Insulin-associated weight gain in obese type 2 diabetes mellitus patients – what can be done?

Adrian Brown[1], Nicola Guess[1,2], Anne Dornhorst[4], Shahrad Taheri[3,4], Gary Frost[1]

1. Nutrition and Dietetic Research Group, Faculty of Medicine, Imperial College, London, UK
2. Diabetes and Nutritional Sciences Division, Kings College London, London, UK
3. Department of Medicine and Clinical Research Core, Weill Cornell Medicine in New York, USA, and Doha, Qatar
4. Department of Metabolic Medicine, Imperial College London, UK

Correspondence: Adrian Brown, Nutrition and Dietetic Research Group, Faculty of Medicine, Imperial College, London, UK. Email: a.brown13@imperial.ac.uk; Professor Shahrad Taheri, Department of Medicine and Clinical Research Core, Weill Cornell Medical College in New York USA, and Doha, Qatar. Email: staheri@me.com.

Abstract

Insulin therapy (IT) is initiated for patients with type 2 diabetes mellitus when glycaemic targets are not met with diet and other hypoglycaemic agents. The initiation of IT improves glycaemic control and reduces the risk of microvascular complications. There is, however, an associated weight gain following IT, which may adversely affect diabetic and cardiovascular morbidity and mortality. A 3 to 9 kg insulin associated weight gain (IAWG) is reported to occur in the first year of initiating IT, consisting predominantly of adipose tissue. The potential causes for this weight gain include: an increase in energy intake linked to a fear of hypoglycaemia, a reduction in glycosuria, catch-up weight, and central effects on weight and appetite regulation. Patients with type 2 diabetes on IT often have multiple co-morbidities, including obesity, that are exacerbated by weight gain, making the management of their diabetes and obesity challenging. There are several treatment strategies for patients with type 2 diabetes, who require IT, that attenuate weight gain, help improve glycaemic control, and help promote body weight homeostasis. This review addresses the effects of insulin initiation and intensification on IAWG, and explores its potential underlying

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.13009

mechanisms, the predictors for this weight gain, and the available treatment options for managing and limiting weight gain.

Introduction

Type 2 diabetes mellitus (T2D) is a serious challenge to healthcare services worldwide [1]. The pathophysiology of T2D is complex, involving multiple mechanisms affecting multiple organs. Insulin resistance and the inability to secrete sufficient insulin to overcome this resistance are central to its pathophysiology. Pancreatic islet beta-cell (β-cell) dysfunction and loss begins prior to the diagnostic glycaemic thresholds for diabetes, as exemplified by only 40–60% of β-cell function being present by the time of diagnosis [2]. Insulin therapy (IT) is required when progressive loss of β-cell function leads to deteriorating glycaemic control. Data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that 44% of patients require IT 6 years after diagnosis [3,4]. IT, followed by intensification,[5-7] is the most effective treatment for glycaemic control, and is associated with reductions in micro-vascular complications (retinopathy, nephropathy, and neuropathy). However, there is an associated weight gain with IT. In the United Kingdom (UK), of the 3.2 million people with diabetes, an estimated 80-85% are overweight or obese [8], in whom weight gain could be potentially detrimental. Several studies have observed a weight gain of 3-9 kg within the first year of insulin treatment [5,9-11]. Most of this insulin associated weight gain (IAWG) has been reported to occur within the first 3 years of IT[12].

While insulin initiation can initially improve glycaemic control, its introduction does not always translate into long-term sustained glycaemic improvement. In a retrospective cohort study, following insulin initiation, the majority of participants (73%) remained with a glycated haemoglobin (HbA1c) ≥7.5% 6 months later[13]. The association of weight gain and worsening insulin resistance could theoretically contribute to the suboptimal HbA1c value at 6-months. Other explanations include patients' reluctance to adhere to IT due to their concerns about potential weight gain. The complexity of managing insulin treated patients who gain weight is a clinical challenge, as these patients may experience cycles of repeated weight gain and declining glycaemic control. This review examines the potential mechanisms for the weight gain observed with insulin therapy, how these may impact on the clinical management of patients with T2D, and the treatment options available for limiting IAWG.

Insulin initiation and intensification in T2D

Clinical guidelines advocate treatment intensification, including insulin initiation, when oral or other agents are unable to maintain a HbA1c at 6.5-7.5% (48-58 mmol/mol) [14,15]. Contrary to these recommendations, insulin initiation occurs much later despite poor glycaemia. A retrospective cohort study of 154 UK general practices, involving 5064 T2D patients on

multiple oral agents, showed that the mean time to insulin initiation was 7.7 years, despite a mean HbA1c of 9.85±1.96% (95 mmol/mol) [13]. This late initiation of insulin was also reported from a study of 155,917 T2D patients in whom insulin initiation was delayed until the mean HbA1c was 9.5±2.3%[16]. Overall, insulin usage among T2D patients in the UK and United States is between 20-29.1% [17,18]. Between 2014-2015, only 66.1% of all UK T2D patients achieved the recommended HbA1c target of ≤7.5% (≤58 mmol/mol) [19]; only 26.6% of insulin treated patients attained this glycaemic target[13].

Many barriers exist that delay the timely introduction and intensification of IT in T2D. Evidence suggests that the two primary obstacles are: the fear of weight gain [5,20] and the fear of hypoglycaemia [5,21]. These two fears were reported in approximately 50% of the 2713 T2D patients surveyed in a global diabetes psychosocial survey involving 13 countries, The Diabetes Attitudes, Wishes and Needs study (DAWN study) [22]. This reluctance to initiate and use IT has been termed 'psychological insulin resistance' (PIR) and is reported to be common among clinicians as well as patients [23]. Among healthcare professionals, despite the known benefits of early insulin initiation, issues attributed to PIR include lack of training, and experience and confidence, in insulin initiation[24,25]. The time required to educate patients in insulin administration is another factor [24,25]. The glycaemic burden associated with not initiating IT may ultimately increase the risk of diabetes-associated complications[26]. Whether delaying IT treatment exacerbates weight gain when insulin is finally started is unclear.

Insulin-associated weight gain

Iatrogenic weight gain with anti-hyperglycaemic drugs is common, this is especially so following sulphonylureas and insulin initiation. For insulin, there is a close association between total exogenous insulin dose and weight gain, and pre-treatment insulin resistance as measured by the hyperinsulinemic euglyacemic clamp [9]. Rapid insulin intensification required to achieve normoglycaemia has been associated with significant weight gain [5,9]. In one study, insulin initiation and intensification over 4 weeks (aimed to achieve normal glycaemia among 14 subjects with T2D) resulted in a body weight increase from 93.5±5.8 to 102.2±6.8 kg (P<0.001). The weight gain correlated with the total exogenous insulin dose (r=0.62, P<0.02) and mean day-long serum insulin levels (r=0.67, P<0.01)[9]. These observations and others[5] suggest that rapid insulin intensification to achieve normoglycaemia can be associated with significant weight gain. Any weight increase is undesirable for the majority of patients with T2D who are already overweight or obese [27]. However, there is inter-individual variation on the amount of IAWG, with some patients gaining and others

actually lose weight [28]. Importantly, although not a universal finding, [29,30] the weight gain associated with IT has mostly been attributed to an increase in fat mass [31,32], with an increase in total body water also seen in poorly controlled subjects with T2D [29,30]. An increase in body fat, particularly in intra-abdominal fat, has the potential to exacerbate further weight gain, insulin resistance, and increased cardiovascular disease risk [33,34].

The risk-benefit relationship between improvement in glycaemic control and the associated weight gain is an important consideration in IT initiation and titration. Although weight gain *per se* is a recognised risk factor for cardiovascular disease risk (CVD), it remains unclear whether IAWG has a similar impact. IAWG has been associated with a worse cardio-metabolic risk profile among patients who gain weight following IT, with higher total and LDL-cholesterol, and greater total body, trunk and subcutaneous fat[28]. Another impact of IAWG is on renal glomerular hyperfiltration, a known CVD risk factor[35]. Insulin therapy has also been reported to increase systolic but not diastolic blood pressure, with a weak positive correlation found between systolic blood pressure and weight gain ($r=0.22$; $P<0.02$)[36]. Despite these potential cardio-metabolic risks, IAWG in T2D patient has not been associated with an increase in CVD mortality or post myocardial infarction re-infarction rates[37]. However, the large number of cardio-protective drugs routinely taken by insulin treated T2D patients may have attenuated or masked the impact of IAWG on CVD risk.

Predictors of insulin associated weight gain

Predicting those individuals most at risk of IAWG would be of clinical benefit. The literature highlights independent predictors of IAWG as diabetes-related distress, initial insulin dose, older age, HbA1c change (improvement in HbA1c), higher baseline body mass index (BMI), pre-treatment insulin resistance and the increase in insulin dose [11,30,38]. The effect of HbA1c change on IAWG is relatively small, accounting for only 12%[39]. Physical activity levels while not predictive of IAWG, a non-significant reduction in physical activity has been reported following insulin initiation [11].

A greater baseline body mass index (BMI) has been associated with less IAWG [16,40]. In a longitudinal study of 155,197 T2D patients starting IT, obese patients gained significantly less weight than those with a BMI <30kg/m^2 [16], with individuals with a BMI >40kg/m^2 actually losing weight over a 24-month period (-2.2kg, (95% CI -2.2 to -1.1). This finding is in agreement with a sub-analysis of the CREDIT (cardiovascular risk evaluation in

people with type 2 diabetes on insulin therapy) study, that showed the independent predictors of IAWG were a higher baseline HbA1c, a higher insulin dose at both baseline and 1 year, and a lower baseline BMI [40]. The reasons why all studies have not observed that patients with higher BMI gain less weight [41,42] remains unclear. Possible explanations include alterations in body composition, greater motivation of obese patients to maintain or lose weight, alterations in insulin absorption, action and or disposal, and reduced patient compliance to IT.

Mechanisms of insulin associated weight gain

The mechanisms behind IAWG are incompletely understood, although much appears related to the known physiological actions of insulin (Figure 1).

