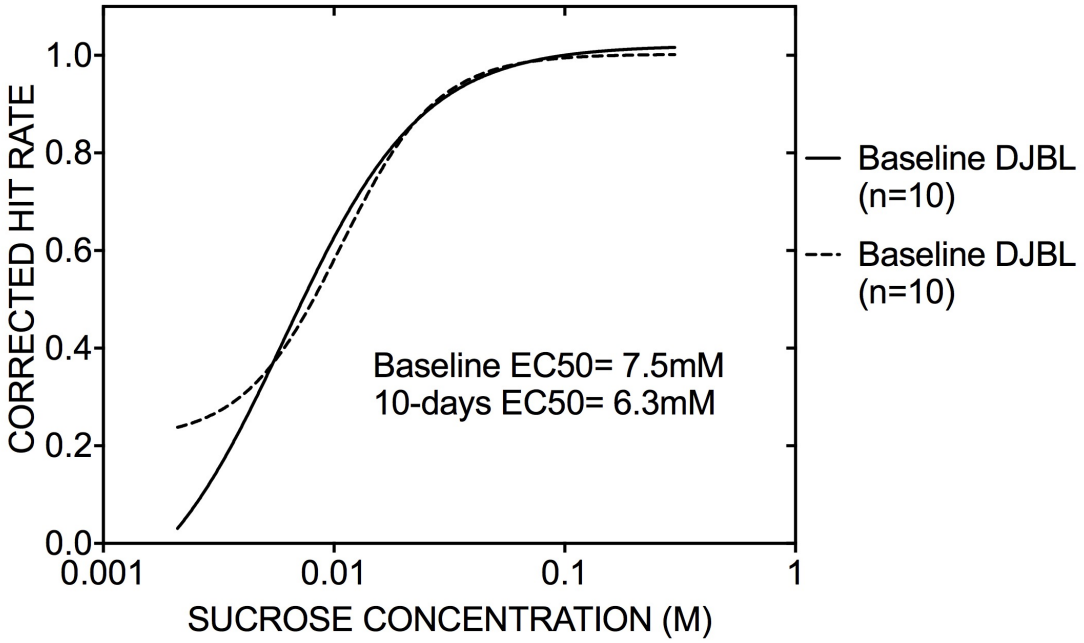
B) SMT group



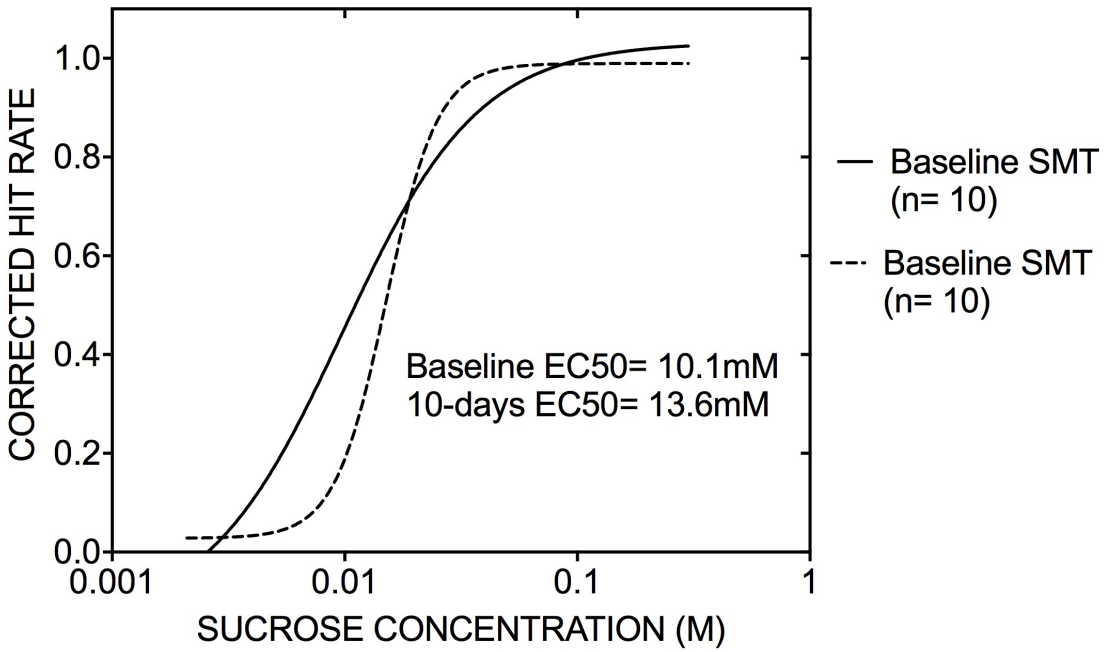
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reached 50% of the maximum asymptote.

Figure 27 (A and B) Change in mean detectability functions at 10-days follow up in the completers analysis as per protocol (DJBL n=10, SMT n=10)

A) DJBL group



B) SMT group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with paired *t*-tests. Data defined significant at $p < 0.05$. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reached 50% of the maximum asymptote.

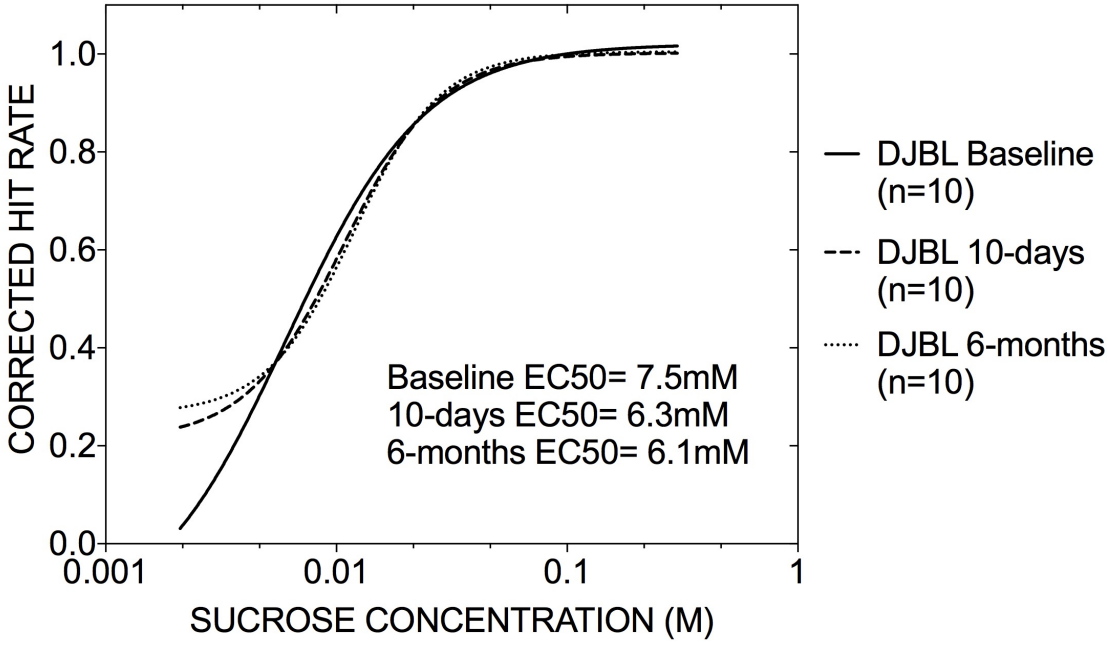
6.3.4 6-months post-intervention (One-way ANOVA and Two-way ANOVA)

A one-way ANOVA revealed no significant changes in taste sensitivity at any time-point during the 6-months treatment in the DJBL and SMT groups (Figure 28 A and B).

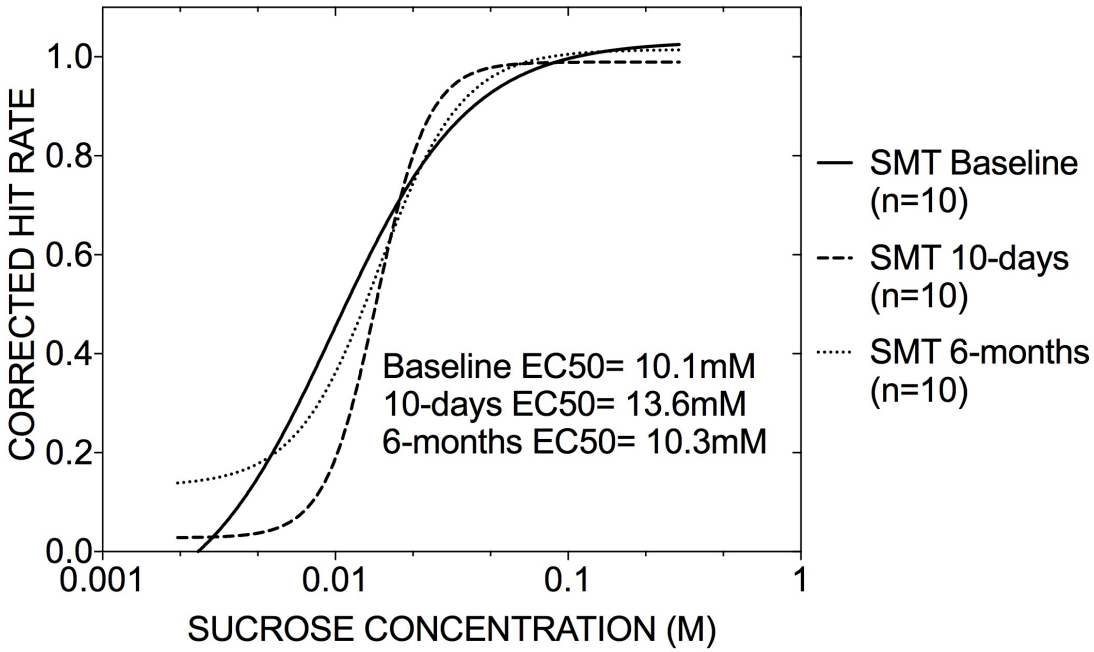
Two–way ANOVA also revealed no significant difference between groups at any-time points (Figure 29).

Figure 28 (A and B) Change in mean ± SEM detectability functions at 10-days and 6-months follow-up

A) DJBL group



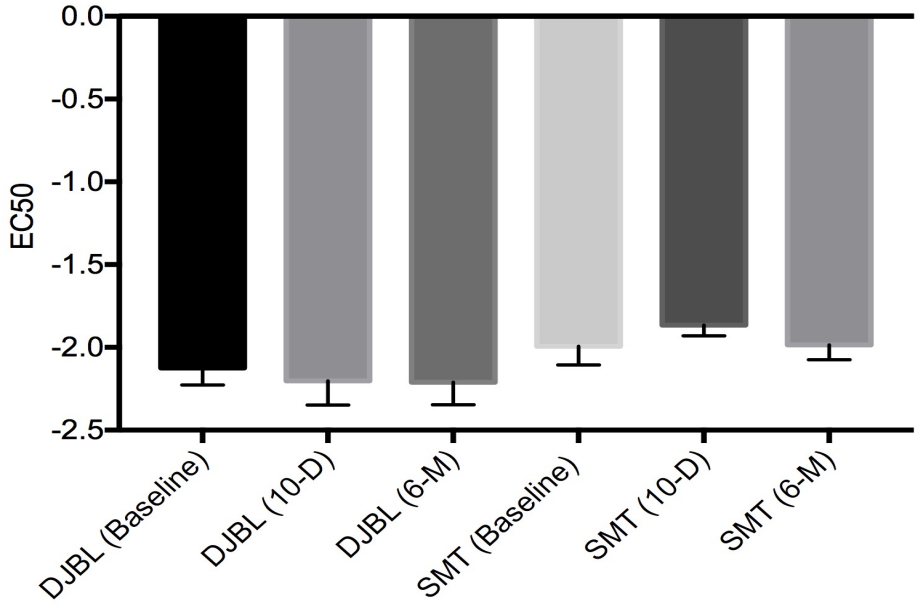
B) SMT group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data within groups were compared with a One-way ANOVA within each group. Data defined significant at $p < 0.05$. Curves were fit to the mean data points using Eq. (2) in text. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reached 50% of the maximum asymptote.

Figure 29 shows the EC50 levels at each visit, presented as the log10 of the sucrose concentrations detected, no significant change was detected within and between any treatment group.

Figure 29 Change in mean ± SEM EC50 at 10-days and 6-months post intervention as measured by the psychometric function test

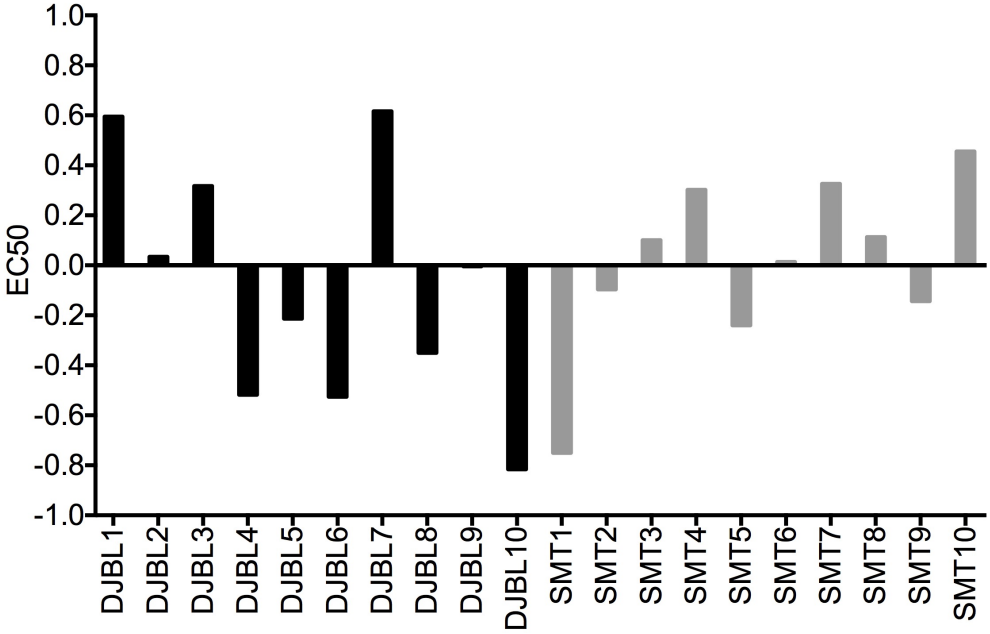


DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reaches 50% of the maximum asymptote. No significant changes were found within the study groups. Significance was measured using a Two-way ANOVA with repeated measure.

6.3.5 Delta EC50 from 10-days to 6-months

Figure 30, shows the delta shifts in the EC50 for individual patients in the DJBL and SMT groups. No trend in the sensitivity shift was observed.

Figure 30 Delta EC50 from 10-days to 6-months post intervention for individual patients

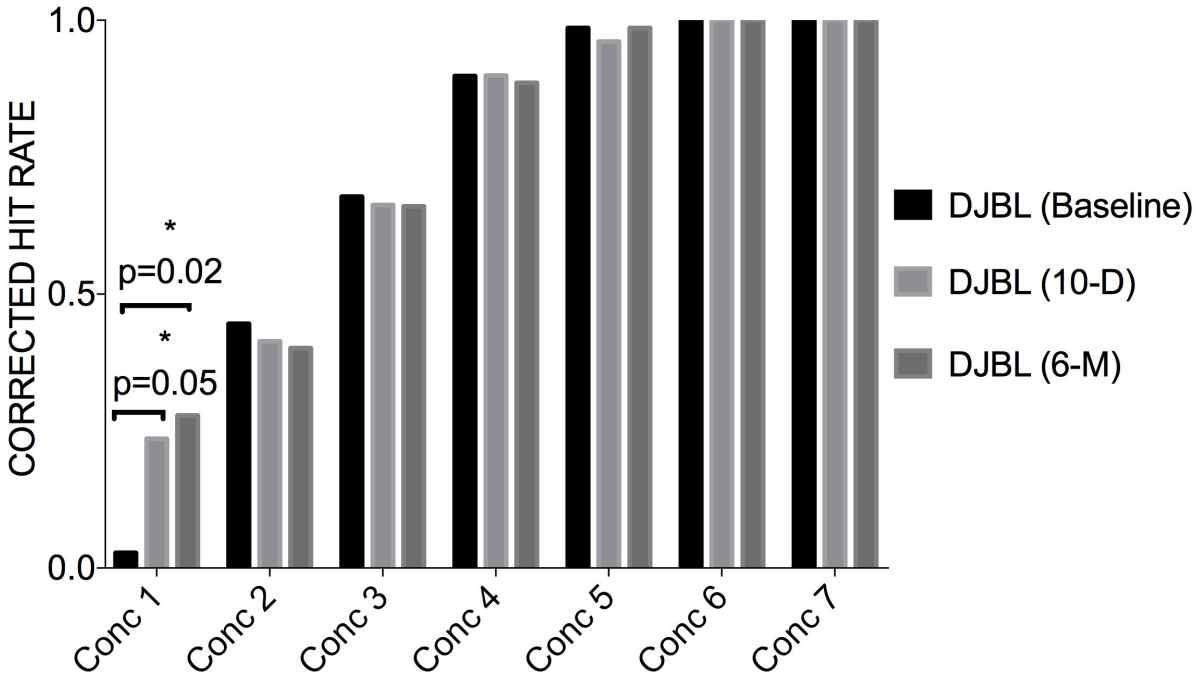


DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. The EC50 was derived from the c-parameter in the curve fit and represents the concentration at which the corrected hit rate reaches 50% of the maximum asymptote. Bars below zero represent leftward shifts in the detectability function indicating an increase in sensitivity.

