Weight loss variability with SGLT2 inhibitors and GLP-1 receptor agonists in type 2 diabetes mellitus and obesity: Mechanistic possibilities

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Summary
We are facing a global epidemic of obesity and type 2 diabetes. Weight loss, in the context of obesity and type 2 diabetes, may improve glycaemic control and weight-related comorbidities, and in some cases, induce diabetes remission. Although lifestyle-based weight loss strategies may be initially successful, most are not effective long-term. There is an increasing need to consider pharmacological approaches to assist weight loss in diabetes-obesity. Older glucose-lowering agents may cause weight gain, whereas the newer drug classes, sodium-glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide receptor agonists (GLP-1 RAs), concomitantly target weight loss and glycaemic control. Clinical trial data suggest that both SGLT2i and GLP1 RAs cause a mean weight loss of approximately 2 to 3 kg but real-world evidence and clinical experience suggests a significant heterogeneity in the magnitude of the weight loss (GLP-1 RAs) or the magnitude of the actual weight loss is significantly less than anticipated (SGLT2i). Why do some individuals lose more weight than others in response to these pharmacological treatments? This review will first explore mechanisms by which body weight is regulated through control of energy balance and its dysregulation in obesity, and then consider how these mechanisms may be modulated therapeutically with SGLT2i and GLP1 RAs.

KEYWORDS
GLP-1 receptor agonists, obesity, SGLT2 inhibitors, type 2 diabetes, weight loss

1 | INTRODUCTION

Obesity has a critical role in the development and progression of type 2 diabetes (T2DM). With the rising prevalence of obesity, the excess risk of T2DM with even modest weight gain is significant, increasing exponentially relative to body mass index (BMI), in men and women.¹²

A BMI of 25 kg m⁻² is associated with a 2- and 8-fold increased risk of T2DM in males and females, respectively; a BMI of 35 is associated with a 42- and 93-fold increased risk, respectively.³

The pathophysiology of T2DM is thought to be mediated by ectopic fat deposition (in visceral fat, skeletal muscle, liver, pancreatic β-cells, and other organs), as subcutaneous fat expansion becomes
saturated, leading to hepatic and peripheral insulin resistance and progressive β-cell failure, ultimately leading to hyperglycaemia. Weight loss is critically important to prevent such ectopic fat deposition, exemplified by the finding that in the Diabetes Prevention Program, every 1 kg weight loss was associated with a 16% relative risk reduction in individuals progressing from impaired glucose tolerance to T2DM. In T2DM, even moderate weight loss (3%-5%) has significant health benefits, beyond improving glycaemic control, improving other weight-related comorbidities in a dose-dependent manner. This is best mechanistically illustrated by the rapid improvement in glucose homeostasis in patients with T2DM with a low calorie diet. The dramatic and rapid metabolic improvement preceding any significant weight loss is explained by mobilization of liver fat (reducing hepatic glucose output with enhanced hepatic insulin resistance) and mobilization of pancreatic fat (restoring first phase of insulin secretory response). Longer-term results from individuals following bariatric surgery show that this is associated with long-term remission of T2DM, a reduced incidence of microvascular and macrovascular complications and reduced mortality. Currently, however, only a minority will have access to either of these interventions, with other structured interventions difficult to implement in clinical practice.

The typical trajectory of weight change with a lifestyle intervention (eg, diet, exercise, and behaviour change) is characterized by early weight loss, plateauing at around 6 months, followed by an insidious and progressive weight gain over the following months. When clinically appropriate, there is increasing attention towards pharmacological approaches, with reinvigorated efforts to reinforce and implement lifestyle changes, to assist weight loss over the longer term. There has been a disappointing history of effective therapies for weight loss, with a number of agents being withdrawn following their approval, including sibutramine (increased risk of adverse cardiovascular events) and rimonabant (mood disorders and suicidal ideation). Currently, five anti-obesity drugs have been approved by the US Food and Drug Administration (FDA): (1) combination of phentermine and topiramate, (2) 5-hydroxytryptamine2C (5-HT2C) serotonin receptor agonist lorcaserin, (3) naltrexone/bupropion, (4) liraglutide 3.0 mg, and (5) orlistat, but only the latter three are available in Europe. Older glucose-lowering therapies (sulfonylureas, thiazolidinediones, and insulin) can exacerbate weight gain but the newer glucose-lowering therapies such as glucagon-like peptide receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) can further enhance weight loss, concomitantly lowering HbA1c and body weight. However, despite contrasting modes of action to reduce body weight, both drug classes are associated with highly variable weight loss and their weight-lowering effect unpredictable (Table 1).