Anabolic effects of Insulin

Insulin is an anabolic hormone that stimulates cell growth and promotes the storage of fatty acids in adipose and muscle tissue, stimulating muscle hypertrophy and inhibiting proteolysis [43,44]. It has been proposed that IAWG might result from supra-physiological levels of serum insulin, producing an anabolic response state that favours an increase in lean mass [45]. However, evidence to support this hypothesis, particularly in humans, is lacking. In rodents, insulin promotes protein synthesis[46], but in humans, this relationship is more complex, and is dependent on amino acid availability and muscle blood flow [47]. Although muscle breakdown (catabolism) is reduced by IT, which could theoretically promote muscle gain, this effect is blunted in both older people and those with insulin resistance [47], who together represent the majority of insulin treated T2D patients. Studies assessing body composition changes following IWAG have reported that despite some increase in lean mass following insulin initiation, there is a significantly greater gain in fat mass, particularly truncal fat [29,31,32]. However, poor glycaemic control often can affect the reliability of body composition measurement techniques [30].

Central effects of insulin on appetite, weight regulation, and inflammation

Insulin has a critical role in maintaining metabolic homeostasis[48]. The peripheral effects of insulin contrast with its central nervous system effects. The hypothalamus is the key regulator of appetite and responds to changing levels of both circulating insulin and the adipocyte hormone, leptin. These two hormones work synergistically to maintain adipose tissue homeostasis by exerting an inhibitory effect on food intake[49]. Central administration of insulin to rodents results in a decrease in food intake and an increase in satiety hormones [50].

In rodents fed a high fat diet, hypothalamic insulin resistance occurs [51]. Selective decreases in insulin receptor expression in the hypothalamus is accompanied by the rapid onset of hyperphagia and increased subcutaneous fat mass, suggesting that the disruption of brain insulin signalling is key to energy storage [52]. The central effects of insulin in humans, however, have been traditionally difficult to study.

Intranasal insulin administration that bypasses the blood-brain barrier enables the elevation of insulin levels in the cerebrospinal fluid[53], allowing for the first time an opportunity to study the central effect of insulin in humans. Intranasal insulin has been reported to increase satiety in the post-prandial state[54] and also to be associated with peripheral insulin sensitivity[55]. These effects appear to be influenced by gender, and are blunted in obese individuals[56], suggesting that the action of insulin within the brain may have inter-individual variability.

Obese compared to lean individuals have increased activation of the brain reward centres in response to palatable food [57]. The concentrations of insulin in the brain are strongly linked to the release of dopamine, a neurotransmitter linked with reward [58]. In non-obese insulin resistant individuals, using [18F] fluorodeoxyglucose positron emission tomography, studies have shown greater brain insulin resistance within the central brain networks involved in reward and appetite, suggesting that this might contribute to difficulties in changing eating behaviours [59]. Consequently, this may contribute to a diminished sense of reward following food ingestion, resulting in compensatory increased intake of palatable foods [60]. Currently, there is limited insight into the action of insulin within obese, insulin-treated patients and how this relates to IAWG. Any potential disruption to hypothalamic insulin sensitivity or signalling could potentially influence eating behaviour, body weight and adiposity [61].

Sustained exposure to nutrient excess in T2D and obesity is associated with systemic and localised inflammation in the liver, muscle and adipose tissue [62], characterised by elevated levels of C-reactive protein, interleukin-6, and tumour necrosis factor-alpha (TNF-α) [62]. These inflammatory cytokines impair the hypothalamic response of insulin on satiety [63], with TNF-α being a key inhibitor of insulin action through its effect on the insulin receptor substrate-1 (IRS-1) [64]. This suggests an-interplay between hypothalamic inflammation and central insulin resistance resulting in a suppression of insulin signalling affecting anorexigenic hormone release, energy homeostasis, and subsequently peripheral insulin resistance. These changes, in theory, would promote weight gain, insulin resistance, and increased exogenous insulin requirement.

Reduction in Glycosuria

Glycosuria is common in uncontrolled diabetes, occurring when the maximal capacity of the renal tubular glucose transporters in the kidney are exceeded. Glucose reabsorption is increased in T2D, which further exacerbates hyperglycaemia. The oral hypoglycaemic class of drugs known as the sodium glucose transporter (SGLT2) inhibitors enhance glycosuria and promote weight loss [65,66]. In T2D patients with poor glycaemic control, glycosuria is proportional to fasting plasma glucose concentration [10]. Part of the weight gain following insulin initiation results from a reduction or elimination of glycosuria and improved glucose utilisation [10,67]. In a randomised control trial using high dose basal bedtime insulin and a daytime sulphonylurea, the 24-hour urinary glucose excretion reduced from 37.4 to 5.6g/day, equivalent to a net calorific retention of 119.3kcal/day accounting for the weight gain reported [67]. This level of calorie retention could result in up to 5kg weight gain over a year. In another study comparing IT initiation alone or in combination with metformin, glycosuria decreased significantly in both groups, causing a net energy increase equivalent to 198kcal/day [10], which in the IT only group resulted in a 7.5 kg gain over the subsequent 12 months. Combining insulin treatment with SGLT2 inhibitors could potentially not only improve hyperglycaemia, but also help attenuate IAWG or even promote weight loss, although this weight loss may be modest in obese T2D patients[65].

Exogenous Insulin Versus Normal Insulin Physiology

The pharmacodynamics/pharmacokinetic (PD/PK) profile of exogenous IT differs markedly from endogenous insulin. In health, insulin is secreted by pancreatic β-cells into the portal circulation where it acts on the liver to suppress endogenous hepatic glucose production and increases glucose uptake before approximately 50% is degraded within the liver [68]. The remaining circulating insulin increases glucose uptake in peripheral tissues before being degraded by the kidneys, the liver and insulin sensitive tissues. Subcutaneous IT administration (s.c) has a non-physiological insulin profile. It requires time to be absorbed into the bloodstream, where it initially circulates in the systemic circulation, increasing peripheral action in muscle and adipose tissue before reaching the liver where it undergoes delayed degradation[69]. The physiological release of endogenous insulin in healthy subjects limits postprandial glucose excursions that occur in T2D. The variability of glucose excursions independent of the elevated mean glucose concentration has been linked with diabetes-related complications[70].

The pharmacodynamics (PD) effect of insulin to lower blood glucose is closely determined by its pharmacokinetic (PK) profile [71]. The PD/PK of the available therapeutic s.c. insulins are determined by their biochemical modifications of the human insulin molecule and their formulations. There is an inevitable time lag between insulin absorption from subcutaneous tissue and its transport to target tissues and the subsequent signalling and metabolic responses[71]. There is a marked variability of insulin absorption and its metabolic action between the different commercial insulin preparations with the older human insulin preparation having a greater intra-individual variation than the newer longer acting insulin analogue preparations [69,72]. The rate of exogenous insulin absorption can be slower and the duration of action longer when insulin doses and BMI are higher [73], common features of insulin resistant T2D patients. Increased glucose variability and reduced suppression of hepatic glucose production has the potential of escalating insulin requirements further and exacerbating IAWG.

The pharmacokinetic limitations of traditional intermediate acting human insulin to create a peakless overnight plasma profile [73,74], may potentiate nocturnal hypoglycaemia, compensatory eating behaviour and glucose variability that leads to weight gain. The basal insulin analogues that produce a flatter and longer insulin profile of action that extend out to 24 hours have the potential to lessen nocturnal hypoglycaemia and glucose variability. Recently, newer ultra-long basal analogue insulins whose PK profiles extend beyond 24 hours have been shown to have a stable steady-state profile and greater reproducibility and less day-to-day variability of action[75]. These properties achieve similar glycaemic control and weight gain reduction, but are associated with fewer hypoglycaemic episodes, particularly at night when compared with the long acting basal insulin analogue insulin [76,77]. More research is needed to assess if there are any longer-term benefits of these new ultra-long acting insulins on IAWG [78].

The risk of Hypoglycaemia

Insulin therapy significantly increases the risk of hypoglycaemia [5]. Irregular meals have been identified as the most common behavioural factor leading to episodes of severe hypoglycaemia [79] and are also linked with poorer weight maintenance [80]. Consequently, in obese insulin treated T2D patients, irregular meal patterns can further increase weight gain, and or, impede weight loss. The potential fear of hypoglycaemia, particularly nocturnal and the associated compensatory consumption of carbohydrates or ‘defensive snacking’ is another factor linked to weight gain [81]. Hypoglycaemia can manifest as hunger, which is

often over-treated with high-calorie, high-fat, high sugar foods. Fear of hypoglycaemia is also a frequent reason for non-adherence to IT, resulting in chronic hyperglycaemia and further IT up-titration by clinicians. Fixed doses of insulin, particularly biphasic human insulin and rapid acting insulin, can increase hypoglycaemia risk if meals are missed or meal timing is irregular, resulting in defensive snacking later on. It is important that clinicians educate patients on the time action profiles of their insulin and how to adjust their insulin and food intake according. Eliminating snacking to treat hypoglycaemia or the fear of hypoglycaemia will reduce energy intakes, glucose variability and potential weight gain. Patients must, however, be informed on how to treat hypoglycaemia appropriately.

'Catch-up' weight gain

Prior to the diagnosis of diabetes and IT initiation, weight loss is commonly reported [12,82] contributed in part to poor glycaemic control and associated glycosuria. The reason that IT encourages weight gain may also be explained by physiological mechanisms regulating body weight that elicit a counter-regulatory response to return to the original weight [83]. This explanation is supported by a retrospective cohort study that showed that the weight at diabetes diagnosis was 6 kg (P=0.0001) less than the reported maximal lifetime weight. While weight loss occurred prior to insulin initiation, patients regained weight gradually, up to 2.6 kg less than their maximal lifetime weight of 86±17.0 kg (P<0.012). The weight gain in this study cohort was highly correlated with maximal lifetime weight prior to T2D diagnosis [12], suggesting that weight gain following insulin initiation may be 'catch-up' weight.