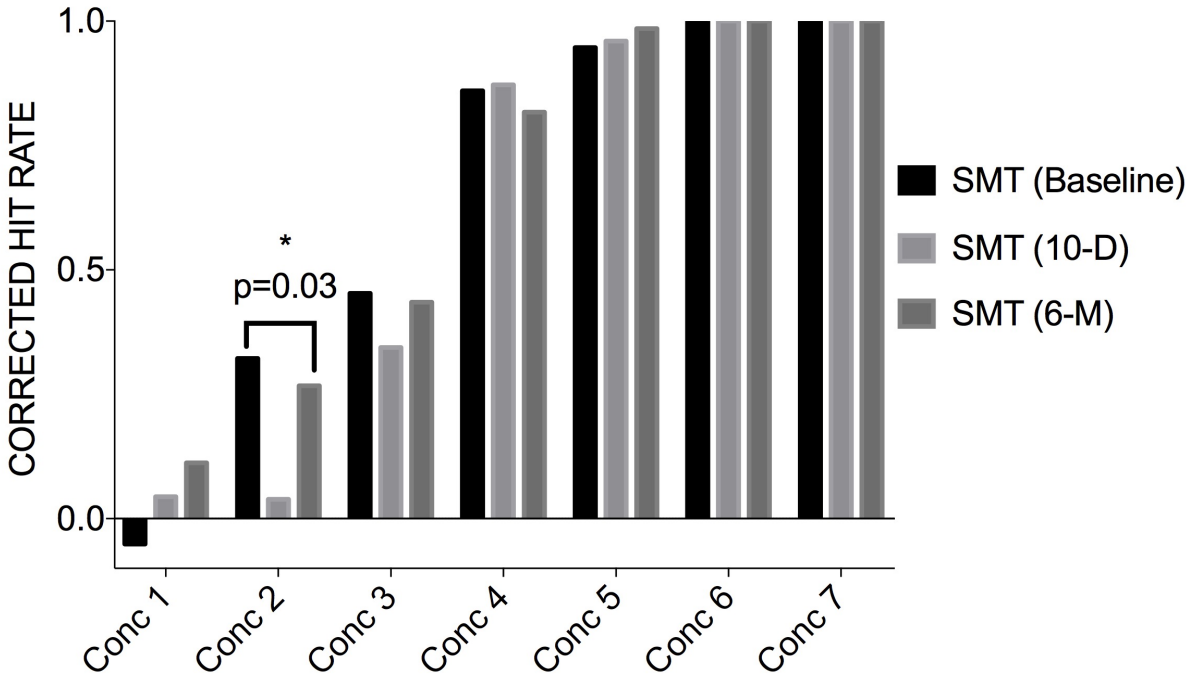
Taste sensitivity was significantly improved between Baseline and 10-days follow up ($p=0.043$) and between baseline and 6-months follow up ($p=0.014$) for the lowest concentration (concentration 1) in the DJBL group. On the other hand, it was significantly lowered at 10-days compared to baseline for concentration 2 in the SMT group (Figure 31).

Figure 31 (A and B) Taste sensitivity of each sucrose concentration at each visit

A) DJBL



B) SMT



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Comparison between Concentrations and Time within each group was performed using a Two-way ANOVA. *Significant at <0.05.

6.4 Discussion

In this chapter, I found that DJBL did not have an effect on the detection threshold for sucrose in obese type 2 diabetic patients. Our results suggest that the bypass of the proximal small bowel might not fundamentally shift the sensory domain of taste and may explain the unchanged food preferences in this group.

Taste acuity was never examined in DJBL patients before, and therefore we cannot compare our results to other studies. However, as the bypass of the proximal small bowel is on of the components of RYGB, we have hypothesised that the DJBL will act on taste acuity in a similar manner to the RYGB surgery, but maybe to a smaller scale of change. Many studies have previously found an improvement in taste acuity after RYGB (109, 110, 408). On the contrary, one study by Pepino *et al.* (2014) found no change in detection thresholds for any of the taste qualities (sucrose, glucose, NaCl, and monosodium glutamate (prototypical savoury stimuli)) after RYGB (414). The discrepancy between the earlier studies may be due to differences in the methodologies employed to measure taste thresholds, variation in the diet composition of subjects at the time of testing, time from surgery and sex differences.

The direct influence of taste sensitivity on food preferences fuels our interest in this field. DeWys and Walters (1975) were the first to report the connection between taste changes and food aversions. They found that increased taste acuity for urea (bitter) in cancer patients correlated with meat aversions (411). Aversions to sweet foods have been associated with increases in taste acuity for sucrose (sweet) (412). Based on these results, Scruggs *et al.* (1994) were the first to suggest that the changes in food preferences after RYGB may be attributed to the permutation in taste acuity (413). However, a previous study carried out by our group on VSG patients showed no changes in taste acuity had occurred after the operation despite a similar shift in food preferences to that seen in RYGB patients. The results of the VSG study suggest that other mechanisms and factors may play a role in food choices including alterations in the hedonic component of taste and conditioned aversion.

The RYGB comprises of many different components including (but not limited to) a smaller gastric pouch, and the bypass of the proximal small bowel. In this study, we attempted to use the DJBL to mimic one component of the RYGB, which is the bypass or proximal small bowel.

The BAND may also to some extent mimic the proximal gastric restriction reduction of the RYGB. BAND did also not change taste sensitivity as assessed by Pepino *et al.* (2014) (414)

A common finding between our study and those that did not find changes in taste acuity is that taste sensitivity did not improve/change despite the significant weight loss that occurred during the studies. Taste sensitivity was enhanced even in diet-induces weight loss and correlated with leptin levels (112). Also, many studies have shown associations between taste thresholds and weight e.g. (97-99). Kawai *et al.* (2000) found that leptin, a satiety hormone made by adipose cells, inhibited specific sweet taste responses in lean mice but not in obese diabetic (db/db) mice, suggesting a role of this hormone in sweet taste sensitivity (100). Kawai et al. (2000) found that Ob-R, a leptin receptor, is also found in the taste cells of circumvallate papillae in mice, indicating that taste cells are a site of leptin action (100). Ob-R is also present at the central nervous system (101), peripheral cells, such as T-cells (102), vascular endothelial cells (103), muscle cells (104), and pancreatic cells (105). It is not surprising that the taste cells of obese diabetic mice were not influenced by the injection of leptin, due to peripheral leptin resistance in obese mice and humans (106). Obese rodents and humans have increased levels of circulating leptin compared to normal weight subjects (107). During weight gain, basal plasma leptin levels would gradually rise, and at the same time, sweet taste sensitivity reduces. Chronic adaptation to high concentrations of leptin may elicit leptin resistance in the taste cells as suggested by Yoshida *et al.* (2015) (108). Therefore, any further increases in leptin concentration would not elicit further suppression (100).

Several gut peptides, including GLP-1 (113), neuropeptide Y (NPY) (114), glucagon (115), and ghrelin (116) are secreted in response to different taste stimuli and may contribute to taste quality coding (117, 118). A recent study by Takai *et al.* (2015) found that GLP-1 is released from the sweet-sensitive taste cells (T1R3) immediately after stimulation with sweet compounds, indicating that GLP-1 might activate sweet-sensitive gustatory nerve fibres (119). RYGB patients have increased postprandial GLP-1 levels (120), which may contribute to the increased sweet taste sensitivity reported in the previously mentioned studies. Future data analysis of the DJBL trial will determine the levels of different gut hormones, particularly GLP-1, a correlation between GLP-1 and taste threshold will be of great interest.

In this study, our cohort consisted of type 2 diabetic patients. Fabbi (1954) was the first researcher who suggested that patients with diabetes may have impaired taste function (121).

It was later suggested that this abnormality might be due to the elevated levels of blood sugar that cause a 'satiation effect' towards sweet taste or neuropathy causing a reduced taste sensitivity overall (122). Some studies were then carried out to confirm those finding, and it is now well established that T2DM patients have higher thresholds for glucose and sucrose detection than Type 1 patients and controls (123-126). Also, hyperglycemia is associated with higher sweet taste thresholds between diabetic and pre-diabetic patients (127, 128). That adds a burden when trying to compare our results with other studies as most of them used obese patients regardless of their diabetes status.

Methodological limitations of the study include the involvement of patients in different tasks during the study day as part of the study protocol. This method of constant stimuli is long and tiring, so there is a risk that our patients where fatigue. In addition, we did not use a token for correct responses. Previous studies ran by our group awarded participants with tokens for correct responses and taking away tokens for incorrect responses, which appeared to maintain subject's vigilance and motivation in a "game-like competitive setting". We decided to skip this technique to avoid overwhelming our participants. On the other hand, many strengths empower our findings. This study has the highest sample number compared with all other published studies on taste sensitivity; the use of 20ml tastant to stimulate all taste receptor cells in the mouth, and finally the use of different concentrations varying from very low to very high to produce a psychometric function test covering all different possible taste thresholds.

In conclusion, we found that DJBL did not decrease the taste detection to sucrose thus there was no increased sensitivity to sweets at either 10-days or 6-months post intervention. These results suggest that taste sensitivity is not affected by the bypass of the proximal small bowel or the effect is not high enough to elect clinical significance. Collectively, our study and the other studies discussed above highlight that RYGB might act through a synergic effect of the multiple components.

CHAPTER 7 AIM FOUR: THE EFFECT OF DJBL ON THE APPETITIVE REWARD VALUE FOR SWEET TASTE

7 Appetitive reward value

7.1 Introduction

Evidence from previous bariatric surgery studies has suggested that the shift to healthier food preferences after RYGB and VSG could be exerted through alterations in the motivational domains of taste function. The ingestive motivation domain of taste promote or discourage the ingestion of food, it defers from the stimulus identification domain in that it represents the hedonic aspects of gustation (93). For example, we can distinguish between the different taste qualities of food and drinks regardless of whether they taste nice or not (pleasant or aversive) by the stimulus identification domain; however, we will only ingest what tastes pleasant by the ingestive motivation domain. Spector A. C. (2000) described the taste related ingestive motivation as having two sub-domains or two components: the appetitive behaviour and the consummatory behaviour (93). The appetitive behaviour describes the 'wanting' actions that bring the animal/subject into contact with the stimulus e.g. searching, foraging, approaching a drinking spout, whereas the consummatory behaviour represents the final act elicited by the contact of the stimulus, in other words, the 'liking' of the stimulus (93).

Our research group has previously found that RYGB and VSG both decrease the appetitive reward value of a sweet and fatty taste stimulus (M&M candies) using the progressive ratio schedule of reinforcement task (146). This task was originally designed by Hodos in 1961 for the use in animal studies (145). Miras 2012 adopted this task for the use in human studies (146). Using the human version of the PRT this is the first study to assess the appetitive reward value in DJBL patients.

7.2 Materials and method

7.2.1 Subjects

Forty-Two subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. SMT via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Progressive Ratio Task was carried out 2-weeks before intervention (Baseline), and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

7.2.2 Procedure for sweet appetitive reward value assessment

Assessment of appetitive sweet reward value was performed following the same method of Progressive Ratio Task (PRT) previously described by Miras *et al.* (2012) (146). Details of the test description and its data analysis are described in chapter two: Materials and Methods, section (2.4.6).

7.2.3 Statistical methods

The data were normally distributed as assessed by D'Agostino & Pearson normality test and are therefore expressed as mean ± standard error of the mean (SEM).

The number of candies consumed, number of clicks in the last completed ratio, and hunger VAS, were compared 'between' groups at baseline using a parametric unpaired t-test. A parametric paired t-test was performed to compare two time-points within each group.

Significance was determined as $p<0.05$. Raw data was analysed using GraphPad Prism® software.

7.3 Results

7.3.1 Attrition

Forty-Two subjects (23 DJBL, 19 SMT) were due to have this task done. However one SMT and two DJBL subjects were not compliant with the task protocol due to technical difficulties and therefor were excluded from this task. A total of Thirty Nine (21 DJBL, 18 SMT) were included in the baseline analysis.

Due to the timelines of this thesis, only 25 subjects (12 DJBL, 13 SMT) were due for the 6-months post-intervention by the time data had to be locked for analysis. Out of those patients, two DJBL patients had the device removed prior to the 6-months follow-up visit and in the SMT groups two subjects were lost to follow up and 1 subject withdrew consent. In addition, two SMT subject were not compliant with the task protocol on their 6-months visits and therefore were excluded from the analysis. Therefore, a total of 18 subjects (10 DJBL, 8 SMT) were included in the 6-months follow-up data analysis.

7.3.2 Baseline assessment

In the intention-to-treat analysis, the two groups were homogeneous in their appetitive behaviour at baseline and did not significantly differ in any of the task parameters. The baseline fasting hunger rating for the DJBL group was 31.4±5.6mm and this was significantly higher than the SMT rating of 14.8±5.1mm (p=0.040) (Table 7-1A).

No significant differences were observed in the baseline data in the ‘completers analysis as per protocol’.

Table 7-1 (A and B) Baseline characteristics of appetitive behaviour and hunger ratings in the two treatment groups

A) Intention-to-treat analysis (DJBL n=21, SMT n=18)

	DJBL (n=21)	SMT (n=18)	P value
Total M&Ms	3.7±0.4	4.2±0.6	0.53
Last completed Ratio (clicks)	122.4±31.2	258.3±80.2	0.10
Hunger rating (mm)	31.4±5.6	14.8±5.1	0.04

B) Completers analysis as per protocol (DJBL n=10, SMT n=8)

	DJBL (n=10)	SMT (n=8)	P value
Total M&Ms	3.6±0.6	3.9±0.9	0.80
Last completed Ratio (clicks)	104±30.9	221.3±98.2	0.22
Hunger rating (mm)	29.9±8.2	20.6±7.2	0.42

DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical Therapy. Data are presented as mean ± standard error of the mean (SEM). All data were normally distributed as assessed by D'Agostino & Pearson normality test. Data between groups were analysed with unpaired *t*-tests. Data defined significant at $p<0.05$

7.3.3 Paired T-test

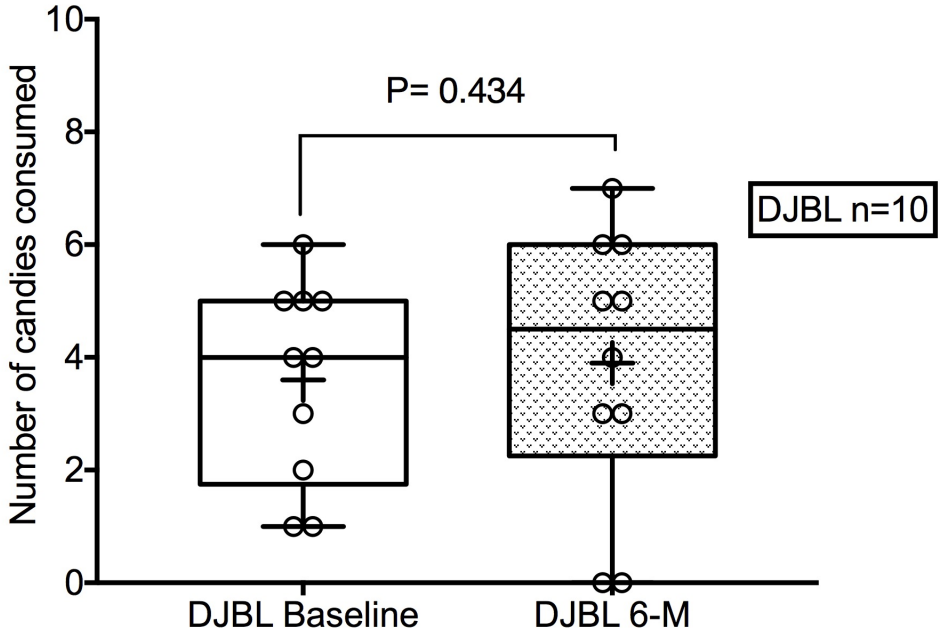
7.3.3.1 Change in number of candies

The total consumption of candies did not differ at 6-months post intervention in any treatment group (Figure 32 A and B). The mean±SEM number of candies consumed at baseline and 6-months post DJBL was 3.6±0.6 clicks and 3.9±0.8 clicks, respectively. The mean±SEM number of candies consumed at baseline and 6-months post SMT was 3.9±0.9 clicks and 4.1±1.0 clicks, respectively.

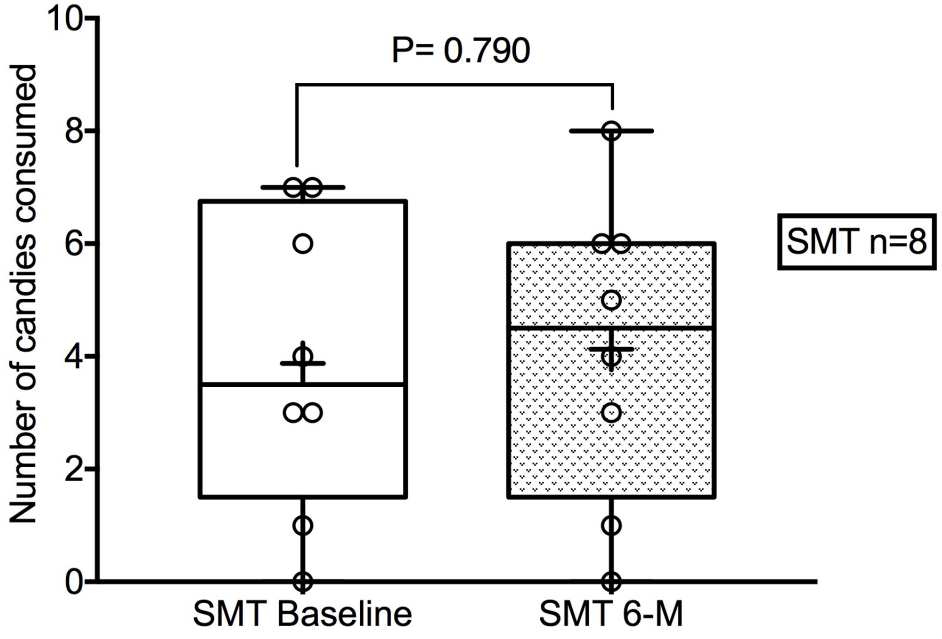
There was no linear correlation in the delta number of candies and the change in weight at 6-months post intervention in the DJBL group. In the SMT there was a weak positive correlation (r=0.390) but it did not reach a statistical significance (p=0.339) (Figure 33 A and B).

Figure 32 (A and B) Number of candies at baseline and 6-months post intervention in the two treatment groups

A) DJBL group



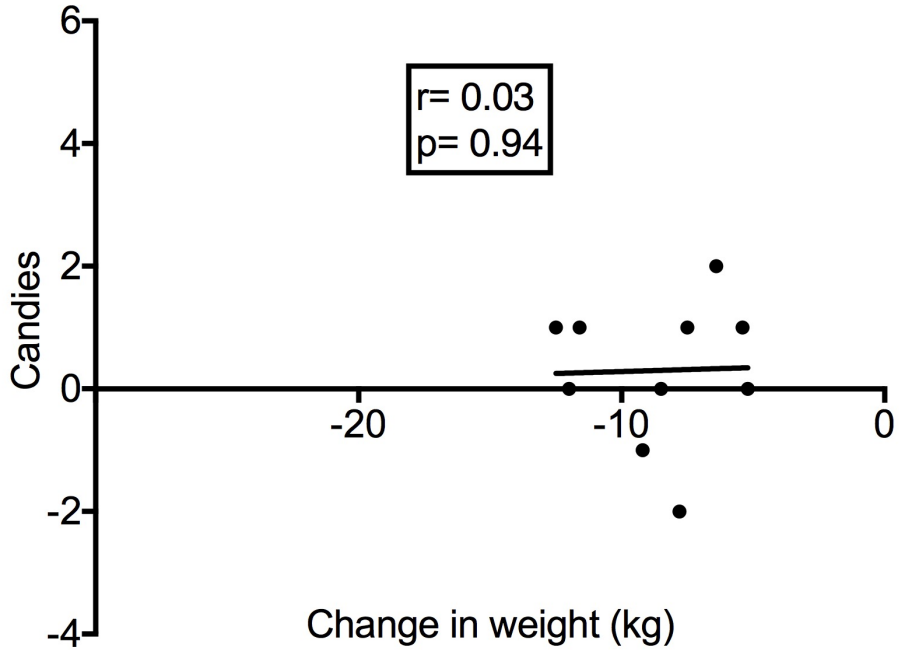
B) SMT group



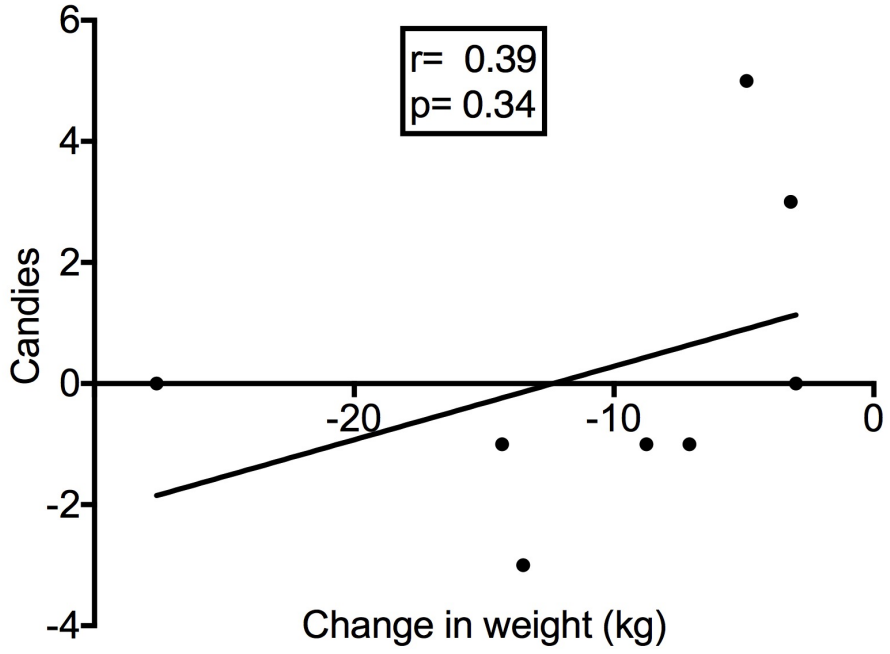
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy. The empty circles represent individual subjects. Data within groups were compared with paired *t*-tests. The lower and upper boundaries of the box represent the 25th and 75th percentiles respectively. The lower and upper whiskers represent the Min to Max respectively. The median is the black line in bold inside the box. The mean is the (+) in bold inside the box.

Figure 33 (A and B) Correlation of delta number of candies consumed with delta weight at 6-months post intervention

A) DJBL group



B) SMT group



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy. No correlation between the numbers of candies consumed and weight change.

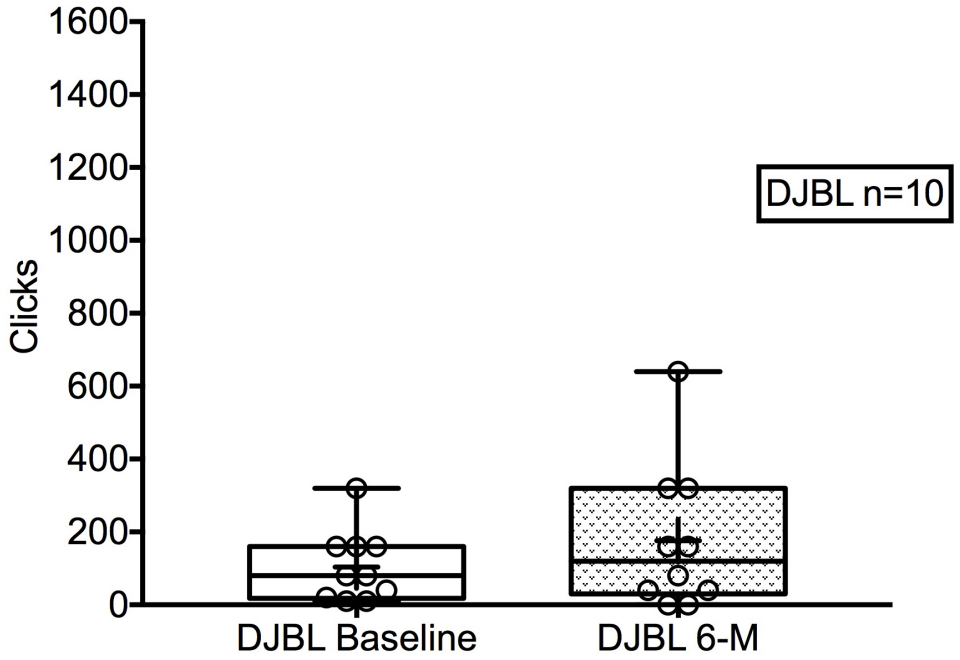
7.3.3.2 Change in number of clicks in the last completed ratio

The number of clicks in the last completed ratio data were inline with the number of candies consumed. There were no significant change in the number of clicks at the last completed ratio between baseline and 6-months follow up in both groups. The mean±SEM of the number of clicks in the last completed ratio at baseline and 6-months post DJBL was 104±30.9 clicks and 176±63.7 clicks, respectively. The mean±SEM number of clicks in the last completed ratio at baseline and 6-months post SMT was 221.3±98.2 clicks and 276.3±150.4 clicks, respectively (Figure 34 A and B).

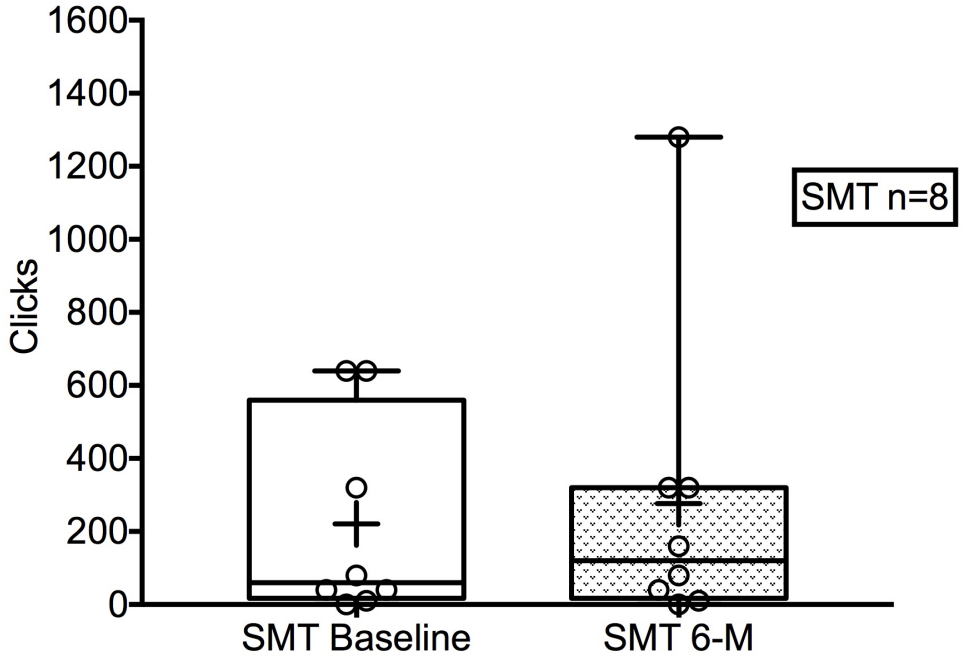
There was weak negative correlation (r= -0.46) in the delta number of clicks in the last completed ratio and the change in weight at 6-months post intervention in the DJBL group but this did not reach statistical significance (p=0.178). In the SMT there was a weak positive correlation (r=0.30) but it also did not reach a statistical significance (p=0.47) (Figure 35 A and B).

Figure 34 (A and B) Number of clicks in the last completed ratio at 6-months post intervention

A) DJBL group



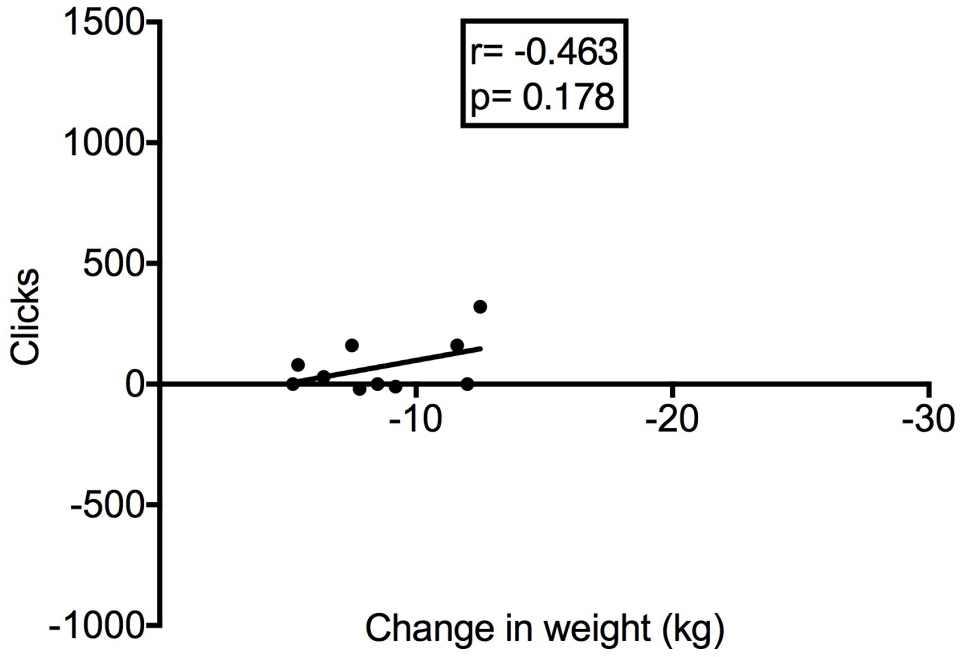
B) SMT group



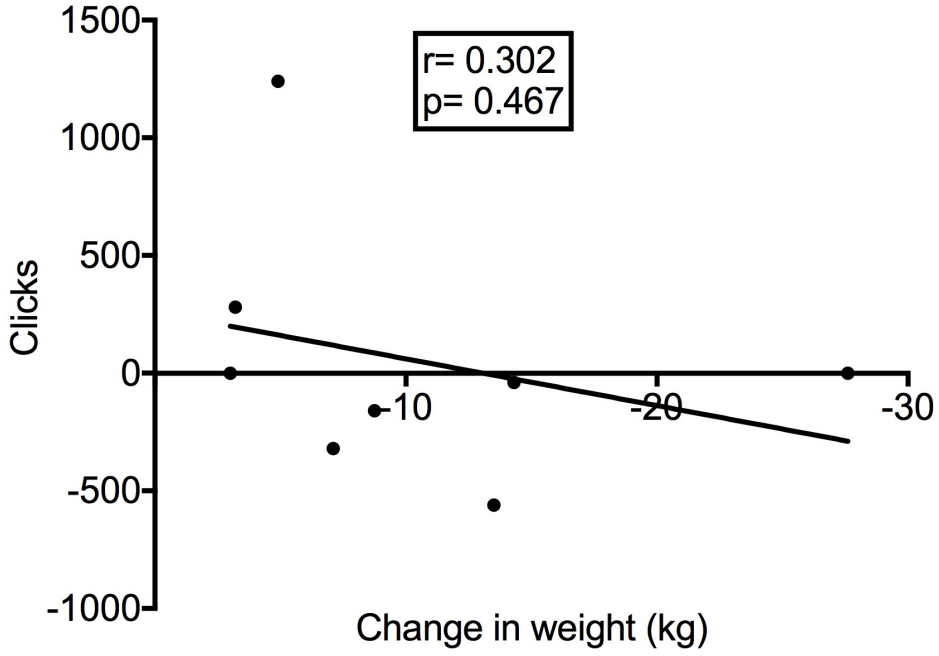
DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy. The empty circles represent individual subjects. Data within groups were compared with paired *t*-tests. The lower and upper boundaries of the box represent the 25th and 75th percentiles respectively. The lower and upper whiskers represent the Min to Max respectively. The median is the black line in bold inside the box. The mean is the (+) in bold inside the box.

Figure 35 A and B) Correlation of delta number of clicks in the last completed ratio with delta weight at 6-months post intervention

A) DJBL



B) SMT



DJBL: Endoluminal Duodeno-jejunal Bypass Liner; SMT: Standard Medical therapy. The solid black circles represent individual subjects. No correlation between the numbers of clicks and weight change.

7.3.4 Two-way ANOVA

There were no significant difference between groups at any time-point for the last completed ratio or number of candies consumed, as assessed with two-way ANOVA (Table 7.2).

Table 7-2 Two-way ANOVA results for the last completed ratio and number of candies

	DJBL (n=10)		SMT (n=8)		Treatment	Time	Treatment X Time
	Baseline	**6-months**	**Baseline**	**6-months**			
Last completed ratio	104.0±30.9	176.0±63.7	221.3±98.2	276.3±150.4	1.67;p=0.24	0.3;p=0.57	0.0001;p=0.99
Number of candies	3.6±0.6	3.9±0.8	3.9±0.9	4.1±1.0	0.04;p=0.86	0.57;p=0.48	0.07;p=0.79

7.3.5 Hunger ratings

Both treatment groups reported increased hunger levels at 6-months post intervention compared to baseline but the p-value did not reach statistical difference in either groups (Table 7-3). There was no linear correlation between the change in hunger ratings and the change in breakpoint at 6-months (Table 7-3).

Table 7-3 Summary of hunger rating results

	Hunger rating [1]	**p-value [2]**	**Correlation of change in hunger rating with change in breakpoint [3]**
DJBL Baseline (n=10)	29.9±8.2	0.49	r_s= 0.043 p= 0.91
DJBL 6-months (n=10)	43.7±12.2		
SMT Baseline (n=8)	20.6±7.15	0.32	r_s= -0.09 p=0.83
SMT 6-months (n=8)	36.1±13.2		

[1] Hunger rating in mm – mean±SEM. [2] Within group comparisons (Baseline vs 6-months post intervention) using the Wilcoxon matched pairs test. [3] $r_{s:}$ Spearman correlation coefficient

7.4 Discussion

In this chapter, I have shown that the type of treatment, DJBL or SMT, did not affect the appetitive reward value of a tastant high in sugar and fat in obese type 2 diabetic subjects.

It has been suggested multiple times that the changes in eating behaviour observed post RYGB may be attributed to the bypass of the small bowel as one, or the prime, component of its mechanism. To our knowledge, this is the first study to assess the effect of non-invasive bypass of the proximal small bowel, mimicking this component of RYGB. However, our results suggest a minimal effect of the proximal small bowel on how hard a person is willing to work to earn a candy high in sweet and fat. This is different to what Miras et al. (2012) has shown where RYGB patients worked half less hard post operation.

We hypothesized that the rise in post-prandial gut hormones post bariatric operation may explain some of this change. Sleeve Gastrostomy causes a similar rise in post-prandial gut hormones to RYGB and also causes similar changes in the appetitive behaviour assessed with PRT. Although I did not measure gut-hormones in this study, it's clear from past studies that post prandial GLP-1 and PYY are elevated in subjects living with the DJBL device.

It was interesting but not surprising noticing the tendency towards elevated levels in the fasting hunger rating in both treatment groups, despite it not being statistically significant. It is well documented that hunger levels are increased in obese subjects who have lost and/or trying to lose weight (388). The significant difference in hunger rating between the two groups at baseline could only be explained as a type 1 error (false positive). Subjects were electronically randomised to the treatment group and were homogenous in their body measurements and body composition (Chapter 3).

These findings are important since hunger feeling might dictate the quantity and how hard a person is willing to work but our results showed no correlation between the two parameters and this was similar to Miras et al 2012 findings. Thus it cannot be speculated that a hungrier person will work harder for a candy. It should be kept in mind that this task does not assess

portion size or how ‘much’ a person can eat but it assesses how ‘hard’ they are willing to work for food.

The results of this chapter adds to the overall findings of this study that the bypass of the proximal small bowel is not behind the changes in eating behaviour observed post RYGB or that RYGB alters the appetitive behaviour via a combined affect of the multiple components.

CHAPTER 8 AIM FIVE: THE EFFECT OF DJBL ON THE CONSUMMATORY REWARD VALUE FOR SWEET TASTE

8 Consummatory reward value

8.1 Introduction

In the previous chapter, I discussed the ingestion of a sweet, fatty food item based on its appetitive reward value, which is how much effort the study participants were willing to do to consume that food item. Taking those findings into consideration, I wanted to explore another dimension of the ingestive motivation domain, which is the ingestion of food based on its liking properties. This function of taste occurs after the appetitive behaviour, for example during an eating episode we require a certain level of motivation to reach to our desired food item (appetitive response), but we decide on how much we want to consume based on how much we like it (consummatory response) (93).