Management of weight gain with insulin therapy

Reduced adiposity in T2D patients improves glycaemic control and lessens CVD risk factors including dyslipidaemia and hypertension [84,85]. Despite this evidence weight issues are infrequently raised by clinicians [86,87], although patients will attempt weight loss if advised by a healthcare practitioner, even if the advice is brief [88]. In a UK primary care study, 52% of physicians and 28% of nurses reported having concerns about raising the issue of weight, with the most common reason being the potential emotional reaction of the patient[87]. Cultural and ethnic backgrounds may also be a barrier among certain at-risk populations [89]. Not mentioning body weight could lead to patients perceiving that their weight is unimportant and unrelated to their diabetes and glycaemic management [90]. This clinical inertia regarding discussing weight places patients at significant risk of sub-optimal care, as it placing greater

focuses on disease markers such as HbA1c and escalation of IT and potentially further weight gain.

Effective use of diabetes pharmacotherapy

A targeted use of diabetes pharmacotherapy can be an effective strategy in helping to manage IAWG. Weight gain following IT is partially attenuated with the addition of metformin, which has an insulin sparing effect of up to 25% compared to placebo [10,91]. Specifically, food intake is reduced[10], possibly mediated by changes in hypothalamic appetite regulatory centres. One proposed mechanism is that improved insulin resistance in the hypothalamus results in decreased orexigenic hormones and increases in the incretin hormone glucagon-like peptide-1 (GLP-1) [92,93]. Another mechanism, although not fully explained, is through metformin's modulatory action on the gastrointestinal microbiome, which may reduce low-grade inflammation [94,95] with a downstream impact on hypothalamic function. Using 4-compartment modelling to assess individual body composition, metformin and insulin use showed a greater deposition of fat free mass compared to insulin alone [29], with improved insulin sensitivity and reduced insulin requirements. Clinically, evidence suggests that adding metformin to an existing stable insulin regimen may prevent weight gain better than combining metformin and insulin at initiation [38].

Obese insulin resistant T2D patients require more exogenous insulin for glycaemic control, resulting in greater hyperinsulinemia and progressive weight gain than less insulin resistant T2D patients. The starting doses of insulin independently predict body weight gain [29]. As hyperinsulinemia is associated with increased hunger, desire for sweet foods and greater food intake, [96] it follows that initiation with the smallest insulin doses to achieve glycaemia is preferable and that any achievable dose reduction could aid weight loss.

Not all insulin preparations predispose equally to IAWG. Recent trial data on the long acting basal insulin analogues have reported reduced nocturnal hypoglycaemia and potentially less weight gain following initiation. Weight gain with the basal insulin analogue insulin detemir [97] has been reported to be less than half that of the intermediate acting insulin Neutral Protamine Hagedorn insulin (NPH; 1.2kg vs. 2.8kg, $P<0.001$, respectively) [97], with the greatest weight loss seen in patients with a BMI above 31kg/m^2 [98]. Recent data suggest that the weight-sparing properties of insulin detemir may not be related to the reduced risk of hypoglycaemia, 'defensive snacking' or hypoglycaemia-induced hunger [97]. Instead, other proposed mechanisms include reduction in energy intake, central nervous system-mediated effects on satiety, and a greater relative effect on the liver, thus restoring the portal/peripheral

gradient[99]. Further studies are required to fully establish the weight neutrality observed with the initiation of insulin detemir. The ultra-long acting insulin, degludec, with a duration of action exceeding 24 hours appears to have no advantage over insulin glargine, a basal analogue insulin with a duration of action up to 24 hours, on limiting IAWG, although the risk of hypoglycaemia was reduced[100,101].

Long acting GLP-1 receptor agonists are novel class of injectable anti-diabetic medications that improve glycaemic control while inducing weight loss[102]. In a meta-analysis, the combination of a GLP-1 receptor agonist with a basal insulin gave a greater mean weight loss (-3.22kg, 95% CI -4.90 to -1.54) compared to insulin alone[103]. Moreover, in combination with basal-bolus insulin, the mean weight loss was -5.66kg (95% CI -9.8 to -1.51). In a randomized clinical trial of insulin glargine and IDegLira, the combination of insulin degludec and the GLP-1 receptor agonist liraglutide, IDegLira was associated with greater weight loss and fewer hypoglycaemic episodes [104]. Although there would appear to be a benefit of combining a GLP-1 receptor agonist with insulin, the between-study heterogeneity of the various clinical trials reported limit the ability to generate best practice advice for clinical care.

By inducing glycosuria, sodium-glucose cotransporter-2 (SGLT-2) inhibitors improve glycaemic control, and reduce body weight and visceral fat mass in T2D patients [66,105]. For T2D patients treated with insulin, the addition of an SGLT-2 inhibitor for T2D patients treated with insulin has resulted in a reported weight loss of 0.96-3.5kg [66,106,107]. This weight loss is significantly less the anticipated weight loss (6-7kg) from the reported energy loss of 300kcal/day. Compensatory metabolic adaptations may account for the difference, although this remains to be confirmed [65]. Reports of euglycaemic diabetes ketoacidosis in insulin treated T2D patients treated with SGLT-2 inhibitors have emerged[65,108], resulting in the US Food and Drug Administration and European Medicines Agency issuing warnings[109,110]. In those insulin treated patients with long-standing T2D and low endogenous insulin secretion, a reduction in food or fluid intake should be closely monitored[110]. If there are concerns, SGLT-2 inhibitors should be stopped or avoided.

Other anti-obesity medications have been used to limit IAWG. Orlistat, a gastrointestinal lipase inhibitor, is one of the few medications licenced to aid weight loss. In obese T2D patients treated with insulin, 120mg orlistat, three times a day, combined with a reduced energy diet resulted in a significantly greater weight loss (-3.89±0.27 kg) compared to placebo (-1.27±0.28 kg, $P<0.001$) [111]. There were also improvements in glycaemic control with reductions in total and LDL cholesterol and insulin dose compared to diet therapy alone

(-8.1 vs. -1.6 units/day, respectively, P=0.007)[111]. Pramlintide, a synthetic amylin analogue, has also been shown to reduce both weight and HbA1c when using with IT in T2D patients[112]. In a post-hoc analysis of two long-term trials[112], 120μg pramlintide given to overweight and obese insulin-treated T2D patients resulted in a very modest mean weight loss of -1.5 kg at week 26, with a placebo-corrected difference of -1.8 kg (P<0.0001). Stratification according to baseline BMI showed that the weight lowering effect of pramlintide was more pronounced as BMI increased (placebo-corrected difference: BMI=35 to 40 kg/m^2, -2.4kg; BMI>40 kg/m^2, -3.2kg). Those with the highest BMI also had the greatest reduction in total daily insulin [112]. Consistent with observed anorexigenic effects of amylin in rodent models [113], pramlintide has been shown to reduce energy intake by approximately 23% (202kcal) in insulin-treated T2D patients [114]. The clinical use of pramlintide remains limited due its commercial cost, nausea and need to adjust insulin to avoid the increased risk of hypoglycaemia. Other recent drugs licensed for obesity, need to be further studied in the context of T2D patients treated with insulin[115-118]. Other licensed anti-obesity drugs have significant side effects including cardiovascular side effects that may preclude their use in insulin treated T2D patients. To date evidence supports consideration of a long-acting GLP-1 receptor agonist to minimise IAWG or promote weight loss in insulin treated T2D[103,104].

Short-term intensive IT in the early stages of diabetes, lasting only 3 weeks, has been reported to significantly improve glycaemic control and β-cell function, and to attenuate weight gain for up to 1 year compared to diet and oral hyperglycaemic agents [119,120]. In contrast, continuous IT resulted in a significant 2.7kg (P=0.01) weight gain [121]. Therefore, early short-term IT may alleviate the potential weight gain caused by insulin initiation [120] Although the underlying mechanisms are unclear, short-term intensive IT might help reduce gluctoxicity and lipotoxicity and attenuate the potential anabolic effect of hyperinsulinaemia on fat mass gains. Another potential mechanism may be early muscle preservation that promotes insulin sensitivity. Failure to meet glycaemic targets not only influence diabetes complications but also quality of life, as psychological wellbeing improves once glycaemic targets are met [122]. Thus, delaying insulin early on in diabetes could be psychologically detrimental. In a randomised study, the greatest predictor of sustained drug-free diabetes remission over 48 weeks following short-term intensive IT was early intervention in disease progression, particularly in the first 2 years after T2D diagnosis [123]. Patients who had a lower baseline HbA1c and better β-cell function also benefited from early IT [123]. These

observations on short-term intensive IT question the current diabetes pharmacotherapy algorithm for T2D in which insulin is introduced late in the management pathway.

Accumulating evidence indicates that different insulin regimes affect weight gain and glycaemic control differently [124,125] although this is not universally seen[40]. The Treating to Target in Type 2 Diabetes (4-T) study compared three different insulin regimes used to initiate insulin in insulin naïve patients with suboptimal glycaemic control on oral agents. Comparison was made between a twice daily biphasic insulin preparation, NovoMix 30, a prandial short acting analogue insulin, aspart, and a once daily basal insulin analogue, insulin detemir. Weight gain over three years in those initially commencing with basal insulin was less (3.6 kg) than with the biphasic insulin (5.7 kg) or prandial insulin (6.4 kg). In addition, those randomised to the basal insulin alone had fewer hypoglycaemic episodes (1.7 per patient per year) than the biphasic (3.0 per patient per year) or prandial (5.7 per patient per year) insulin approaches. Although at 1-year the HbA1c reduction was greatest in patients on the prandial insulin, this not seen at 3-years [124,125]. In a non-interventional observational study, a comparison of basal and premixed insulin found premixed insulin was associated with greater weight gain (2.3kg vs. 1.2kg, $P<0.001$) and more overall and nocturnal hypoglycaemic episodes. Compared to basal plus mealtime insulin, basal insulin was associated with less weight gain (-1.4kg, $P=0.002$), but a higher relative risk of nocturnal hypoglycaemic episodes (RR=2.0, $P=0.021$)[126]. In an analysis of first time insulin users selected from the UK General Practice Research Database, those on premixed insulin gained more weight than other insulin regimes. The specific types of insulins were not identified in this study thus limiting the full clinical relevance of this data [42]. Any cost-effectiveness analysis of the different insulin preparation and insulin regimes should factor in weight gain and risk of hypoglycaemia when choosing insulin regimens for T2D management both initially and long-term.