The study of this sub-domain of taste is quite challenging, particularly in humans. Previous studies have attempted to assess the consummatory reward value of using a taste reactivity test (142). This test is commonly used in animal studies, where an intraoral cannula infuses a taste stimulus directly into the oral cavity, and the facial reactions are videotaped and analysed by the investigator (30). Common ingestive (i.e. positive) animal reactions include tongue protrusions and paw licking, while common aversive (i.e. negative) reactions include gapes and chin rubbing (147). Our research group has adopted this test for the use in human obesity studies ((148) (unpublished work)). In this human study, a 50ml chocolate milkshake flowed directly into the subjects' mouths using gravity to deliver a rate of 25mL/minute from an 'IV giving set bag'. Subjects' facial expressions were recorded on a camera and were later analysed using a Facial Expression Food Preference Rating Scale ((148) (unpublished work)). Standard ingestive human facial reactions to pleasant stimuli include tongue protrusion, mouth movements and ingestion of the stimuli. While aversive facial reactions include gaping, head shaking, wrinkling of the nose, retraction of the head away from the source and fluid expulsion (4, 149, 150). This test carry's the benefit of assessing taste reactivity via a direct measure, but it also has some limitations particularly in human studies including the learned behaviour of adults in hiding their genuine feeling, particularly when being filmed.

In this study, I attempted to examine the consummatory behaviour using indirect assessment and adopt the same methodology that was previously used by our group in RYGB patients (508). This method is based on previously used visual analogue scales (509-511). The general labelled magnitude scale (gLMS) in particular is preferred to other VAS as it can be applied for within group and also cross-sectional evaluations. The “Just About Right” (JAR) scale has also been approved by other taste researchers (512-514). Results of this scale were shown to produce a linear association with log sugar concentration (515). Furthermore, a range of suprathreshold sucrose concentrations can be assessed with no post-ingestive factors due to the sip and spit technique. The “just about right” VAS has been widely used in sensory consumer testing and marketing research because it provides information on the affective value of the stimulus (515, 516).

Surely, indirect measures are less reliable than direct means of estimation, but they are relatively easy and efficient, this is of particular importance in my study considering the number of tasks my patients were involved with. Besides, this is the first study to assess any aspect of eating behaviour in DJBL patients, and therefore indirect measures are a logical first step to this approach.

8.2 Materials and method

8.2.1 Subjects

Forty-Two subjects (23 DJBL, 19 SMT) were recruited to Hammersmith Hospital, Imperial College London and Southampton General Hospital. Patients were randomised into one of the two arms of the study DJBL vs. SMT via the InForm system (the eCRF database for the study). All patients were put onto a liquid diet (Fortisip compact) of 1200Kcal for women and 1500Kcal for men for 21 days (7-days before intervention and 14-days after intervention). Progressive Ratio Task was carried out 2-weeks before intervention (Baseline), and 6-months post intervention. The study was conducted according to the Declaration of Helsinki and all procedures were approved by the National Research Ethics Service NRES committee London-Fulham REC reference 14/LO/0871.

8.2.2 Consummatory taste test

Consummatory taste reward value test for sucrose was performed following the same methodology previously described by Bueter *et al.* (2011) (111). Details of the test description and its data analysis are described in chapter two: Materials and Methods, section (2.4.7).

8.2.3 Statistical analysis

The dependent variables used for 2-way repeated measures ANOVA analysis were created by averaging each set of ratings across the 3 trials for each of the 5 concentrations. Within group comparisons for VAS ratings were performed using concentration as the first factor and time as the second factor.

8.3 Results

8.3.1 Attrition

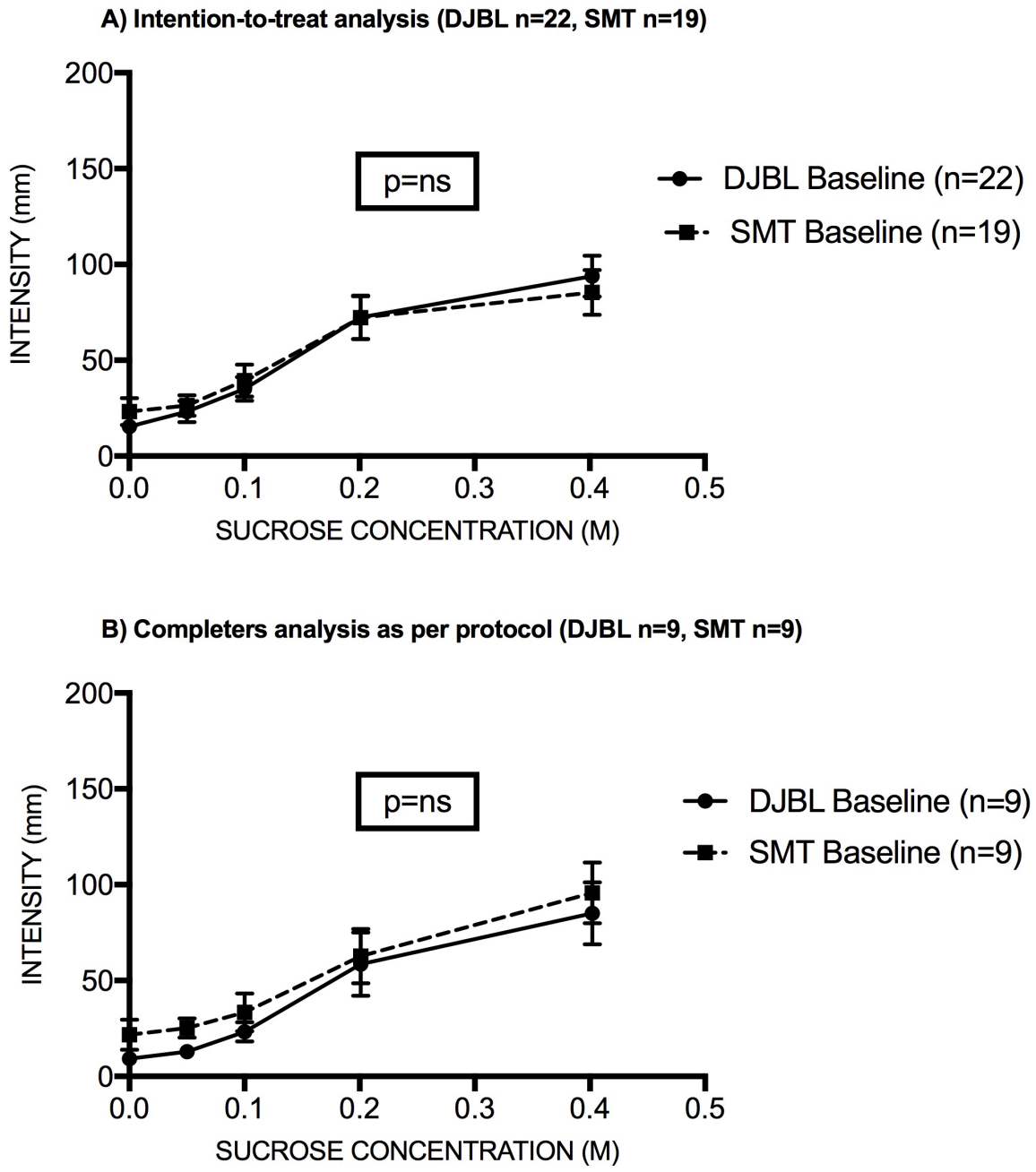
Forty-Two subjects (23 DJBL, 19 SMT) were due to have the consummatory test done. However, one DJBL subjects was not compliant with the task protocol and therefor was excluded from this task. A total of forty-one (22 DJBL, 19 SMT) were included in the baseline analysis.

Due to the timelines of this thesis, only 25 subjects (12 DJBL, 13 SMT) were due for the 6-months post intervention visit by the time data had to be locked for analysis. In The DJBL group, two patients had the device removed prior to the 6-months follow-up visit and one patient did not follow the task instructions so was excluded. In the SMT groups, two subjects were lost to follow up, one subject withdrew consent, and one subject had missing data due to within study-day complications. Therefore, a total of 18 subjects (9 DJBL, 9 SMT) were included in the 6-months post intervention data analysis.

8.3.2 Baseline assessment

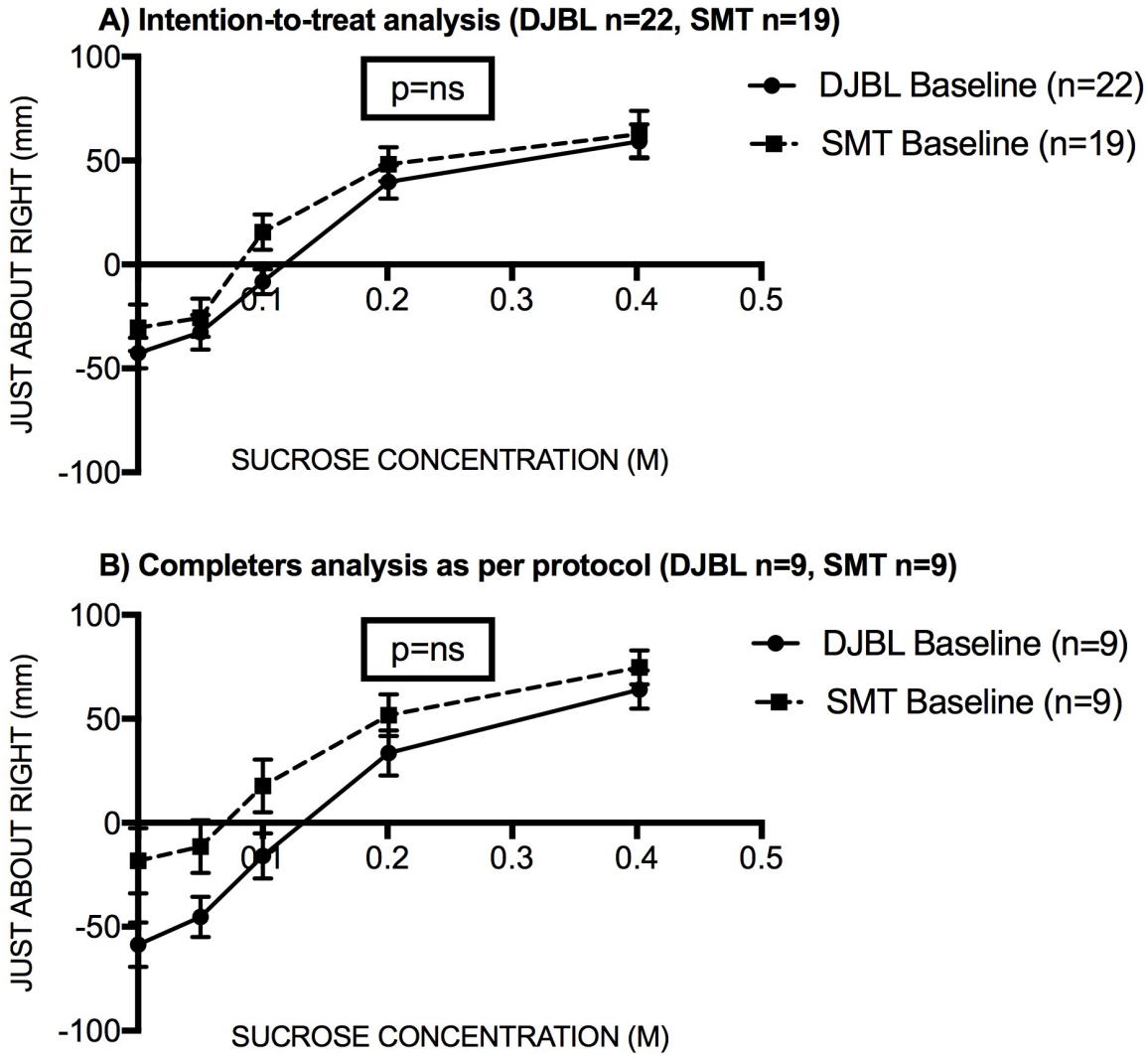
There were no significant differences in the baseline characteristics of sweet consummatory behaviour represented by rating of intensity (Figure 36 A and B), the just about right (Figure 37 A and B), and pleasantness (Figure 38 A and B), in the ‘intention-to-treat analysis’, and ‘completers analysis as per protocol’.

Figure 36 (A and B) Baseline 'intensity' rating



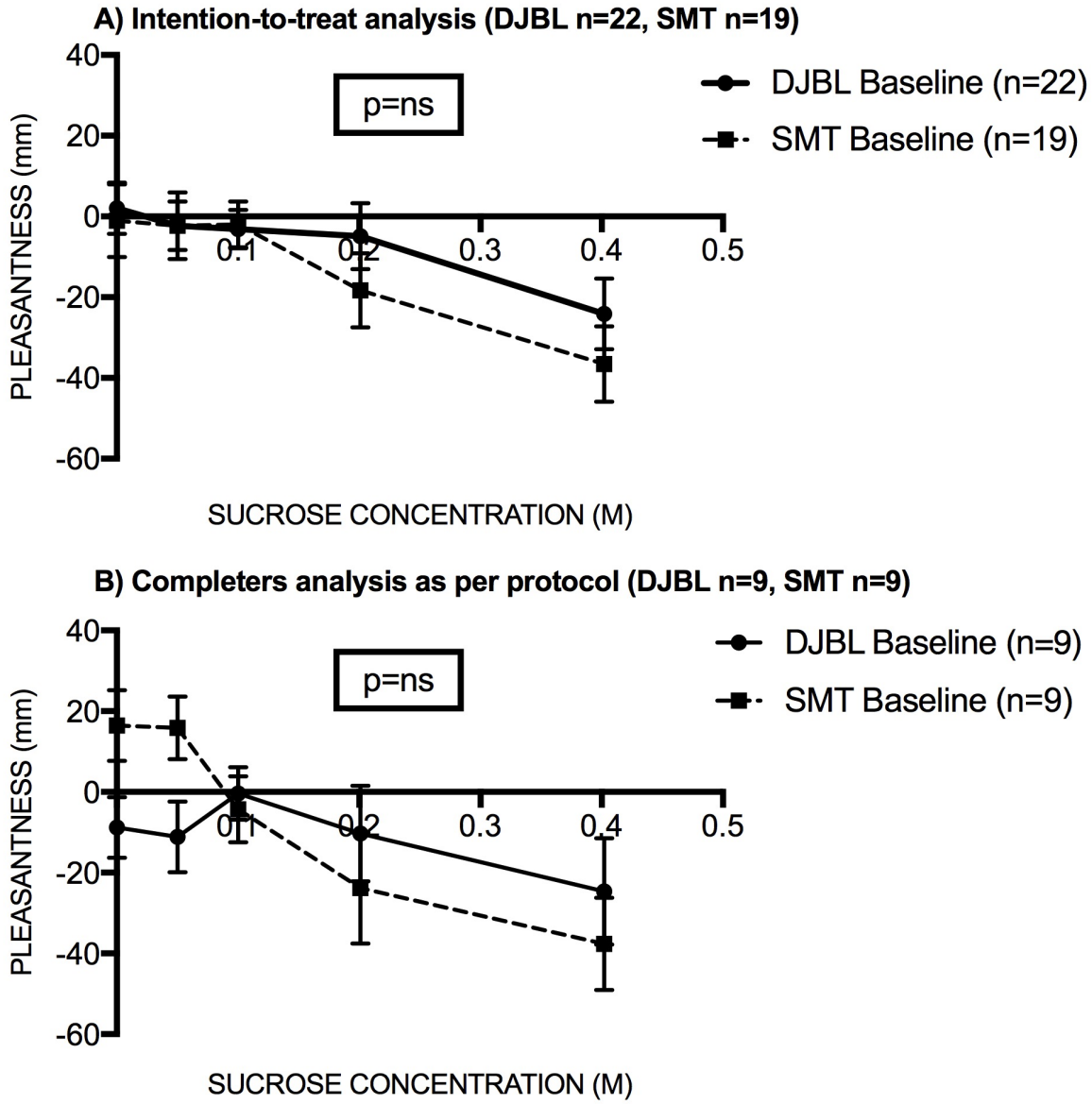
Intensity ratings as functions of the 5 concentrations of sweet. Comparison between groups made using t-test for each of the 5 concentrations.

Figure 37 (A and B) Baseline 'Just About Right' ratings



JAR ratings as functions of the 5 concentrations of sweet. Comparison between groups made using t-test for each of the 5 concentrations.

Figure 38 Baseline 'Pleasantness' ratings



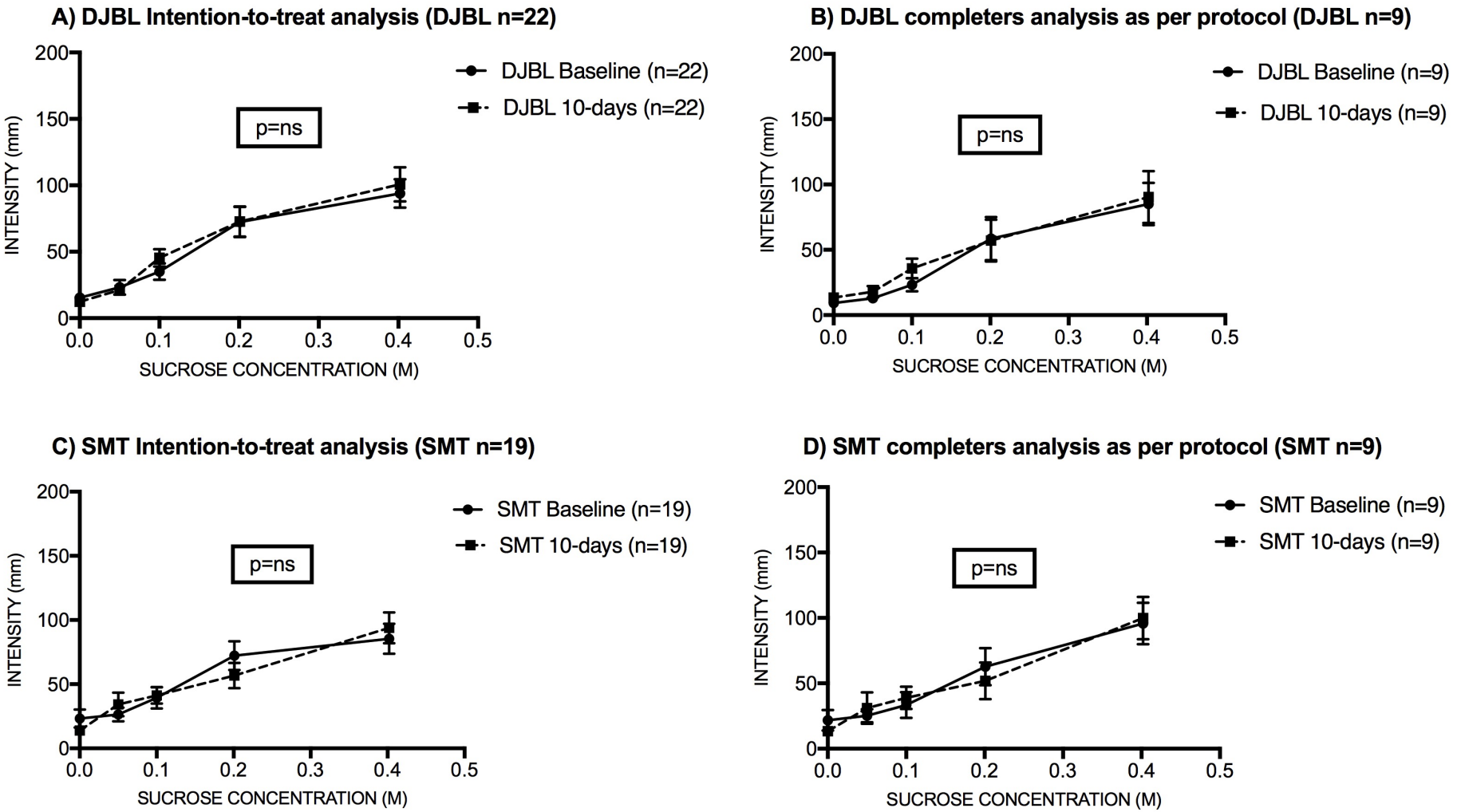
Pleasantness ratings as functions of the 5 concentrations of sweet. Comparison between groups made using t-test for each of the 5 concentrations.

8.3.3 10-days post intervention

At 10-days follow-up there were no changes in any of the taste scales in the intention-to-treat analysis (DJBL n=22, SMT n=19) nor in the completers analysis as per protocol (DJBL n=9, SMT n=9). Figure 39 shows the intensity ratings, Figure 40 shows the Just about right ratings, and Figure 41 shows the Pleasantness ratings.

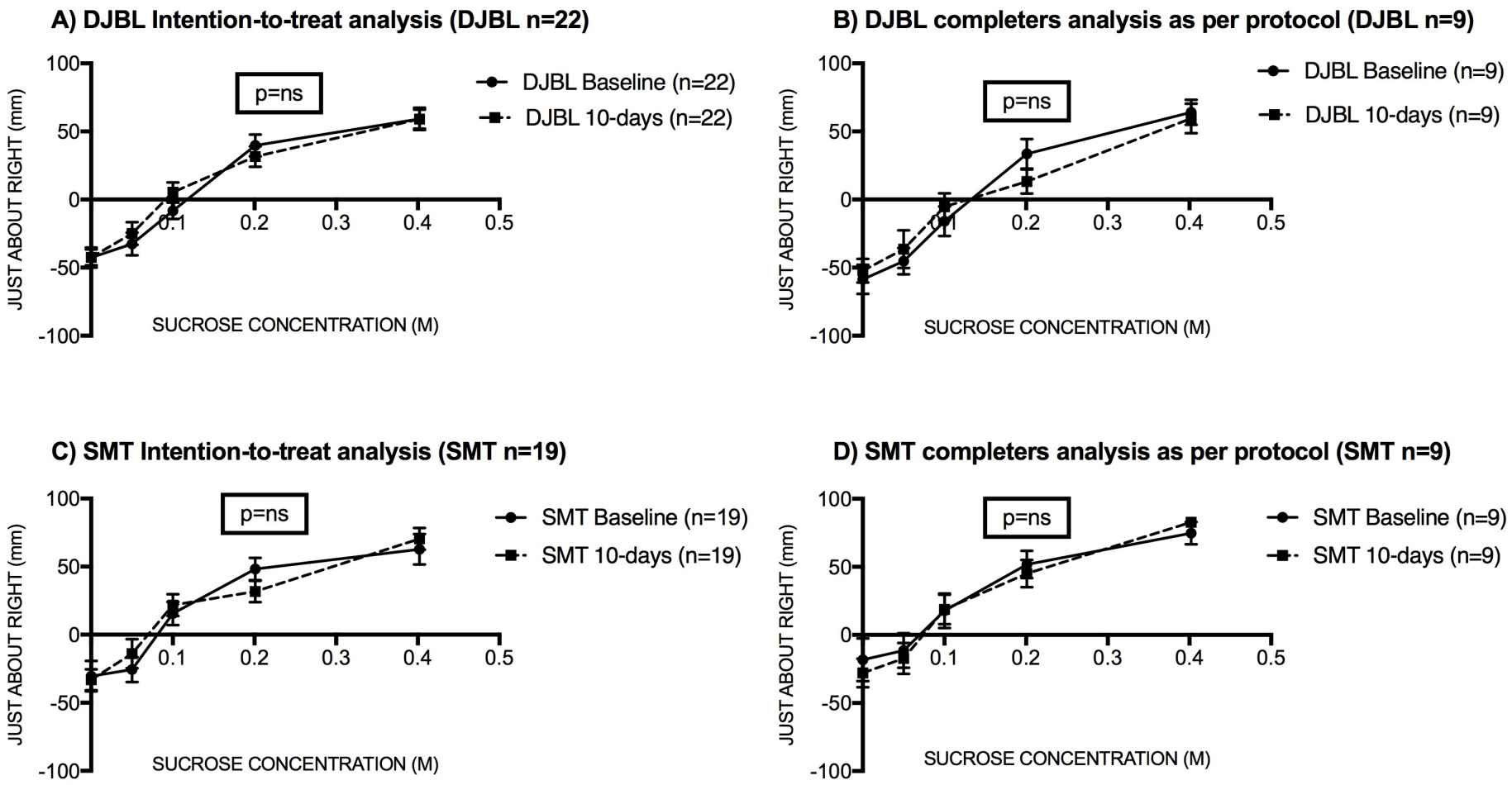
Data within groups were analysed using a two–way ANOVA with repeated measures. Statistical analyses outcomes are presented in Table 8-1.

Figure 39 10-days 'Intensity' taste ratings



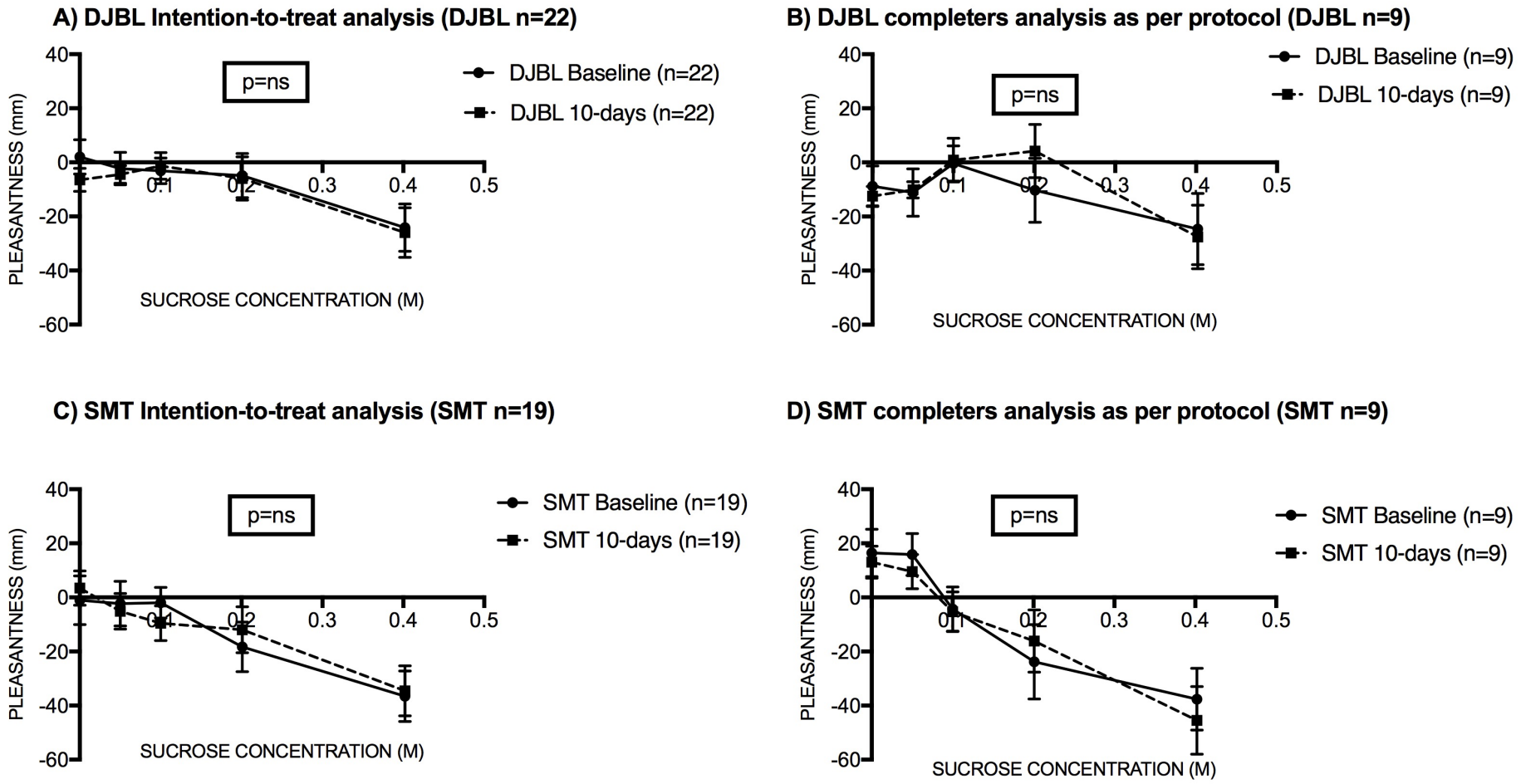
Intensity ratings as a function of the 5 concentrations of sweet taste. Comparisons within groups performed using 2-way repeated measures ANOVA.

Figure 40 10-days 'Just about right' taste ratings



Intensity, ratings as a function of the 5 concentrations of sweet taste. Comparisons within groups performed using 2-way repeated measures ANOVA.

Figure 41 10-days 'Pleasantness' taste ratings



Pleasantness ratings as a function of the 5 concentrations of sweet taste. Comparisons within groups performed using 2-way repeated measures ANOVA.

Table 8-1 10-days two-way ANOVA with repeated measure results for all taste ratings

A) Intention-to-treat analysis (DJBL n=22, SMT n=19)			
Sweet Intensity ratings	**Concentration**	**Time/Treatment**	**Concentration x time/surgery**
DJBL (n=22)	F(4,84)=41.55;p<0.0001	F(1,21)=0.46;p=0.502	F(4,84)=1.27; p=0.29
SMT (n=19)	F(4,64)=36.71;p<0.0001	F(1,16)=0.56;p=0.81	F(4,64)=0.99; p=0.41
Sweet JAR ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL (n=22)	F(4,84)=104.6;p<0.0001	F(1,21)=0.43;p=0.52	F(4,84)=1.66;p=0.17
SMT (n=19)	F(4,64)=58.33;p<0.0001	F(1,16)=0.99;p=0.76	F(4,64)=1.31;p=0.28
Sweet Pleasantness ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL (n=22)	F(4,84)=3.49; p=0.011	F(1,21)=1.68;p=0.42	F(8,84)=0.636;p=0.69
SMT (n=19)	F(4,64)=5.71; p=0.001	F(1,16)=0.01; p=0.93	F(4,64)=0.86; p=0.49
B) Completers analysis as per protocol (DJBL n=9, SMT n=9)			
Sweet Intensity ratings	**Concentration**	**Time/Treatment**	**Concentration x time/surgery**
DJBL (n=9)	F(4,32)=16.22;p<0.0001	F(1,8)=0.59;p=0.46	F(4,32)=0.27; p=0.89
SMT (n=9)	F(4,32)=26.21;p<0.0001	F(1,8)=0.02;p=0.91	F(4,32)=0.61; p=0.66
Sweet JAR ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL (n=9)	F(4,32)=58.32;p<0.0001	F(1,8)=0.002;p=0.96	F(4,32)=2.02;p=0.12
SMT (n=9)	F(4,32)=41.83;p<0.0001	F(1,8)=0.23;p=0.65	F(4,32)=0.59;p=0.67
Sweet Pleasantness ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL (n=9)	F(4,32)=2.42; p=0.07	F(1,8)=0.45;p=0.52	F(4,32)=0.69;p=0.60
SMT (n=9)	F(4,32)=10.56; p<0.0001	F(1,8)=0.21; p=0.66	F(4,32)=1.27; p=0.30

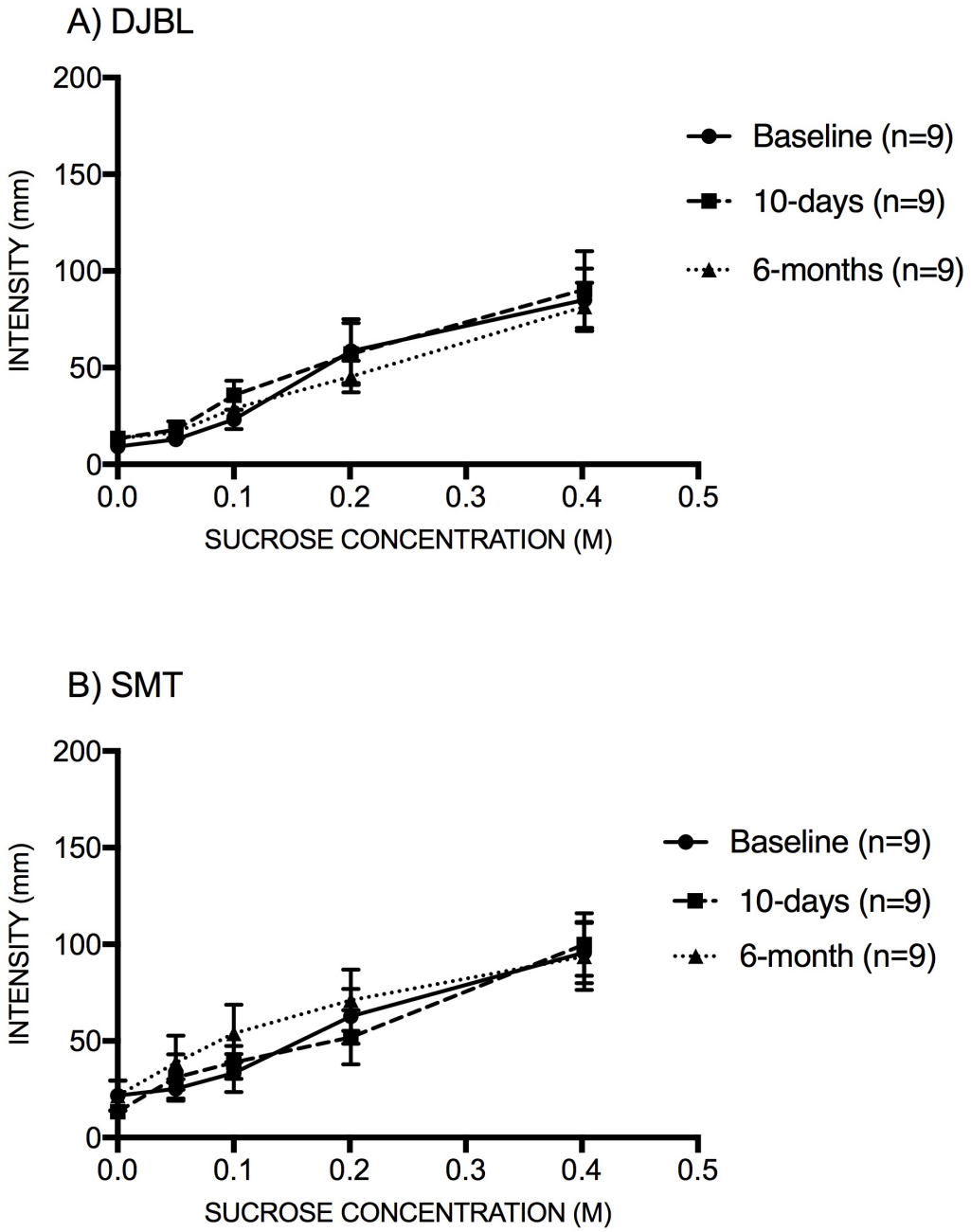
Table summarises the results of the effects of time on the ratings for intensity, just about right (JAR) and pleasantness across the 5 concentrations of sweet solutions. Comparison within groups made using 2-way ANOVA with repeated measures.

8.3.4 6-months post intervention

At 6-months post-intervention, no significant differences were found in any of the taste scales neither in the DJBL group not in the SMT group. Figure 42 shows the intensity ratings, Figure 43 shows the Just about right ratings, Figure 44 shows the Pleasantness ratings.