Therapeutic interventions

Weight loss remains one of the most important aspects of T2D management, and although lifestyle interventions are effective, their long-term success is dependent on weight-loss maintenance [127]. Table 1 summarises the weight loss, glycaemic, CVD and insulin related outcomes of the different interventions available for obese insulin treated T2D patients.

To date, the most effective treatment for both weight reduction and glycaemic control is bariatric (metabolic) surgery [128], with a 58 to 95% reported T2D remission [129] particularly

following either a biliopancreatic diversion (BPD) or Roux-en-Y gastric bypass (RYGB). The percentage of patients achieving T2D remission varies depending on how diabetes remission is defined[130]. Despite high remission rates in non-insulin treated T2D patients, lower remission rates occur in patients on IT [131], both in the short and mid-term[132], with figures ranging from 19.3 to 75.2%[132-134]. Following RYGB, insulin-treated patients were reported to be 7.25 times less likely to have diabetes remission [135]. Studies addressing the predictors for diabetes remission in insulin treated T2D patients include shorter duration of diabetes, lower HbA1c, younger age, and larger percentage excess body weight loss (%EBWL) [132]. In addition, insulin cessation varies between bariatric procedures, with 62% and 34% of RYGB and LAGB patients respectively ceasing IT at 1 year [133], although some have reported completely stopping IT at 60 months follow-up [134]. Independent predictors of IT cessation are the selected procedure, not taking basal bolus IT, age, preoperative BMI and %EBWL [132,133]. It should be noted, that even following bariatric surgery over time glycaemic control often deteriorates and IT is required [132].

Over the last few decades, there has been intense scientific interest and speculation in the mechanisms involved in mediating bariatric surgery's success in patients with T2D. These have included changes in gut hormone profiles, reprogramming intestinal glucose metabolism, bile acid metabolism, changes to gut microbial environment, and energy restriction (independent of weight loss) [136]. Although clearly beneficial, bariatric surgery is invasive and is associated with complications. Its use is limited by constraints on funding and operative capacity, meaning that it is only available to a fraction of potentially eligible subjects. Other clinically effective non-invasive management strategies are needed for the vast majority of obese T2D patients who may prefer a non-surgical approach, are not be eligible for surgery, or are unable to access surgery.

Intensive lifestyle intervention (ILI) consisting of energy restriction, dietary change, physical activity, and behaviour change alongside patient education, has been used to promote weight loss in obese T2D patients [137]. Although T2D patients treated with insulin struggle to lose weight[45,84], studies have shown that ILI may be more effective than conventional approaches. The Look Action for Health in Diabetes (AHEAD) study observed that T2D participants treated with insulin randomised to ILI, lost on average 7.6±7.0% of their initial weight, although taking insulin was associated with a reduced chance of diabetes remission[84,138]. In another study that aimed to attenuate the weight gain associated with commencing insulin [27], the use of ILI allowed patients to achieve a non-significant weight reduction of -0.6kg.

However, compared to the standard care group who gained 4.6 kg, there was an absolute clinically significant difference of 5.2 kg (P<0.001) between the groups. These studies highlight that attenuation of weight gain, and even weight loss, is achievable in T2D patients on insulin using ILI.

Weight loss using ILI can have a dramatic initial effect on reducing insulin doses [139]. The long-term success relies on continuation of these lifestyle changes, which is increasingly difficult following cessation of ILI [140] and also appears even more challenging in patients with T2D [141]. Behaviour change improves weight loss and long-term weight maintenance [142]; and should accompany lifestyle changes. A multidisciplinary team approach is recommended to support obesity and diabetes management to aid outcome [14,143]. The inherent issues around resources and time, and trained personnel, for translating ILI research into clinical practice has resulted in a disparity in the weight loss achieved in the clinical setting.

Low Carbohydrate Diets

Given the importance of weight loss in managing T2D, there has been extensive debate about the most effective dietary approach for weight loss. The variability of postprandial plasma glucose is directly influenced by the quantity and load of dietary carbohydrate [144]. Therefore, the use of low-carbohydrate diets (LC) diets for both weight loss and diabetes management has attracted particular interest[145]. LC diets appear to be more effective than traditional low-fat approaches for weight loss, at least up to one year [146,147], as well as offering greater improvements in both HbA1c and glucose variability [148,149]. This is despite the weight loss difference between LC and low fat diets being between 1-2 kg and hence of questionable clinical significance. Moreover, adherence to any energy-reduced diet is rarely sustained long-term and drop-out rates from clinical trials employing LC diets can be as high as 35-50% [146,147,150].

There is some evidence that diets in which the carbohydrate content is reduced below 50-60 g per day may have a beneficial effect on HbA1c, triglycerides and high density lipoproteins (HDL-C), which may be independent of weight loss [146,147]. Clinically significant reductions in plasma glucose concentrations of approximately 4 mmol/L are also observed on isocaloric low-carbohydrate, high-protein diets [151], an effect not observed with other diets. An important advantage of LC diets for the management of T2D is that they reduce the requirement for exogenous insulin, with evidence showing significant reductions at 6 and 12 months [152,153], but not beyond [154]. The role of LC diets in insulin-treated T2D patients is not clear as studies to date have differed with respect to weight loss achieved and T2D treatment

at baseline [152,155]. Nevertheless, the results to date are promising and highlight the need for future clinical trials with groups matched at baseline for confounding factors such as T2D duration, current insulin regimen and dose, and use of hypoglycaemic agents.

Since exogenous insulin dose is related to weight gain, for those who can follow and enjoy a LC diet over the long-term, one advantage would be reduced weight gain. For clinicians wishing to employ this approach in practice, several caveats exist. First, the cut-off below which carbohydrate restriction is most effective is unclear, and mere restriction (for instance from 50% to 35% of calories from carbohydrate) does not appear to affect glycaemic control in the absence of weight loss. Furthermore, replacement of carbohydrate with foods high in saturated fat can lead to increases in low-density lipoprotein cholesterol (LDL-C)[150]. By contrast, reducing saturated fat to less than 10% results in a favourable reduction of LDL-C and other markers of CVD risk [148]. Finally, within clinical practice, close supervision is required to adjust hypoglycaemic agents and insulin to avoid hypoglycaemia.

Very low and low energy formula diets

Obesity guidelines from the Scottish Intercollegiate Guidelines Network (SIGN) in 2010, suggested that patients with a BMI over 35kg/m^2 require a 15-20% weight loss to cause sustained improvement in morbidity [156]. Despite persistent efforts in clinical practice, weight loss remains significantly less than recommend by SIGN [157]. Acute energy restriction, in the form of formula very low energy diets (VLED) of less than 800kcal/day, has been shown to produce clinically significant weight loss[158]. According to the twin cycle hypothesis, the combined accumulation of fat in the liver and secondarily in the pancreas promotes the onset and progression of T2D [159]. Liver and pancreatic fat can be dramatically reduced by rapid and pronounced (~15%) weight loss [160]. While this approach appears to be attractive, there are concerns about the rapidity of weight loss, and the likelihood of weight regain following diet cessation [143], possibly due to alterations in counter-regulatory gut hormones [161] and a return to old eating habits. Reassuringly, recent evidence suggests that after weight loss with VLED, long-term weight maintenance is achievable [162].

In early onset T2D patients who are insulin naive, the use of an 8-week VLED has been shown to normalise hepatic insulin sensitivity and first phase and total insulin secretion, corresponding with reductions in hepatic and pancreatic fat [160]. Improvements maintained in 40% of patients for up to 6 months. Offering acute energy restriction has the potential to result in remission of T2D in those patients that respond[163]. The use of VLED in insulin treated obese T2D patients has been observed to result in significant weight loss, metabolic

improvements, reduction of pericardial fat, and improved quality of life [164,165]. Methodological limitations preclude the generalisability of these findings within routine clinical practice. Although there is evidence for the use of VLED for T2D patients managed by diet alone or alongside oral-hyperglycaemic medications, there is a lack of comparable evidence to help guide their use with those currently treated on insulin. An ongoing randomised control trial "Diabetes Intervention Accentuating Diet and Enhancing Metabolism II" (DIADEM-II, ISRCTN21335883) will hopefully on completion provide this guidance.

Conclusions

IAWG is multifactorial, involving biological, systemic, peripheral and behavioural mechanisms. Although weight gain is typically seen after insulin initiation, this is not inevitable, as with the appropriate education and interventions weight gain may be preventable. The benefits of weight loss are clear, both in terms of improving glycaemic control and reducing medication burden. Clinical treatment tends to focus on intensification of pharmacotherapy as the solution for inadequate glycaemic control, resulting in disempowerment of patients from managing their own condition. There is a need for a shift in clinical practice from the traditional focus on achieving glycaemic targets through insulin intensification to a greater focus on weight loss and limiting weight gain.

The key mechanisms causing IAWG appear to be the reduction of glycosuria, 'defensive snacking' against hypoglycaemia, 'catch-up' weight gain and the un-physiological route of administration of exogenous insulin. The challenges and limitations of traditional lifestyle approaches, particularly the translation of research findings into clinical practice, have resulted in other treatment options being sought. Bariatric surgery is currently the most effective treatment for obese T2D, even for insulin treated patients, but constraints on funding and accessibility mean that this option is unavailable to the many who would benefit. The use of low carbohydrate diets and very low energy diets have gained interest as potentially viable treatment options for T2D patients struggling with their weight or unable to access bariatric surgery. Questions still remain regarding the long-term application and sustainability of these diets, but on-going clinical trials should shed light on their utility in clinical practice. It is clear from recent evidence that not all individuals will respond to either acute energy restriction or bariatric surgery, and there remain questions about the predictors of success around diabetes improvement and remission. Although remission and insulin cessation is possible, this tends to be temporary and therefore patient counselling regarding

the potential need for reinstatement of insulin treatment should be included during clinical consultations. Further research is required to understand the factors mediating IAWG to allow the tailoring of different approaches employed in clinical practice to mitigate the vicious cycle of weight gain, poor glycaemia, and treatment intensification.