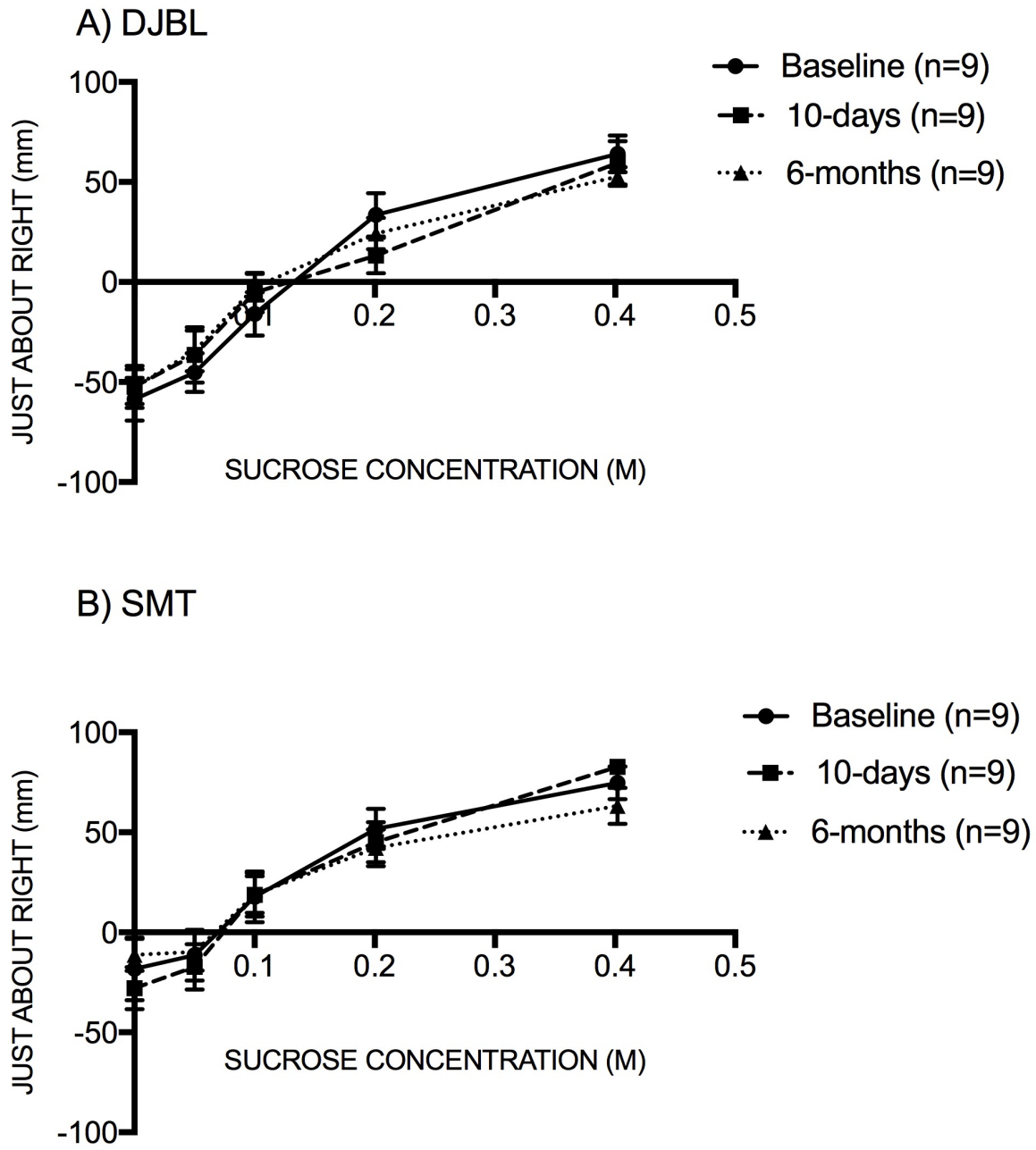
Data within groups were analysed using a two–way ANOVA with repeated measures. Statistical analyses outcomes are presented in Table 8-2.

Figure 42 (A and B) Intensity ratings for DJBL and SMT groups at baseline, 10-days, and 6-months post intervention



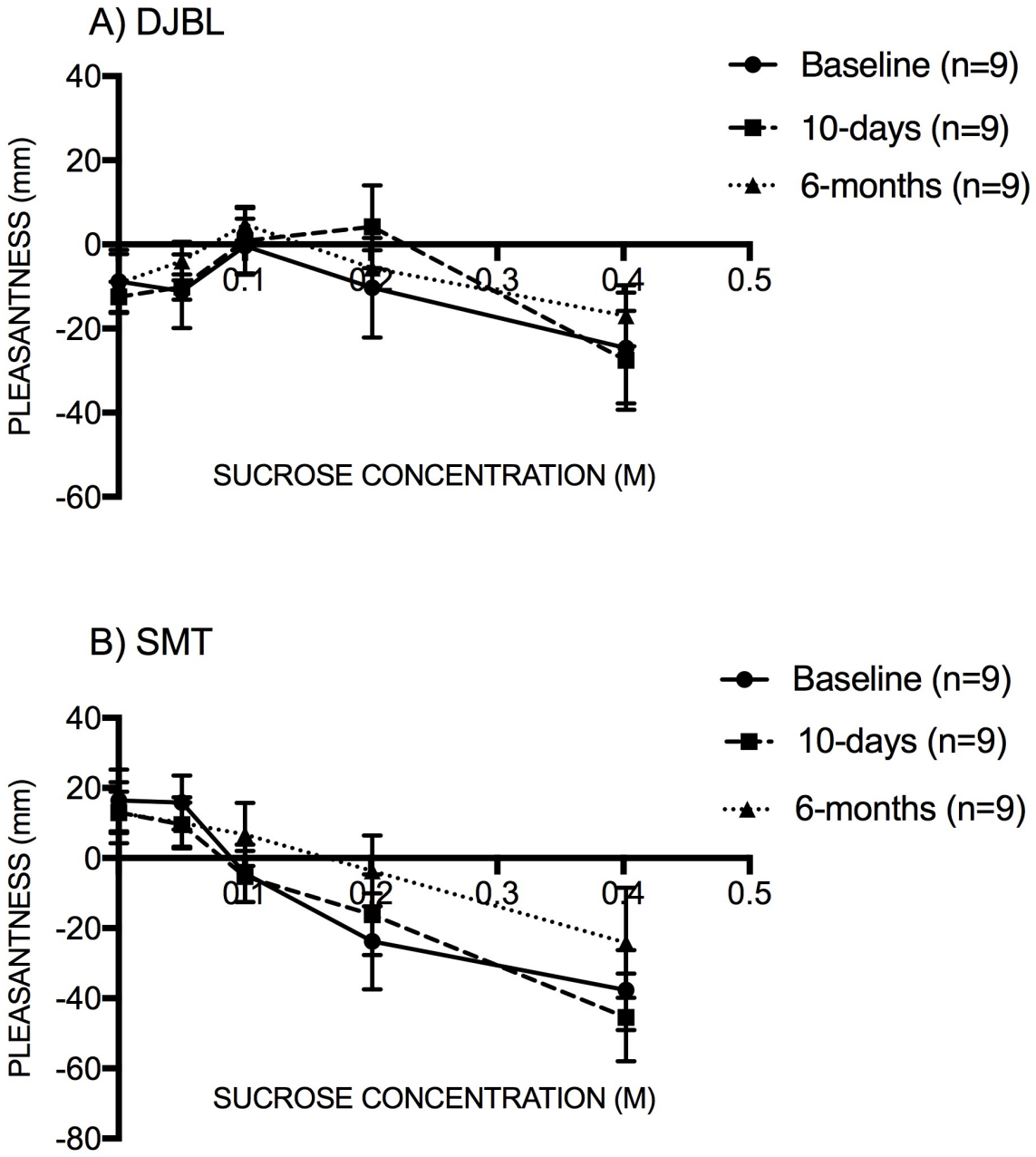
Intensity ratings as a function of the 5 concentrations of sweet in A)DJBL subjects and B)SMT subjects. Comparisons performed using 2-way repeated measures ANOVA.

Figure 43 (A and B) Just about right



'Just about right" ratings as a function of the 5 concentrations of sweet in A)DJBL subjects and B)SMT subjects. Comparisons performed using 2-way repeated measures ANOVA.

Figure 44 (A and B) Pleasantness ratings



Pleasantness ratings as a function of the 5 concentrations of sweet in A)DJBL subjects and B)SMT subjects. Comparisons performed using 2-way repeated measures ANOVA.

Table 8-2 6-months post-intervention results of taste ratings

Sweet Intensity ratings	**Concentration**	**Time/Treatment**	**Concentration x time/surgery**
DJBL	F(4,32)=21.96;p<0.0001	F(2,16)=0.44;p=0.65	F(8,64)=0.46; p=0.88
SMT	F(4,32)=23.63;p<0.0001	F(2,16)=0.78;p=0.48	F(8,64)=0.77; p=0.63
Sweet JAR ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL	F(4,32)=74.56;p<0.0001	F(2,16)=0.07;p=0.93	F(8,64)=1.27;p=0.274
SMT	F(4,32)=41.96;p<0.0001	F(2,16)=0.13;p=0.88	F(8,64)=1.82;p=0.089
Sweet Pleasantness ratings	**Concentration**	**Time/Surgery**	**Concentration x time/surgery**
DJBL	F(4,32)=2.80; p=0.042	F(2,16)=1.069;p=0.367	F(8,64)=0.701;p=0.6898
SMT	F(4,32)=9.38; p<0.0001	F(2,16)=2.21; p=0.142	F(8,64)=1.79; p=0.096

Table summarises the results of the effects of time on the ratings for intensity, just about right (JAR) and pleasantness across the 5 concentrations of sweet solutions. Comparison within groups made using 2-way ANOVAs.

8.4 Discussion

In this chapter, I found that the consummatory hedonic value a sweet stimulus was neither altered after treatment with DJBL nor with the conventional Standard Medical Therapy (SMT).

The consummatory behaviour is one of the hedonic domain's components (consummatory and appetitive) and accounts for how much the stimulus is like or disliked (95). It's been hypothesised that the change in food preferences that occur post most bariatric surgeries is attributed to the change in the reward value of food. Nevertheless, the actual mechanism that drives this shift is still to be unravelled.

Exaggerated levels of bile acid in RYGB patients were found together with changes in the hedonic value of sweet and fatty food. Neither of those changes occurred post BAND (55). In RYGB the two parameters were not significantly associated with each other, but bile acid continues a potential modulator of central hedonic processing of food (55). Bile acids cross the blood–brain barrier (517), and its receptor TGR5 is present in the brain (518). Activation of TGR5 stimulates the release of fibroblast growth factor 19 (FGF19) and GLP-1 (467, 519) which both reduces food intake (519, 520), and are both increased after RYGB (517, 521).

The bypass of the proximal small bowel with DJBL also results in increased bile acid, FGF-19 and moderate (but not significant) rise in GLP-1, and they normalize following explanation (522). Despite the similarity of change in those hormonal profiles between DJBL and RYGB, I obtained no shift in consummatory hedonic changes with DJBL.In this study, I did not measure the physiological satiety mediators, but the data was collected and will be analysed as part of the ongoing DJBL trial. Results of the association between the satiety mediators with changes in all the dimensions of taste are going to be an essential and remarkable outcome.

It is important to note that despite the consensus that RYGB alters the hedonic value of food. The study of RYGB patients on the consummatory behaviour had detected no changes in the sucrose concentration that is 'just about right' before and after surgery (111). On the

contrary, Pepino *et al.* (2014) found that RYGB surgery, but not BAND, caused a rapid shift in sweetness palatability from pleasant to unpleasant, with sucrose tasting (414).

Animal studies also have yielded mixed results. Post-operative decreases in consummatory responsiveness to sucrose (417-419) and fat emulsion (417), was found. Still, it led to no changes in other studies (420, 421).

Weight loss via a standard medical therapy in this study also had no effect on any of the taste ratings, as expected. Published data on the effects of intentional weight loss on the liking or intensity of sweet taste appear to be in scarce. The effect of VLCD on the pleasantness ratings of food was shown to decrease (509, 523), increase (510, 524, 525), or remain unchanged (525). The differences between the studies are due to differences in stimuli used (pure vs. mixed), types of scales used to determine intensity or pleasantness, the administration of a preload before testing, type of dietary intervention and its length. In this we showed that both groups had the same levels of ratings in all three scales (pleasantness, JAR, and intensity), which shows the validity in the measuments of scales considering this is a randomized study and both groups have similar starting characteristics. Previous studies showed that suing the scales on a different cohort of patients yield different results (96, 526).

The merits of this study include the design of the study being a randomised controlled trial, and a relatively large sample size compared to previous studies of the same method. Also, the use of VAS led to ease and standardisation in interpreting and measuring the results. I also modified the experiment to use five instead of seven concentrations to reduced confusion as was suggested by Miras A. (2013) (527). On the other hand, some of the limitations include the use of a pure sucrose stimulus. Pure stimuli taste different to flavoured drinks, of which conditioned aversion to them would have led to different results.

To conclude, the no change in consummatory behaviour may add to the reasons why there was no change in food intake and a tiny change in food preferences in this cohort of patients. This study adds to the pool of literature investigating the mechanisms of change in eating behaviour in bariatric surgery.

CHAPTER 9 GENERAL DISCUSSION

9 Generall Discussion

9.1 Introduction

The prevalence of obesity is constantly spreading and has now reached dramatic levels with 27% of the UK adult population are now obese (528). Obesity was for long considered a condition affecting only those with a weak willpower or lazy but our understanding of this condition has now changed. Obesity is complex and chronic brain disease caused by the physiology of the body and only to a small extent by the psychology of the brain.

With a conventional weight treatment, only 20% of people respond to diet therapy and manage to maintain the weight off. However, up to 80% who diet do not lose the weight off, or regain it shortly afterwards, and it is not their fault. Research shows that body weight is centrally regulated, peripheral hormone signals from the GI tract, pancreas, and adipose tissue are sent to the brain, primarily in the hypothalamus, to control satiety and energy expenditure. Out of those people who diet, 2 out of 10 people respond well to those signals, and the remainders require stronger signals from the gut to the brain. We have also learnt that those 'poor responders' also exist in more invasive treatments like bariatric surgery but estimations of the rates as still in scarce.

Therefore, our aim in obesity research, in general, is to understand the physiology of obesity to our best ability and use this knowledge to develop more personalised treatments that can help us to combat obesity and its associated comorbidities. In this PhD thesis, I tried to use what we already know about the most effective treatment for obesity and T2DM, the RYGB procedure, and use a reductionist approach to learn in more depth the changes that can contribute to its benefits. In this thesis, I assessed the changes in eating behaviour following the bypass of the proximal small bowel using the DJBL as compared to standard medical therapy (standard clinical treatment for obesity with T2DM).

9.2 Most important findings

All the data presented and discussed in this thesis are novel and add to the current literature in the fields of ingestive behaviour, obesity and bariatric surgery.

In the present study, the DJBL patients lost an average of 9kg, which was not different to what the SMT groups had lost during the same treatment period. The similarity in weight loss during those 6-months was explicable by the unpredicted lack of change in different measured dimensions of eating behaviour.

Food intake at 6-months was reduced (not significantly) within both groups and was not significantly different between groups. Nevertheless, the DJBL group consumed around 600kcal less, compared to only about 300kcal less in the SMT, at 6-months compared to pre-intervention. Despite it not making a significant impact on weight loss at this stage, it can be an advantage for longer-term results. Also, food intake in this study was not associated with weight loss, which shows that other variables with the diet may have contributed to the achieved weight results. Macronutrients preferences did not change when presented as a percentage of total food intake. Nevertheless, the grammes of food consumed from fats and oils were reduced, and those from fish and fish products were increased, in the DJBL group but not changed in the SMT group.

Despite the similarity in weight loss results, I showed that the DJBL might exert its benefits by making weight loss or weight loss maintenance slightly easier than dieting alone. This was suggested by the psychological changes during the 6-months intervention. Food appeared to be less rewarding and had less power on people with DJBL as measured by BAS/BIS and Power of Food, questionnaires. The style of eating was changed differently between the two treatment, the DJBL lowered external eating with no change in other styles of eating; and the SMT reduced emotional eating with no change in other styles of eating.

Taste seemed not to have been altered by the bypass of the proximal small bowel. I measured two out of three domains of taste (sensory, reward, and physiology). In the reward domain of taste, I measure both the consummatory and appetitive behaviours. No change in any of the domains or sub-domains was found.

9.3 Discussion

Changes in almost all aspects of eating behaviour following different bariatric procedures, particularly RYGB, have been studied extensively over the last few years. Multiple components of the RYGB were attributed to the positive change in eating behaviour, but the bypass of the proximal small bowel remained the prime modulator.

The bypass of the proximal small bowel results in a physical shortcut for the nutrients ingested to reach the distal bowel and mix with the concentrated bile juice, This mechanism is known as the hindgut hypothesis (529). Concentrated bile acid hyperstimulates TGR5 receptors to release GLP-1 and fibroblast growth factor 19 (FGF19) (467, 519) which both reduce food intake (519, 520) and are both increased after RYGB (517, 521) and DJBL (479, 522). Nevertheless, the rise in postprandial GLP-1 post-DJBL has not been consistent in all studies. Some studies found a substantial increase (479, 530), another found only a modest increase (522), and one observed that GLP-1 was only raised post-prandial in subjects with T2DM but not in those with normal glucose levels (503).

Another satiety-promoting and food intake-lowering effect hormone produced by the L cells of the distal bowel is PYY. PYY was also found to increase in DJBL patients. Surprisingly, neither GLP-1 nor PYY influenced satiety or food intake in T2D patients treated with DJBL (503). Measuring gut hormones was beyond the scope of this thesis. However, there is no reason why I should consider that our patients would physiologically behave in a different way. Based on verbal reporting, food intake was reduced up to 6-months, but it was not significantly different between the DJBL and the SMT group. Suggesting that both groups were following the dietary counselling advice, and it was the primary modulator of the reduced food intake. It is worth noting that the DJBL did lower their food intake to a greater extent than the SMT, which could be attributed to the modest increase in postprandial GLP-1 and PYY or other unmeasured satiety hormones.