Acknowledgements: ST is funded by the Biomedical Research Program at Weill Cornell Medicine in Qatar, supported by the Qatar Foundation. ST also receives funding from the following grant from the Qatar National Research Fund: NPRP 8-912-3-192. GF is an NIHR senior investigator.

Author Contributions: AB and GF contributed to the conceptualisation of the review. AB, GF and ST planned the review. AB researched the literature and wrote the first draft. AB, AD, NG, GF and ST prepared subsequent drafts. All authors reviewed the final draft prior to submission.

Conflict of interests: AB and GF and ST have received funding for investigator-initiated research through an educational grant from Cambridge Weight Plan Ltd.

References

1. World Health Organization. Global Report on Diabetes 2016:1-88.
2. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes.* 2003;52(1):102-110.
3. Matthews DR, Cull CA, Stratton IM, Holman RR, Turner RC. UKPDS 26: Sulphonylurea failure in non-insulin-dependent diabetic patients over six years. UK Prospective Diabetes Study (UKPDS) Group. *Diabetic medicine : a journal of the British Diabetic Association.* 1998;15(4):297-303.
4. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA : the journal of the American Medical Association.* 1999;281(21):2005-2012.
5. UKPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837 - 853.
6. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *The New England journal of medicine.* 2008;358(24):2560-2572.
7. Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *The New England journal of medicine.* 1993;329(5):304-309.
8. Diabetes U. *State of the Nation Challenhes for 2015 and beyond.* London2014.
9. Henry RR, Gumbiner B, Ditzler T, Wallace P, Lyon R, Glauber HS. Intensive conventional insulin therapy for type II diabetes. Metabolic effects during a 6-mo outpatient trial. *Diabetes care.* 1993;16(1):21-31.
10. Makimattila S, Nikkila K, Yki-Jarvinen H. Causes of weight gain during insulin therapy with and without metformin in patients with Type II diabetes mellitus. *Diabetologia.* 1999;42(4):406-412.
11. Jansen HJ, Vervoort GM, de Haan AF, Netten PM, de Grauw WJ, Tack CJ. Diabetes-related distress, insulin dose, and age contribute to insulin-associated weight gain in patients with type 2 diabetes: results of a prospective study. *Diabetes care.* 2014;37(10):2710-2717.
12. Larger E, Rufat P, Dubois-Laforgue D, Ledoux S. Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. *Diabetes care.* 2001;24(10):1849-1850.
13. Calvert MJ, McManus RJ, Freemantle N. Management of type 2 diabetes with multiple oral hypoglycaemic agents or insulin in primary care: retrospective cohort study. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2007;57(539):455-460.
14. NICE. National Institute for Health and Clinical Excellence: Guideline NG28 Type 2 diabetes in adults: management. *National Institute for Health and Clinical Excellence: Guideline NG28 Type 2 diabetes in adults: management*. London: National Institute for Health and Care Excellence (UK) 2015.
15. Association AD. Standards of Medical Care in Diabetes - Approaches to Glycemic Treatment. *Diabetes care.* 2016;39 Suppl 1:S52-59.
16. Paul SK, Shaw JE, Montvida O, Klein K. Weight gain in insulin-treated patients by body mass index category at treatment initiation: new evidence from real-world data in patients with type 2 diabetes. *Diabetes, obesity & metabolism.* 2016.
17. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ open.* 2016;6(1):e010210.

18. Selvin E, Parrinello CM, Daya N, Bergenstal RM. Trends in Insulin Use and Diabetes Control in the U.S.: 1988-1994 and 1999-2012. *Diabetes care.* 2016;39(3):e33-35.
19. Centre HaSCI. National Diabetes Audit 2012-2013 and 2014-2015 Report 1: Care Processes and Treatment Targets. 2015.
20. Morgan CL, Jenkins-Jones S, Evans M, Barnett AH, Poole CD, Currie CJ. Weight change in people with type 2 diabetes: secular trends and the impact of alternative antihyperglycaemic drugs. *Diabetes, obesity & metabolism.* 2012;14(5):424-432.
21. Sorli C, Heile MK. Identifying and meeting the challenges of insulin therapy in type 2 diabetes. *Journal of multidisciplinary healthcare.* 2014;7:267-282.
22. Federation ID. The DAWN (Diabetes Attitudes, Wishes and Needs) study. *Practical Diabetes International.* 2002;19(1):22-24a.
23. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Primary care diabetes.* 2010;4 Suppl 1:S11-18.
24. Greaves CJ, Brown P, Terry RT, Eiser C, Lings P, Stead JW. Converting to insulin in primary care: an exploration of the needs of practice nurses. *J Adv Nurs.* 2003;42(5):487-496.
25. Cuddihy RM, Philis-Tsimikas A, Nazeri A. Type 2 diabetes care and insulin intensification: is a more multidisciplinary approach needed? Results from the MODIFY survey. *The Diabetes educator.* 2011;37(1):111-123.
26. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S. Intensive insulin therapy prevents the progression of diabetic micro-vascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes research and clinical practice.* 1995;28(2):103 - 117.
27. Barratt R, Frost G, Millward DJ, Truby H. A randomised controlled trial investigating the effect of an intensive lifestyle intervention v. standard care in adults with type 2 diabetes immediately after initiating insulin therapy. *The British journal of nutrition.* 2008;99(5):1025-1031.
28. Jansen HJ, Vervoort G, van der Graaf M, Tack CJ. Pronounced weight gain in insulin-treated patients with type 2 diabetes mellitus is associated with an unfavourable cardiometabolic risk profile. *The Netherlands journal of medicine.* 2010;68(11):359-366.
29. Packianathan IC, Fuller NJ, Peterson DB, Wright A, Coward WA, Finer N. Use of a reference four-component model to define the effects of insulin treatment on body composition in type 2 diabetes: the 'Darwin study'. *Diabetologia.* 2005;48(2):222-229.
30. Salle A, Ryan M, Guilloteau G, Bouhanick B, Berrut G, Ritz P. 'Glucose control-related' and 'non-glucose control-related' effects of insulin on weight gain in newly insulin-treated type 2 diabetic patients. *The British journal of nutrition.* 2005;94(6):931-937.
31. Sinha A, Formica C, Tsalamandris C, et al. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 1996;13(1):40-46.
32. Rigalleau V, Delafaye C, Baillet L, et al. Composition of insulin-induced body weight gain in diabetic patients: a bio-impedance study. *Diabetes & metabolism.* 1999;25(4):321-328.
33. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet.* 2004;364(9438):937-952.
34. Wagenknecht LE, Langefeld CD, Scherzinger AL, et al. Insulin sensitivity, insulin secretion, and abdominal fat: the Insulin Resistance Atherosclerosis Study (IRAS) Family Study. *Diabetes.* 2003;52(10):2490-2496.
35. Tomaszewski M, Charchar FJ, Maric C, et al. Glomerular hyperfiltration: a new marker of metabolic risk. *Kidney international.* 2007;71(8):816-821.

36. Yki-Jarvinen H, Ryysy L, Kauppila M, et al. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *The Journal of clinical endocrinology and metabolism.* 1997;82(12):4037-4043.
37. Aas AM, Ohrvik J, Malmberg K, Ryden L, Birkeland KI. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes, obesity & metabolism.* 2009;11(4):323-329.
38. Jacob AN, Salinas K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. *Diabetes, obesity & metabolism.* 2007;9(3):386-393.
39. Jansen HJ, Hendriks JC, de Galan BE, Penders G, Tack CJ, Vervoort G. Contribution of change in glycosylated haemoglobin to insulin-associated weight gain: results of a longitudinal study in type 2 diabetic patients. *Endocrine.* 2011;39(2):190-197.
40. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes care.* 2014;37(8):2108-2113.
41. Biesenbach G, Raml A, Alsaraji N. Weight gain and insulin requirement in type 2 diabetic patients during the first year after initiating insulin therapy dependent on baseline BMI. *Diabetes, obesity & metabolism.* 2006;8(6):669-673.
42. Watson L, Wilson BP, Alsop J, Kumar S. Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? *Diabetes, obesity & metabolism.* 2011;13(9):823-831.
43. Wolfe RR. Effects of insulin on muscle tissue. *Current opinion in clinical nutrition and metabolic care.* 2000;3(1):67-71.
44. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414(6865):799-806.
45. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes, obesity & metabolism.* 2007;9(6):799-812.
46. Kimball SR, Jefferson LS. Regulation of initiation of protein synthesis by insulin in skeletal muscle. *Acta diabetologica.* 1991;28(2):134-139.
47. Abdulla H, Smith K, Atherton PJ, Idris I. Role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown: a systematic review and meta-analysis. *Diabetologia.* 2016;59(1):44-55.
48. Porte D, Jr., Baskin DG, Schwartz MW. Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes.* 2005;54(5):1264-1276.
49. Porte D, Jr., Baskin DG, Schwartz MW. Leptin and insulin action in the central nervous system. *Nutrition reviews.* 2002;60(10 Pt 2):S20-29; discussion S68-84, 85-27.
50. Sipols AJ, Baskin DG, Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. *Diabetes.* 1995;44(2):147-151.
51. Clegg DJ, Gotoh K, Kemp C, et al. Consumption of a high-fat diet induces central insulin resistance independent of adiposity. *Physiology & behavior.* 2011;103(1):10-16.
52. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nature neuroscience.* 2002;5(6):566-572.
53. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nature neuroscience.* 2002;5(6):514-516.
54. Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H. Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes.* 2012;61(4):782-789.

55. Heni M, Kullmann S, Ketterer C, et al. Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions. *Diabetologia.* 2012;55(6):1773-1782.
56. Heni M, Wagner R, Kullmann S, et al. Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. *Diabetes.* 2014;63(12):4083-4088.
57. Kenny PJ. Reward mechanisms in obesity: new insights and future directions. *Neuron.* 2011;69(4):664-679.
58. Stouffer MA, Woods CA, Patel JC, et al. Insulin enhances striatal dopamine release by activating cholinergic interneurons and thereby signals reward. *Nature communications.* 2015;6:8543.
59. Anthony K, Reed LJ, Dunn JT, et al. Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome? *Diabetes.* 2006;55(11):2986-2992.
60. Johnson PM, Kenny PJ. Dopamine D2 receptors in addiction-like reward dysfunction and compulsive eating in obese rats. *Nature neuroscience.* 2010;13(5):635-641.
61. Wisse BE, Schwartz MW. Does hypothalamic inflammation cause obesity? *Cell Metab.* 2009;10(4):241-242.
62. Hotamisligil GS. Inflammation and metabolic disorders. *Nature.* 2006;444(7121):860-867.
63. Souza CTD, Araujo EP, Bordin S, et al. Consumption of a Fat-Rich Diet Activates a Proinflammatory Response and Induces Insulin Resistance in the Hypothalamus. *Endocrinology.* 2005;146(10):4192-4199.
64. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. *Science (New York, N.Y.).* 1996;271(5249):665-668.
65. Rajeev SP, Cuthbertson DJ, Wilding JP. Energy balance and metabolic changes with sodium-glucose co-transporter 2 inhibition. *Diabetes, obesity & metabolism.* 2016;18(2):125-134.
66. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes, obesity & metabolism.* 2016;18(8):783-794.
67. Shank ML, Del Prato S, DeFronzo RA. Bedtime insulin/daytime glipizide. Effective therapy for sulfonylurea failures in NIDDM. *Diabetes.* 1995;44(2):165-172.
68. Bergman RN. Non-esterified fatty acids and the liver: why is insulin secreted into the portal vein? *Diabetologia.* 2000;43(7):946-952.
69. Lindholm A. New insulins in the treatment of diabetes mellitus. *Best practice & research. Clinical gastroenterology.* 2002;16(3):475-492.
70. Smith-Palmer J, Brandle M, Trevisan R, Orsini Federici M, Liabat S, Valentine W. Assessment of the association between glycemic variability and diabetes-related complications in type 1 and type 2 diabetes. *Diabetes research and clinical practice.* 2014;105(3):273-284.
71. Vora J, Heise T. Variability of glucose-lowering effect as a limiting factor in optimizing basal insulin therapy: a review. *Diabetes, obesity & metabolism.* 2013;15(8):701-712.
72. Heinemann L. Variability of insulin absorption and insulin action. *Diabetes Technol Ther.* 2002;4(5):673-682.
73. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes, obesity & metabolism.* 2007;9(5):648-659.

36. Yki-Jarvinen H, Ryysy L, Kauppila M, et al. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. *The Journal of clinical endocrinology and metabolism.* 1997;82(12):4037-4043.
37. Aas AM, Ohrvik J, Malmberg K, Ryden L, Birkeland KI. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. *Diabetes, obesity & metabolism.* 2009;11(4):323-329.
38. Jacob AN, Salinas K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. *Diabetes, obesity & metabolism.* 2007;9(3):386-393.
39. Jansen HJ, Hendriks JC, de Galan BE, Penders G, Tack CJ, Vervoort G. Contribution of change in glycosylated haemoglobin to insulin-associated weight gain: results of a longitudinal study in type 2 diabetic patients. *Endocrine.* 2011;39(2):190-197.
40. Balkau B, Home PD, Vincent M, Marre M, Freemantle N. Factors associated with weight gain in people with type 2 diabetes starting on insulin. *Diabetes care.* 2014;37(8):2108-2113.
41. Biesenbach G, Raml A, Alsaraji N. Weight gain and insulin requirement in type 2 diabetic patients during the first year after initiating insulin therapy dependent on baseline BMI. *Diabetes, obesity & metabolism.* 2006;8(6):669-673.
42. Watson L, Wilson BP, Alsop J, Kumar S. Weight and glycaemic control in type 2 diabetes: what is the outcome of insulin initiation? *Diabetes, obesity & metabolism.* 2011;13(9):823-831.
43. Wolfe RR. Effects of insulin on muscle tissue. *Current opinion in clinical nutrition and metabolic care.* 2000;3(1):67-71.
44. Saltiel AR, Kahn CR. Insulin signalling and the regulation of glucose and lipid metabolism. *Nature.* 2001;414(6865):799-806.
45. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes--causes, effects and coping strategies. *Diabetes, obesity & metabolism.* 2007;9(6):799-812.
46. Kimball SR, Jefferson LS. Regulation of initiation of protein synthesis by insulin in skeletal muscle. *Acta diabetologica.* 1991;28(2):134-139.
47. Abdulla H, Smith K, Atherton PJ, Idris I. Role of insulin in the regulation of human skeletal muscle protein synthesis and breakdown: a systematic review and meta-analysis. *Diabetologia.* 2016;59(1):44-55.
48. Porte D, Jr., Baskin DG, Schwartz MW. Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from C. elegans to humans. *Diabetes.* 2005;54(5):1264-1276.
49. Porte D, Jr., Baskin DG, Schwartz MW. Leptin and insulin action in the central nervous system. *Nutrition reviews.* 2002;60(10 Pt 2):S20-29; discussion S68-84, 85-27.
50. Sipols AJ, Baskin DG, Schwartz MW. Effect of intracerebroventricular insulin infusion on diabetic hyperphagia and hypothalamic neuropeptide gene expression. *Diabetes.* 1995;44(2):147-151.
51. Clegg DJ, Gotoh K, Kemp C, et al. Consumption of a high-fat diet induces central insulin resistance independent of adiposity. *Physiology & behavior.* 2011;103(1):10-16.
52. Obici S, Feng Z, Karkanias G, Baskin DG, Rossetti L. Decreasing hypothalamic insulin receptors causes hyperphagia and insulin resistance in rats. *Nature neuroscience.* 2002;5(6):566-572.
53. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nature neuroscience.* 2002;5(6):514-516.
54. Hallschmid M, Higgs S, Thienel M, Ott V, Lehnert H. Postprandial administration of intranasal insulin intensifies satiety and reduces intake of palatable snacks in women. *Diabetes.* 2012;61(4):782-789.

92. Lv WS, Wen JP, Li L, et al. The effect of metformin on food intake and its potential role in hypothalamic regulation in obese diabetic rats. *Brain research.* 2012;1444:11-19.
93. Mannucci E, Tesi F, Bardini G, et al. Effects of metformin on glucagon-like peptide-1 levels in obese patients with and without Type 2 diabetes. *Diabetes, nutrition & metabolism.* 2004;17(6):336-342.
94. Napolitano A, Miller S, Nicholls AW, et al. Novel gut-based pharmacology of metformin in patients with type 2 diabetes mellitus. *PloS one.* 2014;9(7):e100778.
95. Lee H, Ko G. Effect of metformin on metabolic improvement and gut microbiota. *Applied and environmental microbiology.* 2014;80(19):5935-5943.
96. Rodin J, Wack J, Ferrannini E, DeFronzo RA. Effect of insulin and glucose on feeding behavior. *Metabolism.* 1985;34(9):826-831.
97. Davies MJ, Derezinski T, Pedersen CB, Clauson P. Reduced weight gain with insulin detemir compared to NPH insulin is not explained by a reduction in hypoglycemia. *Diabetes technology & therapeutics.* 2008;10(4):273-277.
98. Dornhorst A, Luddeke HJ, Sreenan S, et al. Insulin detemir improves glycaemic control without weight gain in insulin-naive patients with type 2 diabetes: subgroup analysis from the PREDICTIVE study. *Int J Clin Pract.* 2008;62(4):659-665.
99. Russell-Jones D, Danne T, Hermansen K, et al. Weight-sparing effect of insulin detemir: a consequence of central nervous system-mediated reduced energy intake? *Diabetes, obesity & metabolism.* 2015;17(10):919-927.
100. Vora J, Cariou B, Evans M, et al. Clinical use of insulin degludec. *Diabetes research and clinical practice.* 2015;109(1):19-31.
101. Josse RG, Woo V. Flexibly timed once-daily dosing with degludec: a new ultra-long-acting basal insulin. *Diabetes, obesity & metabolism.* 2013;15(12):1077-1084.
102. Vilsboll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *Bmj.* 2012;344:d7771.
103. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet.* 2014;384(9961):2228-2234.
104. Lingvay I, Manghi FP, Garcia-Hernandez P, et al. Effect of Insulin Glargine Up-titration vs Insulin Degludec/Liraglutide on Glycated Hemoglobin Levels in Patients With Uncontrolled Type 2 Diabetes: The DUAL V Randomized Clinical Trial. *JAMA : the journal of the American Medical Association.* 2016;315(9):898-907.
105. Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *The Journal of clinical endocrinology and metabolism.* 2012;97(3):1020-1031.
106. Neal B, Perkovic V, de Zeeuw D, et al. Efficacy and safety of canagliflozin, an inhibitor of sodium-glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. *Diabetes care.* 2015;38(3):403-411.
107. Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. *Diabetes, obesity & metabolism.* 2014;16(2):124-136.
108. Rosenstock J, Ferrannini E. Euglycemic Diabetic Ketoacidosis: A Predictable, Detectable, and Preventable Safety Concern With SGLT2 Inhibitors. *Diabetes care.* 2015;38(9):1638-1642.
109. US Food and Drug Administration: Drug Safety Communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