The DJBL does not result in reduced gastric emptying of liquid meals (503) but may lead to higher retention of solid meals (453). Based on the hindgut hypothesis, exaggerated satiety

hormones result in reduced gastric motility and increased ileal break. I did not measure gastric emptying as such, but I recorded hunger and fullness over a 180min post an MMT drink. Both, DJBL, and SMT, groups did not report any changes in satiety which was supported by results from Rhode et al. (2016) (503). The type of diet consumed during the study experiment could be behind the difference found in gastric emptying and reported levels of satiety. The device is anchored into the duodenal bulb, 0.5 cm distally from the pylorus. It is possible that soft or liquid food can pass through the anchors and come into early contact with the bile acid resulting in a lower rise of satiety hormones i.e. similar to not having the device. Whereas solid food, despite it being semi-digested, it still contains chunks, which prevent it from leaking into the duodenum. Escalona *et al.* (531) used DJBL combined with a restrictor orifice (flow restrictor) to avoid semi-digested food from passing to the duodenum and found a reduced gastric emptying.

In the study of Escalona *et al.* (2009), they found additive benefits of the flow restrictor, not only on gastric emptying but also on weight loss. Their patients had a total of 40% EWL and increased satiety compared to 22% EWL at 12 weeks, in other studies published around the same time (477). This finding lead us to the hypothesis that the position of the DJBL anchors may be slightly altered in some patients depending on endoscopic/implantation techniques, implantation obstacles, or simply due to a migration of the device post implantation, which can be asymptomatic in some patients (442). In this study, our patients were treated at two different sites in the UK, at Imperial College London and Southampton General Hospital. Therefore, we cannot exclude positioning variation unless we would have done an abdominal MRI at the start and possibly at the end of the study. Correlation of the DJBL position with patient's weight achievement and even with changes in food preferences can be fascinating but maybe unfeasible.

I have suggested earlier in my discussion that there was a possibility that the DJBL patients did not have to work as hard to achieve the same weight loss results. Or perhaps the opposite for the SMT. This judgment is based on the results of the psychological questionnaires and even on personal clinical observations. The DJBL patients frequently reported that they were feeling fuller earlier; not being always hungry, and they even had to be reminded to eat. Whereas the SMT repeatedly showed concerns over their weight and diet control, they also verbally reported doing more physical exercise and going to more gym sessions. These anecdotal reports bring us back to the study that was carried out by Gersin *et al.* (2010) where they randomised 21 obese subjects to receive the DJBL device and 26 to have sham mock implantation (465). Both groups received identical nutritional counselling. In

this study, the DJBL groups had superior weight loss achievement at 12-weeks post intervention with -8.2kg compared to -2.1kg in the sham group. This study shows the powerfulness of relying on the benefits of the treatment intervention without exerting much effort.

Regarding the taste function, many mediators were described in the literature that could alter taste post-RYGB and led us to investigate it further in DJBL. The taste system has been shown to have receptors and to be modulated by the action of GLP-1, and leptin (532). In mice, taste cells produce PYY and its elevation in the saliva can reduce food intake (533). As discussed earlier, the levels of both GLP-1 and PYY are higher post-DJBL, postprandial but not fasting. These hormones may exert their effects to modulate either the sensory, reward or physiological (salivation) domains of taste function.

GLP-1 is expressed in murine taste bud cells and is considered as a potential paracrine modulator of the peripheral gustatory apparatus, as GLP-1 receptors are found on intragemmal taste afferent nerve fibres (113, 534). GLP-1 receptor knock-out mice have been reported to be less responsive to low sucrose concentrations in a brief-access licking test. Thus, sufficiently high plasma levels of GLP-1 may affect peripheral taste signalling. Reception and transduction of sweet-tasting compounds have been shown to involve, in part, α-gustducin and the sugar binding receptor subunit T1R3 (535-537) but these proteins also partly mediate the glucose-dependent GLP-1 secretion from enteroendocrine L cells of the gut (538). The close cellular and functional relationship of GLP-1, T1R3, and α-gustducin may allow the elevated levels of GLP-1 seen after gastric bypass to influence T1R-related signal pathways at multiple levels. Decreased detection thresholds in humans seen after gastric bypass are consistent with this possibility. DJBL does not increase GLP-1 levels to the same extent as RYGB and therefore might not have reached the clinical significance levels for optimised taste detection threshold.

Leptin, a satiety hormone made by adipose cells, is also known to modulate taste and brain reward responses. Leptin may act on dopaminergic neurones expressing the leptin receptor on the gateway to the mesolimbic system, the ventral tegmental area, to reduce food intake and the preference for palatable food through projections to limbic nuclei (539). Leptin inhibits orexin neurones but not melanin concentrating hormone neurones in the lateral hypothalamus (540). Central administration of leptin inhibits dopamine release in the nucleus

accumbens and suppresses the preference for high fat and sucrose (540). Food restriction in mice increases the rewarding value of sucrose and administration of leptin decreases it (541). In an fMRI study of obese, but not leptin-deficient subjects, 10% weight loss through dietary means was associated with higher activation of brain reward systems, including the brainstem and parahippocampal gyrus, in response to food pictures compared to baseline (542).

Kawai et al. (2000) found that Ob-R, a leptin receptor, is also found in the taste cells of circumvallate papillae in mice, indicating that taste cells are a site of leptin action (100). Ob-R is also present in the central nervous system (101) peripheral cells, such as T-cells (102), vascular endothelial cells (103), muscle cells (104), and pancreatic cells (105). It is not surprising that the taste cells of obese diabetic mice were not influenced by the injection of leptin, due to peripheral leptin resistance in obese mice and humans (106). Obese rodents and humans have increased levels of circulating leptin compared to normal weight subjects (107). During weight gain, basal plasma leptin levels would gradually rise, and at the same time, sweet taste sensitivity reduces. The chronic adaptation to high concentrations of leptin may elicit leptin resistance in the taste cells as suggested by Yoshida *et al*. (2015) (108). This means that any further increases in leptin concentration would not elicit further suppression (100).

During weight loss, leptin levels decrease, and sweet taste sensitivity improves i.e. decreased thresholds, in invasive- i.e. surgical induced weight loss (109-111) and non-invasive- i.e. Diet-induced weight loss (112) procedures. Taste sensitivity is also correlated with the reduction in leptin levels (112).

In this study, I did not measure leptin, but the similarity in weight loss and % fat loss suggests similar changes in leptin if there was any. Nevertheless, I think that patients require a massive change in weight to cause such a change, such that found in RYGB. This is supported by the set-point theory. Tam *et al.* also suggested the possibility of multiple steady states for body weight at different environments **(543)**. He suggested that once the system settles into the higher steady state, it will be challenging for it to be lowered due to opposed physiological mechanisms rising it back, unless the force is strong enough to reset the steady state **(543)**. Possibly similar to the force produced by bariatric surgery.

An additional burden was added to the interpretation of my results is the fact that all my patients were poorly controlled T2D patients. Fabbi (1954) was the first researcher who suggested that patients with diabetes may have impaired taste function (121). It was later

suggested that this abnormality might be due to the elevated levels of blood sugar that cause a 'satiation effect' towards sweet taste and/or neuropathy causing a reduced taste sensitivity overall (122). Some studies were then carried out to confirm those finding and it is now well established that T2DM patients have higher thresholds for glucose and sucrose detection than Type 1 patients and controls (123-126). In addition, hyperglycemia is associated with higher sweet taste thresholds between diabetic and pre-diabetic patients (127, 128). Previous RYGB studies used a mix of diabetic and non-diabetic patients, and therefore this could explain the poor taste changes result we found as opposed to those studies.

9.4 Limitations

Specific limitations of each study task 'chapter' were described throughout the thesis. In this section, I want to highlight a few limitations concerning the overall design of the study or study cohorts.

This eating behaviour study was a sub-group of a larger clinical trial investigating the effect of DJBL on diabetes remission and different mechanistic. As outlined in my methods chapter, the study day was long (8am-3.30pm) and consisted of all the tasks described in this thesis. Not to forget to mention that they were fasting until around 12 pm when they were served the MMT drink. Eating behaviour is challenging to assess and many variables interchange to make an outcome. Tiredness, sleepiness, hunger, taste buds fatigue, mood, stress resulting from a clinical environment, can all have an impact on my results.

A possible limitation of the observed weight results is that our patients were poorly controlled diabetic patients on various oral medications. Conventional medical treatment for glycemic control is challenging because some oral hypoglycemic agents may result in weight gain or make weight loss a more challenging task.

Another limitation is that all taste testing was carried out in the fasting state to reduce variability. However, the DJBL device only results in a postprandial rise in gut-hormones and may therefore only have an immediate affect all taste domains. Debate whether satiated or fasted states affect the recognition domain of taste or only the hedonic domain of gustatory perception exists (544).

9.5 Conclusion

To conclude, this is the first study looking at the effect of DJBL on eating behaviour. I explored different aspects of eating behaviour including general food intake, food preferences, psychological factors, as well as taste domains, sensory, consummatory reward, and appetite reward.

My findings initially showed that weight loss was predominantly due to calorie restriction and that there was no additional benefit on weight loss by the endoscopic bypass of the proximal small bowel in the first 6-months. I also found that the DJBL resulted in only modest change in food preferences away from food containing fats and oils and more towards fish and fish products. However, I then showed that the DJBL device had a modest effect on some eating behaviour and psychological entities that may reflect the physiological change caused by the device. Among patients treated with DJBL, more patients had improved reward responsiveness and reduced external eating, which could have made weight loss slightly easier when compared to the SMT group.

Obesity is associated with complex alterations in food reward functions at the neural and behavioural level. DJBL was not able to cause changes in the hedonic value, the reward domain in the brain, resulting from the appetitive and consummatory behaviour, and showed no effect on the sensory domain, sweet sensitivity, at the short and long term post implantation

The taste function findings complemented the food intake and food preferences results to explain the lack or modest changes found in this cohort of patients. This study adds to the pool of literature investigating the mechanisms of change in eating behaviour in bariatric surgery. I conclude, that the bypass of the proximal small bowel is not behind the changes in eating behaviour observed post-RYGB or that RYGB alters eating behaviour via a combined/synergistic effect of the multiple components and the profound changes in the GI tract.

CHAPTER 10 FUTURE WORK

10 Future work

The findings of this study raise several areas of further research. Firstly, The results of my study should be replicated in the future to allow for more safe conclusions. Ideally, the future study should have more participants in each group and investigate them in the fasted and fed state. More mechanistic conclusions can be made if the release/action of the most likely mediators of the eating behaviour (e.g. gut hormones, bile acids) are experimentally manipulated.

At Imperial College London we have recently started, for the first time, co-infusing GLP-1, oxyntomodulin and PYY. We are in the process of replicating the experiments of this thesis before and 28-days post chronic infusion. With this study we are following on from an acute study where we demonstrated a reduction in food intake with the triple hormone infusion. The results of this study will provide information on the contribution of elevated gut hormones on the beneficial metabolic and behavioural effects of RYGB. In addition, it will provide answers regarding the feasibility of delivering gut hormones via a subcutaneous pump and potentially represent a step closer to combination gut hormone therapy becoming a treatment for obesity.

In addition, we know that following RYGB, good responders secrete significant amounts of GLP-1 in response to a meal. In our lab we have previously shown that poor responders secrete less GLP-1 during a standardised test meal compared to good responders after RYGB (545, 546). Therefor, we have started a trial looking at the impact of GLP-1 analogue 'Liraglutide' on changes in taste in those who are considered as poor responders. Liraglutide have been used successfully for the treatment of patients with T2DM for the last 8 years. It also cause weight loss by suppressing appetite, food intake and potentially by changing food preferences (547-549). This trial can be a step forward to optimising this 'gold-standard' therapy.

I would also like to continue the work I started and analyse the gut hormone samples collected but not used for this thesis. Those will be analysed, as part of the main DJBL trial currently being run at Imperial College London and the results will be available in 2018.

Association of the gut hormones with the EC50 levels of the sensory domain, intensity, JAR, pleasantness, and with the appetitive responses will be fascinating.

As for the hedonic aspect, neuroimaging with functional (f)MRI is a better method to assess the activation in the regions responsible for motivation to the different food. Taste signals arise from the oral cavity and are carried through the brainstem to the insula (primary taste cortex) and the orbitofrontal cortex (secondary taste cortex) (550). In the orbitofrontal cortex, different dimensions of taste including olfactory, texture and even vision are processed and their reward value encoded (204). From the brainstem, the ventral forebrain pathway conveys taste to the central and basolateral amygdala (551, 552). The amygdala projects taste to the other structures of the mesolimbic system, including the nucleus accumbens and anterior cingulate cortex to command behaviour response (551, 552). A sub-group of the DJBL trial did indeed have fMRI scans and results of this sub study are eagerly awaited to confirm my findings.

Verbal reporting of food intake almost entirely relies on self-reporting and measure which have produced in the past disparities among studies on food selection and intake (553). A previous study carried out by Stubbs *et al.* (2014) provided clear evidence on the discrepancy between actual and reported food intake of energy balance (554). They studied participants while they stayed for 12 days at a controlled and monitored Feeding Behaviour Suite. All participants had an ad libitum access to their own kitchen and food store. All food consumed and leftovers were directly measured by the study staff. At they same time conventional self diet-reports were collected. Misreporting comprised two phenomena. Female subjects decreased energy intake when self reported their energy intake; and reported energy intake was 5 to 21 % lower than the actual intake, depending on the reporting method used. Stubbs et al. study opened the door to the design of a ‘gold standard’ method for measuring food intake. In our lab we aim to adopt this this method and apply it to bariatric surgery patients to resolve the controversy over changed in food selection postoperatively. We have indeed started this novel project as part of my post-doctoral training at University College Dublin. In this study we are assessing RYGB patients’ food intake and food selection using a direct measure method in residential settings similar to Stubbs et al. study described above; and also during a lunch meal ‘buffet style’ under controlled circumstances.

All the above will add to the interrogation of potential mechanisms that will accelerate the development of efficacious, cheaper, and safer non-surgical treatments for obesity.

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CHAPTER 12 APPENDICES

Appendix 1 3-DAY DIETARY RECORD

3 DAY
DIETARY RECORD

Name:_____

Subject ID:_____

Date:_____

This record is designed to obtain accurate information about the type and quantity of food that you eat.

Please answer the General Question section and then go on to the Food Record.

Please return to:

GENERAL QUESTIONS

Which type of bread do you **usually** eat?

- ❑ White
- ❑ Brown/Hovis
- ❑ Granary
- ❑ Wholemeal
- ❑ None

Do you **usually** buy large or small loaves, sliced or unsliced?

- ❑ Large
- ❑ Small
- ❑ Sliced
- ❑ Unsliced

If you eat any type of biscuit regularly, please specify which brands?

_____
_____
_____
__

Which type of milk do you **usually** use?

- ❑ Full cream milk (blue cap)
- ❑ Semi-skimmed milk (green cap)
- ❑ Skimmed milk (red cap)
- ❑ None

How much milk do you **usually** use?

- ❑ 1-2 pints daily
- ❑ ½-1 pint
- ❑ ¼-½ pint
- ❑ None

How many tablespoons of milk do you take in tea and coffee?

_____ tablespoons milk in a cup of tea

_____ tablespoons milk in coffee

_____ None.

Which kind of fat do you usually use on bread, crispbreads etc?

- ❑ Butter
- ❑ Margarine
- ❑ Low fat spread

Which brand do you usually use? _____

What do you do with the visible fat on your meat?

- ❑ Eat most of the fat
- ❑ Eat as little as possible
- ❑ Eat some of the fat
- ❑ Don't eat meat

How often do you eat food that is fried?

- ❑ Daily
- ❑ 1-3 times/week
- ❑ 4-6 times/week
- ❑ Less than once/week

Do you drink alcoholic drinks?

❑ YES ❑ NO

If the answer is **Yes**, please indicate how many units you drink per week?

1 unit = ½ pint beer/lager
1 glass wine,
1 tot spirit.

_____ units per week.

Who tends to do the shopping and cooking?

_____

FOOD RECORD

Read through these instructions and the example carefully once or twice before you start.

We would like you to record, as accurately as possible, what you eat and drink for 4 days.

Please record **ALL** food and drink consumed. Record at the time of eating and **NOT** from memory at the end of the day. Keep this record sheet with you throughout the day.

You should include all meals and snacks, plus sweets, drinks etc. When recording food eaten at meals, please include any sauces, dressing or extras eg: gravy, salad dressing, pickles, as well as the main food.

If you do not eat a particular meal or snack simply draw a line across the page at this point.

Guidelines for describing food & drink:

1. Please give details of method of cooking eg: grilled, boiled, roasted.

2. Give as many details as possible about the type of food you eat:

   a) State brand name where applicable

      eg: 'Princes' sardines in tomato sauce OR
      'Sainsburys' half-fat Edam cheese.

   b) Name the type of biscuit, cake or cereal

      eg: Rich Tea, Madeira, Branflakes.

   c) Name the type of cheese, fish or meat

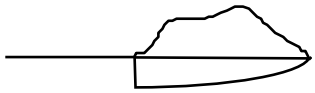
      eg: Cheshire cheese, haddock fillet, pork chop.

3. Suggestions for recording quantity of food and drink:

a) For many foods such as vegetables, cereals and some fruit a household measure is adequate, state the number of teaspoons (tsp) or tablespoons (tbsp) or cups, and whether level, rounded or heaped.

Level

Rounded



Heaped

b) All convenience foods have their weight on the packaging and this can be quoted

eg: 150g carton Ski raspberry yoghurt OR
½ 15 oz can baked beans.

c) Bread, fruit loaves etc. Indicate the size of the loaf and the thickness of the slice

eg: 1 thick slice granary bread, small loaf.

d) Cheese, fish, meat. When possible, please weigh your portions of these foods. Otherwise describe as well as you can.

eg: 2 large thin slices ham OR
2 small lamb chops (no fat eaten) OR
Medium fillet of cod grilled with 1 tsp flora OR
Cube of cheddar cheese the size of a matchbox.

Remember to include everything you eat and drink including snacks and nibbles.
Please do not change what you normally eat just because you are filling in this record - Be Honest!

Look at the example of how to fill in you record - you may find this helpful.

THANK YOU VERY MUCH FOR YOUR HELP

DIETARY RECORD SHEET - EXAMPLE

Record **ALL** food and drink consumed during the day including snacks, nibbles, sauces and dressings.

Record method of cooking, type and quantity of food
eg: 6 tbsp boiled wholemeal spaghetti
2 egg sized roast potatoes.