[Internet], 15 May 2015. Available from URL: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM446954.pdf. Accessed 1 May 2017
110. European Medicine Agency. EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes: Healthcare professionals should be aware of possible atypical cases. [Internet], 24 April 2016. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/European_Commission_final_decision/WC500202393.pdf. Accessed 1 May 2017
111. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial. *Diabetes care.* 2002;25(6):1033-1041.
112. Hollander P, Maggs DG, Ruggles JA, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. *Obesity research.* 2004;12(4):661-668.
113. Rushing PA, Hagan MM, Seeley RJ, Lutz TA, Woods SC. Amylin: a novel action in the brain to reduce body weight. *Endocrinology.* 2000;141(2):850-853.
114. Chapman I, Parker B, Doran S, et al. Effect of pramlintide on satiety and food intake in obese subjects and subjects with type 2 diabetes. *Diabetologia.* 2005;48(5):838-848.
115. O'Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity.* 2012;20(7):1426-1436.
116. Garvey WT, Ryan DH, Bohannon NJ, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. *Diabetes care.* 2014;37(12):3309-3316.
117. Gadde KM, Allison DB, Ryan DH, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet.* 2011;377(9774):1341-1352.
118. Hollander P, Gupta AK, Plodkowski R, et al. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. *Diabetes care.* 2013;36(12):4022-4029.
119. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet.* 2008;371(9626):1753-1760.
120. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes care.* 2004;27(5):1028-1032.
121. Alvarsson M, Sundkvist G, Lager I, et al. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes care.* 2003;26(8):2231-2237.
122. Tamir O, Wainstein J, Raz I, Shemer J, Heymann A. Quality of life and patient-perceived difficulties in the treatment of type 2 diabetes. *The review of diabetic studies : RDS.* 2012;9(1):46-54.
123. Kramer CK, Zinman B, Choi H, Retnakaran R. Predictors of sustained drug-free diabetes remission over 48 weeks following short-term intensive insulin therapy in early type 2 diabetes. *BMJ open diabetes research & care.* 2016;4(1):e000270.
124. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *The New England journal of medicine.* 2007;357(17):1716-1730.
125. Holman RR, Farmer AJ, Davies MJ, et al. Three-Year Efficacy of Complex Insulin Regimens in Type 2 Diabetes. *New England Journal of Medicine.* 2009;361(18):1736-1747.

126. Freemantle N, Balkau B, Home PD. A propensity score matched comparison of different insulin regimens 1 year after beginning insulin in people with type 2 diabetes. *Diabetes, obesity & metabolism.* 2013;15(12):1120-1127.
127. Norris SL, Zhang X, Avenell A, et al. Long-term non-pharmacologic weight loss interventions for adults with type 2 diabetes. *The Cochrane database of systematic reviews.* 2005(2):Cd004095.
128. Leong WB, Taheri, S. The role of bariatric surgery in the treatment of type 2 diabetes mellitus. *J R Coll Physicians Edinb.* 2012;42:194-198.
129. Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *The American journal of medicine.* 2009;122(3):248-256.e245.
130. Mas-Lorenzo A, Benaiges D, Flores-Le-Roux JA, et al. Impact of different criteria on type 2 diabetes remission rate after bariatric surgery. *Obesity surgery.* 2014;24(11):1881-1887.
131. Casella G, Abbatini F, Cali B, Capoccia D, Leonetti F, Basso N. Ten-year duration of type 2 diabetes as prognostic factor for remission after sleeve gastrectomy. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* 2011;7(6):697-702.
132. Ghio BJ, A.; Corcelles, R.; Flores, L.; Lacy, A.; Vidal, J. Midterm effects bariatric surgery in patients with insulin-treated type 2 diabetes. *Surgery for Obesity and Related Diseases, in Press. Available from:*http://www.soard.org/article/S1550-7289(16)30894-2/fulltext*.* 2017.
133. Ardestani A, Rhoads D, Tavakkoli A. Insulin cessation and diabetes remission after bariatric surgery in adults with insulin-treated type 2 diabetes. *Diabetes care.* 2015;38(4):659-664.
134. Jimenez A, Casamitjana R, Flores L, et al. Long-term effects of sleeve gastrectomy and Roux-en-Y gastric bypass surgery on type 2 diabetes mellitus in morbidly obese subjects. *Annals of surgery.* 2012;256(6):1023-1029.
135. Still CD, Wood GC, Benotti P, et al. Preoperative prediction of type 2 diabetes remission after Roux-en-Y gastric bypass surgery: a retrospective cohort study. *The lancet. Diabetes & endocrinology.* 2014;2(1):38-45.
136. Makaronidis JM, Batterham RL. Potential Mechanisms Mediating Sustained Weight Loss Following Roux-en-Y Gastric Bypass and Sleeve Gastrectomy. *Endocrinology and metabolism clinics of North America.* 2016;45(3):539-552.
137. National Collaborating Centre for Chronic C. National Institute for Health and Clinical Excellence: Guidance. *Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update)*. London: Royal College of Physicians (UK), Royal College of Physicians of London.; 2008.
138. Gregg EW, Chen H, Wagenknecht LE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA : the journal of the American Medical Association.* 2012;308(23):2489-2496.
139. Reaven GM. Beneficial effect of moderate weight loss in older patients with non-insulin-dependent diabetes mellitus poorly controlled with insulin. *Journal of the American Geriatrics Society.* 1985;33(2):93-95.
140. McGuire MT, Wing RR, Hill JO. The prevalence of weight loss maintenance among American adults. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity.* 1999;23(12):1314-1319.
141. Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes care.* 2005;28(6):1526-1527.

142. Avenell A, Broom J, Brown TJ, et al. Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement. *Health technology assessment.* 2004;8(21):iii-iv, 1-182.
143. NICE. National Institute for Health and Clinical Excellence: Guidance. *Obesity: Identification, Assessment and Management of Overweight and Obesity in Children, Young People and Adults: Partial Update of CG43*. London: National Institute for Health and Care Excellence (UK) 2014.
144. Franz MJ, Powers MA, Leontos C, et al. The Evidence for Medical Nutrition Therapy for Type 1 and Type 2 Diabetes in Adults. *Journal of the American Dietetic Association.* 2010;110(12):1852-1889.
145. Dyson PA, Kelly T, Deakin T, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabetic medicine : a journal of the British Diabetic Association.* 2011;28(11):1282-1288.
146. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *The British journal of nutrition.* 2013;110(7):1178-1187.
147. Nordmann AJ, Nordmann A, Briel M, et al. Effects of low-carbohydrate vs low-fat diets on weight loss and cardiovascular risk factors: a meta-analysis of randomized controlled trials. *Archives of internal medicine.* 2006;166(3):285-293.
148. Tay J, Luscombe-Marsh ND, Thompson CH, et al. A very low-carbohydrate, low-saturated fat diet for type 2 diabetes management: a randomized trial. *Diabetes care.* 2014;37(11):2909-2918.
149. Kirk JK, Graves DE, Craven TE, Lipkin EW, Austin M, Margolis KL. Restricted-carbohydrate diets in patients with type 2 diabetes: a meta-analysis. *J Am Diet Assoc.* 2008;108(1):91-100.
150. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *The New England journal of medicine.* 2003;348(21):2082-2090.
151. Gannon MC, Nuttall FQ. Effect of a high-protein, low-carbohydrate diet on blood glucose control in people with type 2 diabetes. *Diabetes.* 2004;53(9):2375-2382.
152. Westman EC, Yancy WS, Jr., Mavropoulos JC, Marquart M, McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutrition & metabolism.* 2008;5:36.
153. Larsen RN, Mann NJ, Maclean E, Shaw JE. The effect of high-protein, low-carbohydrate diets in the treatment of type 2 diabetes: a 12 month randomised controlled trial. *Diabetologia.* 2011;54(4):731-740.
154. Guldbrand H, Dizdar B, Bunjaku B, et al. In type 2 diabetes, randomisation to advice to follow a low-carbohydrate diet transiently improves glycaemic control compared with advice to follow a low-fat diet producing a similar weight loss. *Diabetologia.* 2012;55(8):2118-2127.
155. Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutrition & metabolism.* 2008;5:14.
156. SIGN. 115 Management of Obesity: a national clinical guideline. In: Scotland N, ed. Edinburgh2010.
157. Jolly K, Lewis A, Beach J, et al. Comparison of range of commercial or primary care led weight reduction programmes with minimal intervention control for weight loss in obesity: lighten Up randomised controlled trial. *Bmj.* 2011;343:d6500.
158. Brown A, Frost G and Taheri, S. Is there a place for low-energy formula diets in weight management. *British Journal of Obesity.* 2015;3(Volume 1, No 3):84-119.

159. Taylor R. Type 2 diabetes: etiology and reversibility. *Diabetes care.* 2013;36(4):1047-1055.
160. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia.* 2011;54(10):2506-2514.
161. Sumithran P, Prendergast LA, Delbridge E, et al. Ketosis and appetite-mediating nutrients and hormones after weight loss. *European journal of clinical nutrition.* 2013;67(7):759-764.
162. Johansson K, Neovius M, Hemmingsson E. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. *The American journal of clinical nutrition.* 2014;99(1):14-23.
163. Steven S, Hollingsworth KG, Al-Mrabeh A, et al. Very-Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiologic Changes in Responders and Nonresponders. *Diabetes care.* 2016.
164. Snel M, Sleddering MA, Vd Peijl ID, et al. Quality of life in type 2 diabetes mellitus after a very low calorie diet and exercise. *European journal of internal medicine.* 2012;23(2):143-149.
165. Snel M, Jonker JT, Hammer S, et al. Long-term beneficial effect of a 16-week very low calorie diet on pericardial fat in obese type 2 diabetes mellitus patients. *Obesity.* 2012;20(8):1572-1576.
166. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes. *New England Journal of Medicine.* 2017;376(7):641-651.
167. Aas AM, Bergstad I, Thorsby PM, Johannesen O, Solberg M, Birkeland KI. An intensified lifestyle intervention programme may be superior to insulin treatment in poorly controlled Type 2 diabetic patients on oral hypoglycaemic agents: results of a feasibility study. *Diabetic medicine : a journal of the British Diabetic Association.* 2005;22(3):316-322.
168. Rowe R, Cowx M, Poole C, McEwan P, Morgan C, Walker M. The effects of orlistat in patients with diabetes: improvement in glycaemic control and weight loss. *Current medical research and opinion.* 2005;21(11):1885-1890.
169. de Wit HM, Vervoort GM, Jansen HJ, de Grauw WJ, de Galan BE, Tack CJ. Liraglutide reverses pronounced insulin-associated weight gain, improves glycaemic control and decreases insulin dose in patients with type 2 diabetes: a 26 week, randomised clinical trial (ELEGANT). *Diabetologia.* 2014;57(9):1812-1819.
170. Lind M, Hirsch IB, Tuomilehto J, et al. Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial). *Bmj.* 2015;351:h5364.
171. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes care.* 2003;26(3):784-790.
172. Riddle M, Frias J, Zhang B, et al. Pramlintide improved glycemic control and reduced weight in patients with type 2 diabetes using basal insulin. *Diabetes care.* 2007;30(11):2794-2799.
173. Riddle M, Pencek R, Charenkavanich S, Lutz K, Wilhelm K, Porter L. Randomized comparison of pramlintide or mealtime insulin added to basal insulin treatment for patients with type 2 diabetes. *Diabetes care.* 2009;32(9):1577-1582.
174. Wilding JP, Woo V, Soler NG, et al. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. *Annals of internal medicine.* 2012;156(6):405-415.

175. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *The American journal of clinical nutrition.* 2013;97(3):505-516.
176. Davis NJ, Tomuta N, Schechter C, et al. Comparative study of the effects of a 1-year dietary intervention of a low-carbohydrate diet versus a low-fat diet on weight and glycemic control in type 2 diabetes. *Diabetes care.* 2009;32(7):1147-1152.
177. Iqbal N, Vetter ML, Moore RH, et al. Effects of a low-intensity intervention that prescribed a low-carbohydrate vs. a low-fat diet in obese, diabetic participants. *Obesity.* 2010;18(9):1733-1738.
178. Wing RR, Blair E, Marcus M, Epstein LH, Harvey J. Year-long weight loss treatment for obese patients with type II diabetes: does including an intermittent very-low-calorie diet improve outcome? *The American journal of medicine.* 1994;97(4):354-362.
179. Wing RR, Marcus MD, Salata R, Epstein LH, Miaskiewicz S, Blair EH. Effects of a very-low-calorie diet on long-term glycemic control in obese type 2 diabetic subjects. *Archives of internal medicine.* 1991;151(7):1334-1340.
180. Singhal R, Ahmed M, Krempic A, Kitchen M, Super P. Medium-term outcomes of patients with insulin-dependent diabetes after laparoscopic adjustable gastric banding. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* 2013;9(1):42-47.
181. Brethauer SA, Aminian A, Romero-Talamas H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus. *Annals of surgery.* 2013;258(4):628-636; discussion 636-627.
182. Kadera BE, Lum K, Grant J, Pryor AD, Portenier DD, DeMaria EJ. Remission of type 2 diabetes after Roux-en-Y gastric bypass is associated with greater weight loss. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* 2009;5(3):305-309.

Figure Legends:

Figure 1 - Mechanisms of weight gain associated with insulin treatment

Insulin associated weight gain (IAWG) is multifaceted. A) Insulin is key to appetite and reward regulation in the hypothalamus and ventral striatum. Nutrient excess can cause hypothalamic insulin resistance and low-grade inflammation, with TNF-α inhibiting insulin action through suppression of IRS-1 (insulin receptor substrate-1). Insulin resistance reduces insulin activation of POMC/CART (pro-opiomelanocortin/cocaine and amphetamine regulated transcript) neurons and suppression of AgRP/NPY (agouti related peptide/neuropeptide Y) neurons, therefore potentially increasing appetite and dietary intake. B) Weight gain is often seen before diabetes diagnosis, but in the year preceding diabetes diagnosis and prior to insulin initiation, patients often lose weight. IAWG has been proposed to be due to the body 'catching-up' to the maximal weight before diabetes. C) Insulin is an anabolic hormone and as such increases FA (fatty acid) storage in adipose tissue, proteolysis and muscle hypertrophy. With super-physiological levels of exogenous insulin within the periphery, this may in part be responsible for gains in fat and lean tissue. D) Uncontrolled hyperglycaemia can cause glycosuria within T2D; thus, insulin causes the re-uptake of the calories that would be lost within the urine, causing weight gain seen following insulin initiation. E) Episodes of hypoglycaemia increase with the introduction of insulin therapy, the un-physiological nature of exogenous insulin, and irregular meal intake. This can cause weight gain through 'defensive snacking', non-adherence of medication causing hyperglycaemia and escalation of insulin therapy and a feeling of increased hunger and therefore nutrient excess causing weight gain.

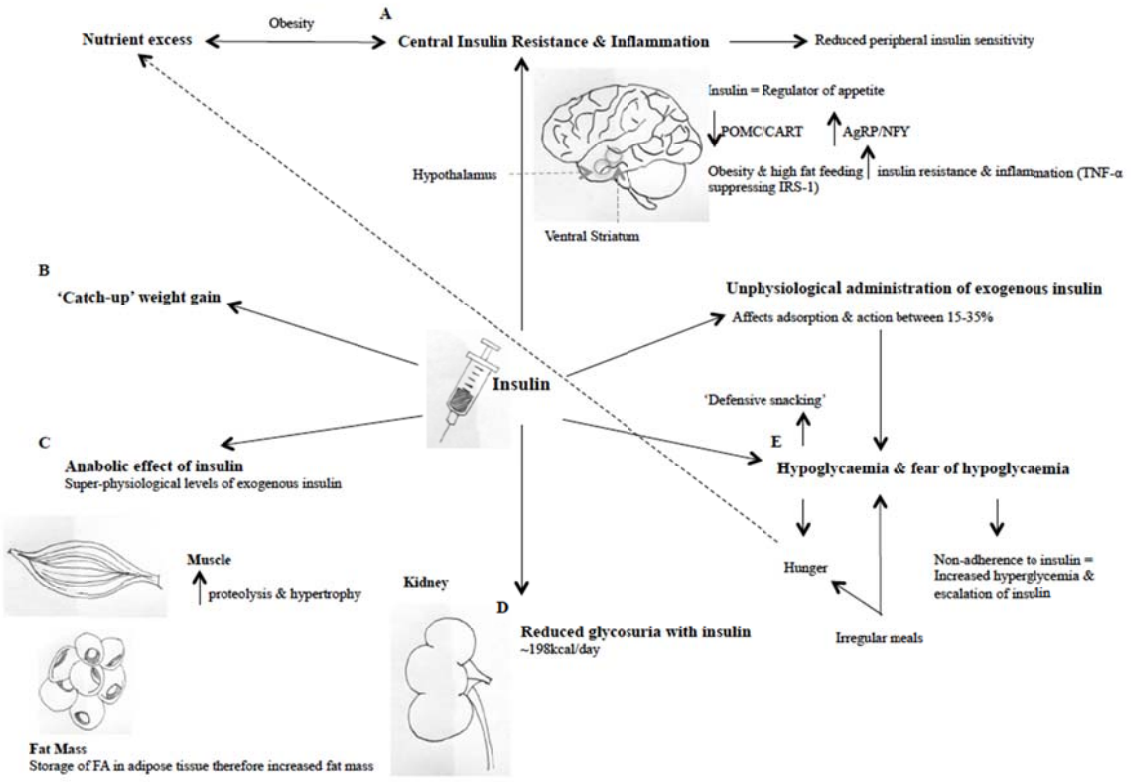

Table 1: Summary of weight loss strategies for insulin associated weight gain: This table summarises the effects of the different weight loss strategies on weight loss, surrogate markers of cardiovascular disease and insulin reduction.

Weight Loss Strategies	FU (months)	WL (kg)	HbA1c (%)	FPG	BP (mmHg)		Lipids (mmol/mol)		Insulin Reduction (unit)	Insulin (U kg^{-1} day^{-1})
					SBP	DBP	T. Chol	LDL-Chol		
Intensive Lifestyle[27,84,166,167]	**6-60**	**-7.7 to +3.5**	**-1- to +0.3**	**-0.8**	**-1.9 to -4**	**-2 to -4.2**	**-0.2**	**-0.1**	**-**	**-**
Orlistat[111,168]	**6-12**	**-3.9 to -7.1**	**-0.62**	**-**	**-**	**-**	**-**	**-**	**-8.1 to -30**	**0.64-0.85**
GLP-1[103,104,169,170]	**6**	**-1.4 to -5.7**	**-0.1 to -1.81**	**-**	**7**	**2**	**-0.12**	**-0.07**	**-18.1 to -29**	**0.25-0.89**
Pramlintide [112,171-173]	**4-12**	**-1.1 to -2.5**	**-0.53 to -0.73**	**-1.6 to -1.7**	**-**	**-**	**-**	**-**	**-2.1 to 11.7**	**0.48-0.73**
SGLT-2 Inhibitor[106,174]	**12-24**	**-0.9 to -3.5**	**-0.58 to -1.01**	**-1.05 to -1.89**	**-0.5 to -7.5**	**-1.2 to -2.9**	**-4.1 to +0.7**	**-9.3 to +1.7**	**-0.9 to +4.1**	**0.61-0.9**
Low CHO diets[152-154,175-177]	**6-24**	**-0.7 to -11.1**	**-0.02 to -1.5**	**-0.1 to -1.1**	**-16.6 to +5**	**-8.1 to +0.2**	**-0.1 to -0.7**	**-0.5 to +0.1**	**-7 to -49.3**	**0.45-0.69**
VLED - Initial	**1-4**	**-12.4 to -27.2**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
VLED – Long term[163-165,178,179]	**4-18**	**-8.6 to -15.4**	**-0.2 to -3.8**	**-0.3 to -4.3**	**-16 to +1**	**-9 to +1**	**-0.02 to -1.1**		**-**	**0-0.34**
Bariatric Surgery[132,133,134,135,166,180-182]	**12-60**	**53.8 to 68.8 (%EWL)**	**-1 to -2.1**	**-2.3 to -4**	**-3.3 to -8.3**	**-5.8 to -8.1**		**-0.5 to +0.1**	**-62.3 to -72**	**0.47-0.77**

NOTE: FU = follow up, WL = weight loss, EBWL = excess body weight loss, HbA1c = glycated haemoglobin, FBG = fasting blood glucose, BP = blood pressure, SBP = systolic blood pressure, DBP diastolic blood pressure, T. Chol = total cholesterol, LDL-Chol= low density lipoprotein cholesterol, DM=diabetes, U kg^{-1} day^{-1}=units per kilogram per day