DAY: Example DATE: 1st June 1995

MEAL/ SNACK	QUANTITY EATEN	DETAILS OF FOOD & DRINK	Leave Blank
Early Morning:	1 cup 1 tbsp	Tea with Skimmed milk	
Breakfast:	3 heaped tbsp ¼ pint 1 medium slice 1 tsp 2 mugs	Branflakes (Kellogg's) Skimmed milk for cereal & drinks Wholemeal bread (large loaf) Flora extra light margarine Coffee	
During Morning:	1 mug 1 tbsp 1 medium	Coffee with skimmed milk Apple (eaten with skin)	
Midday:	4 slices 4 level tsp 2 thin slices 1 large 1 large 1 can (330ml)	Sandwiches: wholemeal bread (Allinsons) large loaf, sliced Flora extra light margarine Ham (no fat) Tomato Banana Diet Tango	

Appendix 2 24h Dietary Recall

Portion Description

- Cups for liquids, chopped fruit/vegetables
- Spoons for powder and loose items (like rice, cereal, sugar)
- Pieces for whole fruits/vegetables
- Palm of hand for meat, chicken and fish
- Dinner Plate for pizza size, dessert might be. Ask questions such as, “Did it take up the whole plate? Was it half a plate a fourth of the plate?”
- Weight in grams for any known items

Information required for food items

- What **type** of food or drink was it?
- **How was it bought**? – fresh, canned, frozen, etc?
- Was the item smoked or not e.g. ham, bacon etc.
- Was it homemade – if so – what were the ingredients?
- How was it **cooked** – boiled, poached, fried etc?
- If it was cooked in fat, fat was used in pastry or cakes or any other dish, or if any fat was added to e.g. a sandwich or baked potato, what sort of fat or oil was used?
- If it was a dried / dehydrated product e.g. hot chocolate was it reconstituted using water, milk (specify type e.g. skimmed, semi-skimmed, whole) or both? etc
- Was the item **coated** before cooking? E.g. flour, batter, egg, breadcrumbs
- Was it unsweetened, or sweetened with sugar or artificial sweeteners e.g. Candarel?
- Was it low or reduced fat / low or reduced calorie?
- Where possible, you need to ask the respondent for the brand name of foods they have consumed e.g. Heinz baked beans, Kellogg’s Cornflakes etc.

Procedure

1. Explain to the participant that you need to know only what she (he) actually ate. She (he) should not feel embarrassed about any food, as there are no “good” or “bad” foods. No one eats just the right foods all the time.

2. Do not express in words or facial expressions either approval or disapproval of foods mentioned by the participant.

3. Do not ask questions that would lead the participant to feel she (he) "should" have had a certain item and, thus say that they did.

4. Use the portion description to determine the amounts of foods consumed.

5. Start with the most recent meal or snack that the participant consumed. Work backwards to cover all foods and beverage consumed in the last 24 hours.

6. Quick List:

Record the list of foods as the participant remembers them; portion sizes and preparation methods will be recorded in the next step. This list of foods is termed the quick list.

To obtain this list of foods from the participant use the following types of probes to find what foods were eaten:

A. The first type of probing is related to <u>time</u>.

Examples:

"At what time was this? Did you eat or drink anything before or after that?"

B. The second type of probe is related to the participant's <u>activities.</u>

Examples:

"While you were working around the house, did you take a break to have something to eat or drink?"

"Did you watch TV last night? When you watched TV, did you eat anything?"

C. The third type of probe tries to get more complete <u>information about foods already reported.</u>

Examples:

"Do you remember anything else that you ate or drank with this food?"

"What else did you have at this meal?"

"Was the (bread, vegetable) eaten plain or did you put something on it?

"Did you have anything in your coffee?"

7. **Detailed Description**:

After you have recorded the participant's quick list, you can then complete the detailed description of foods consumed. This will include recording preparation method, brand name, portion size, and the time the food or beverage was consumed. To get more information on the amounts and the type of foods eaten use the following techniques:

A. Determine if all of the food was eaten or if some food was left on the plate.

B. Encourage the participant to describe foods as clearly as possible. The interviewer may have to restate questions to get more information.

C. Describe combination dishes carefully. Mixtures such as sandwiches, soups, stew, pizza, casseroles, etc. can be prepared in many ways.

8. **Review:**

Once the 24 hour food recall is complete read the list back to the participant.

Ask the participant if the recall is correct or if they forgot to mention any food that was consumed.

9. Thank the participant for their cooperation. Do not comment on the recall, unless the participant asks a specific question.

24hr Dietary Recall

Quick list	Description	Time

Appendix 3 EPIC Food Frequency Questionnaire

This is an example of the EPIC FFQ, full version can be found on http://www.srl.cam.ac.uk/epic/epicffq/index.html

Please estimate your average food use as best you can, and please answer every question - do not leave ANY lines blank. PLEASE PUT A TICK (✓) ON EVERY LINE

FOODS AND AMOUNTS	AVERAGE USE LAST YEAR								
MEAT AND FISH (medium serving)	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day
Beef: roast, steak, mince, stew or casserole									
Beefburgers									
Pork: roast, chops, stew or slices									
Lamb: roast, chops or stew									
Chicken or other poultry eg. turkey									
Bacon									
Ham									
Corned beef, Spam, luncheon meats									
Sausages									
Savoury pies, eg. meat pie, pork pie, pasties, steak & kidney pie, sausage rolls									
Liver, liver paté, liver sausage									
Fried fish in batter, as in fish and chips									
Fish fingers, fish cakes									
Other white fish, fresh or frozen, eg. cod, haddock, plaice, sole, halibut									
Oily fish, fresh or canned, eg. mackerel, kippers, tuna, salmon, sardines, herring									
Shellfish, eg. crab, prawns, mussels									
Fish roe, taramasalata									
	Never or less than once/month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once a day	2-3 per day	4-5 per day	6+ per day

Please check that you have a tick (✓) on EVERY line

Appendix 4 Scoring Sheets and cups allocation for Sweet Taste Detection

Please put ✓where solution is correctly identified and ☒ where it was not identified

A: 2-weeks before intervention

B1	1 S6	2 S1	3 W	4 S5	5 W	6 S3	7 W	8 S4	9 W	10 S2	11 W	12 W	13 S7	14 W
B2	15 S6	16 W	17 W	18 S4	19 W	20 S3	21 W	22 S7	23 W	24 S5	25 S1	26 W	27 S2	28 W
B3	29 W	30 S7	31 W	32 W	33 S2	34 S5	35 S6	36 W	37 S4	38 W	39 W	40 S3	41 S1	42 W
B4	43 S3	44 W	45 S2	46 S6	47 W	48 W	49 S7	50 W	51 W	52 W	53 S1	54 W	55 S4	56 S5
B5	57 W	58 S3	59 S2	60 W	61 S1	62 S7	63 W	64 S5	65 S6	66 W	67 S4	68 W	69 W	70 W
B6	71 W	72 S6	73 W	74 S5	75 W	76 S4	77 S1	78 W	79 W	80 W	81 S7	82 W	83 S3	84 S2
B7	85 W	86 S5	87 W	88 W	89 S2	90 W	91 S3	92 W	93 S6	94 S1	95 W	96 S4	97 W	98 S7
B8	99 S1	100 S6	101 W	102 S5	103 S7	104 W	105 W	106 W	107 W	108 S2	109 S3	110 W	111 S4	112 W

Please put ✓where solution is correctly identified and ☒ where it was not identified

B: 10-days after intervention

B1	1 W	2 S6	3 W	4 W	5 W	6 S7	7 S2	8 W	9 S5	10 S1	11 S3	12 W	13 S4	14 W
B2	15 W	16 S5	17 S3	18 S6	19 S2	20 W	21 S7	22 S1	23 W	24 W	25 W	26 W	27 S4	28 W
B3	29 S6	30 S2	31 W	32 W	33 W	34 S1	35 W	36 S5	37 W	38 S4	39 W	40 S3	41 W	42 S7
B4	43 W	44 S7	45 W	46 S1	47 S5	48 W	49 S3	50 S6	51 W	52 W	53 S2	54 W	55 S4	56 W
B5	57 W	58 W	59 S1	60 S2	61 S3	62 W	63 S6	64 W	65 W	66 S4	67 W	68 S7	69 S5	70 W
B6	71 W	72 S3	73 S1	74 W	75 S4	76 W	77 S7	78 S6	79 W	80 W	81 W	82 S2	83 S5	84 W
B7	85 S7	86 W	87 S4	88 W	89 S2	90 W	91 S6	92 W	93 S3	94 W	95 S1	96 W	97 S5	98 W
B8	99 S2	100 W	101 S4	102 W	103 S5	104 W	105 W	106 W	107 W	108 S7	109 S6	110 S3	111 S1	112 W

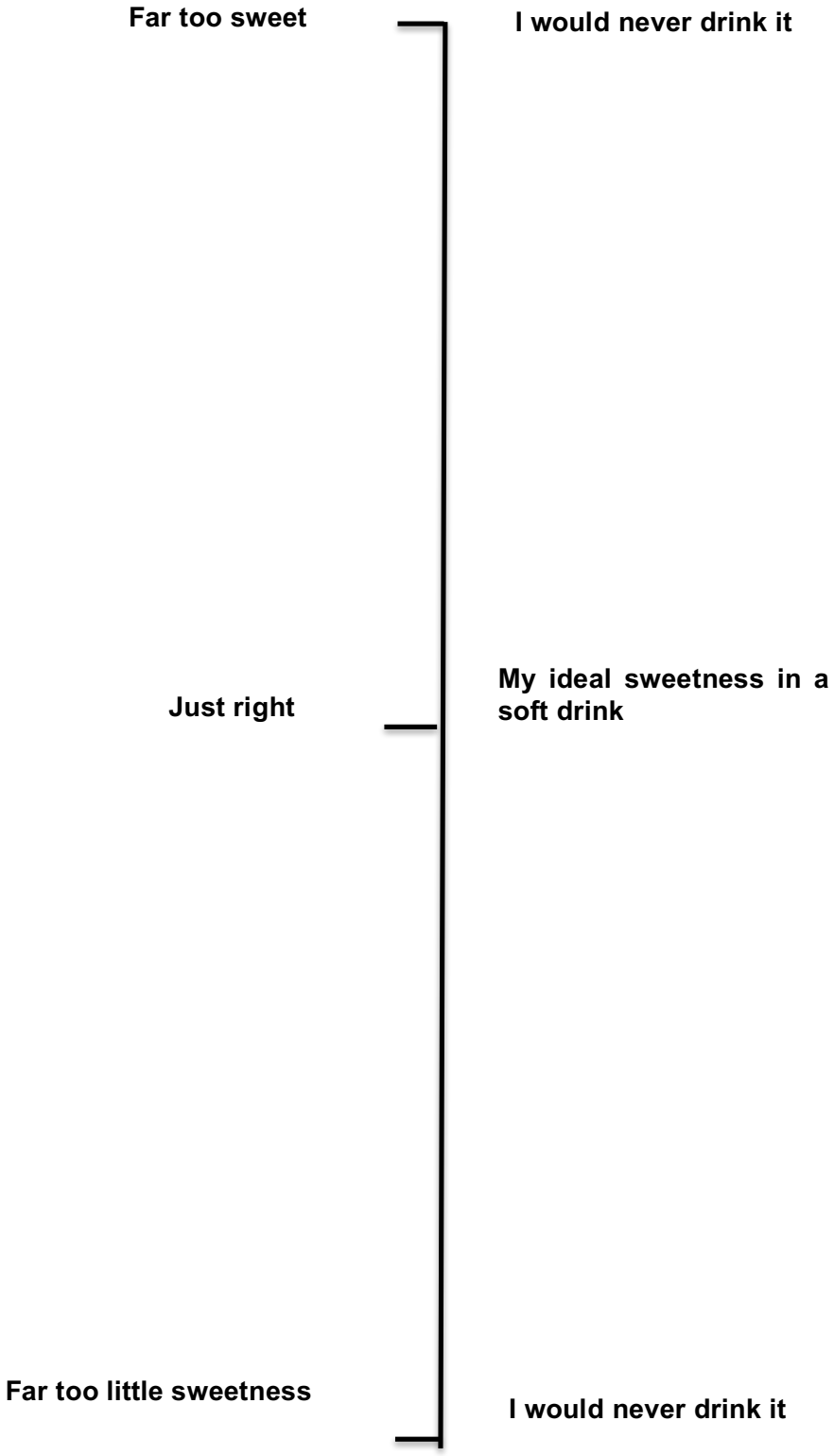
Please put ✓ where solution is correctly identified and ☒ where it was not identified

C: 6-months post intervention

B1	1 W	2 S7	3 W	4 W	5 S2	6 S5	7 S6	8 W	9 S4	10 W	11 W	12 S3	13 S1	14 W
B2	15 S1	16 W	17 S6	18 S4	19 W	20 W	21 S2	22 W	23 S5	24 W	25 S3	26 W	27 S7	28 W
B3	29 S7	30 W	31 S4	32 W	33 S2	34 W	35 S6	36 W	37 S3	38 W	39 S1	40 W	41 W	42 S5
B4	43 W	44 S1	45 S6	46 W	47 S2	48 S5	49 W	50 W	51 S4	52 S7	53 W	54 S3	55 W	56 W
B5	57 W	58 S3	59 S1	60 W	61 S4	62 W	63 S7	64 S6	65 W	66 W	67 W	68 S2	69 W	70 S5
B6	71 W	72 S4	73 W	74 W	75 W	76 W	77 S1	78 S7	79 W	80 S2	81 S6	82 S3	83 S5	84 W
B7	85 S3	86 W	87 S2	88 S6	89 W	90 W	91 S7	92 W	93 W	94 W	95 S1	96 W	97 S4	98 S5
B8	99 S6	100 S1	101 W	102 S5	103 W	104 S3	105 W	106 S4	107 W	108 S2	109 W	110 W	111 S7	112 W

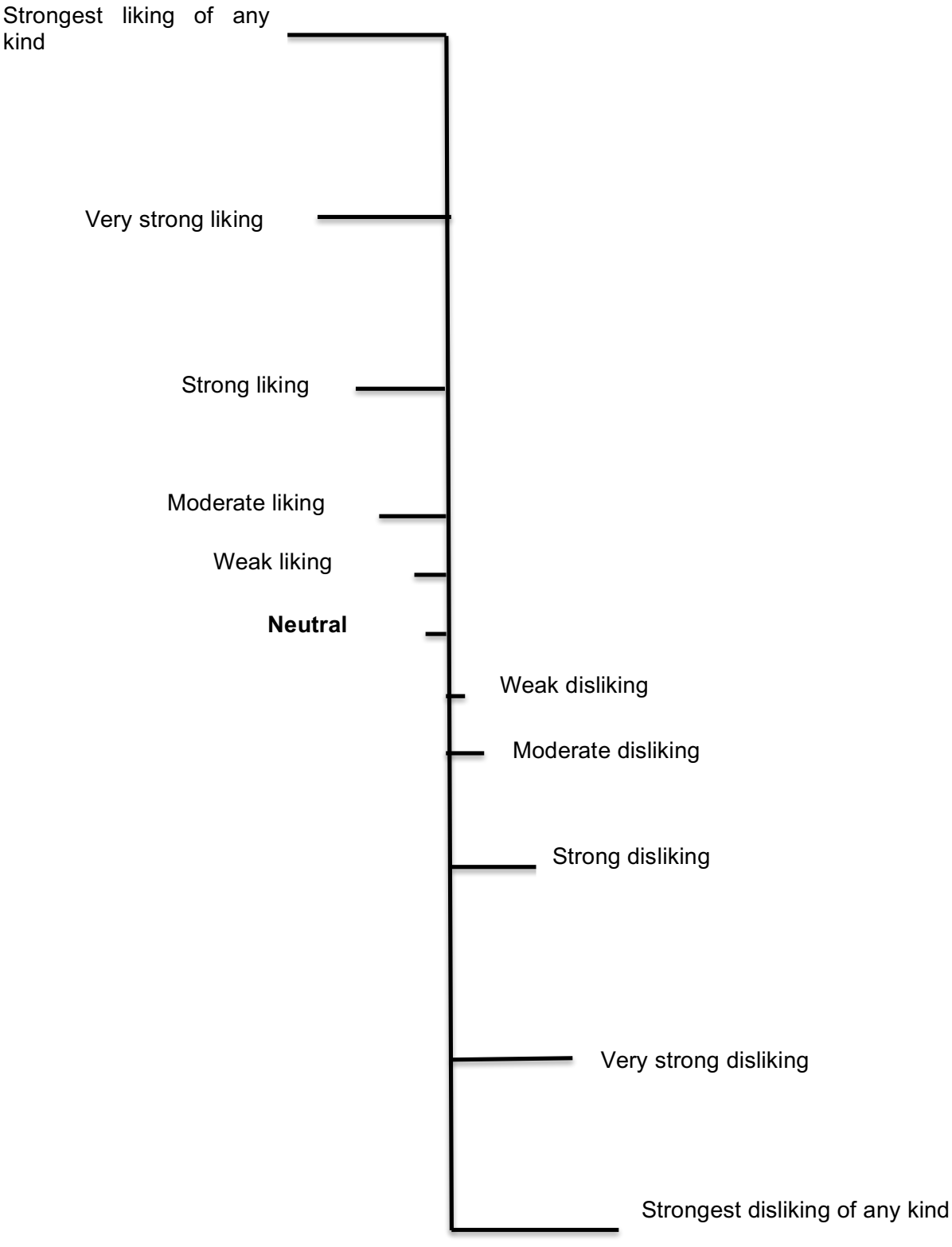
Appendix 5 The Consummatory Reward Scales

Just About Right (JAR) scale
On the scale below, please indicate, using a horizontal mark, how close the SWEETNESS of the solution you have just tasted is to <u>your ideal sweetness in a soft drink</u>.



gLMS Hedonic scale

On the scale below, please indicate, using a horizontal mark, how much you LIKE the drink you have just tasted relative to any "liking" you have ever experienced <u>of any kind</u> (i.e. of any sensation).



Intensity Scale

On the scale below, please indicate, using a horizontal mark, the INTENSITY of the sweet taste relative to sensations you have ever experienced <u>of any kind</u>, not just taste (e.g. sight, sound).