Weight loss variability between individuals in response to SGLT2i or GLP-1 RAs is clearly not explained wholly by heterogeneity in the pharmacological response. Ongoing mechanistic studies and further clinical experience of these agents, alone and in combination in different populations, will provide insights into the physiological, psychological, and pharmacogenetic basis for weight loss variability. A better understanding of the mechanisms involved and the possibility to predict treatment outcomes could lead to a change in patient treatment and help optimize outcomes. This review will consider the variability of the specific metabolic and appetitive adaptations that may attenuate weight loss with SGLT2i and provide possible mechanistic insight for weight loss variability with GLP1 RAs. However, we emphasize that the physiological basis for weight loss variability is likely generic across all weight loss interventions, be it achieved through lifestyle, pharmacological, or surgical interventions.

### TABLE 1 Weight change achieved in published Phase III trials with available glucagon-like peptide receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2i)

| Drug | Properties | Route of Administration/Dosing | Weight Change in T2DM Trials: Absolute (kg) |
|------|------------|-------------------------------|------------------------------------------|
| **GLP-1 RA** | | | |
| Dulaglutide | GLP-1 RA peptide fused to IgG4 molecule | sc 0.75-1.5 mg weekly | −0.8 to 2.9<sup>12</sup> |
| Exenatide | 39 AA peptide | sc 5-10mcg bd | −1.4 to 4<sup>13-18</sup> |
| Exenatide-QW | Encapsulated in biodegradable polymer microspheres | sc 2 mg weekly | −1.6 to 3.7<sup>12,13,18</sup> |
| Liraglutide | C-16 fatty acid to lys26, non-covalent bond to albumin | sc 1.2 mg-1.8 mg od | −2 to 5.6<sup>11,14,19-21</sup> |
| Lixisenatide | 44 AA derivative of exenatide | sc titrate in 0.6 mg weekly increments to 3 mg od | −6.0<sup>19</sup> |
| **SGLT2i** | SGLT2:SGLT1 relative specificity | | |
| Canagliflozin | 200 | po 100-300 mg od | −2.5 to 4.0<sup>22,23</sup> |
| Dapagliflozin | 1,200 | po 5-10 mg od | −2.65 to 3.2<sup>24-27</sup> |
| Empagliflozin | 2,500 | po 10-25 mg od | −2.08 to 2.5<sup>28,29</sup> |
| Ertugliflozin | 2,235 | po 5-10 mg od | −2.5 to 3.5<sup>30-32</sup> |

Abbreviations: bd, twice daily; od, once daily; po, oral; sc, subcutaneous. These data are from separately published studies and, therefore, are not intended to indicate comparative efficacy.
2 | MECHANISMS FOR REGULATION OF BODY WEIGHT

2.1 | When weight is stable

When weight is stable, it is maintained by a dynamic equilibrium involving regulation of energy intake and of energy expenditure. Appetite/energy intake is controlled by homeostatic mechanisms (based on nutrient/energy requirements during periods of fasting) and hedonic mechanisms (based on desire for palatable food driven by pleasurable properties, incorporating sight, smell, and taste, rather than metabolic need), with interaction with environmental factors (Figure 1). The two mechanisms are interrelated and synergistic. Homeostatic mechanisms depend on efferent signals (e.g., leptin) from long-term tissue stores, especially adipose tissue, and episodic signals (e.g., GLP-1); arising largely from the gastrointestinal (GI) tract generated by eating, relaying information to the brain, mainly to the hypothalamus. We also know that variables other than energy intake and satiety have a profound effect on food intake, such as the pleasurable (hedonic) properties of food. Hedonic appetite is mediated through a central reward pathway, predominantly driven by dopamine and opioid transmission in the striatum.33

2.2 | With weight gain

In obesity/weight gain, not only is there a homeostatic deficit (reduced satiety or fullness) but this is also potentially coupled with an overactive hedonic/reward system (failure of satiety to impact on hunger responsiveness to food cues), with a resulting preference for energy-dense food and potentially greater influence from environmental factors.34 For example, if you have ever eaten a piece of chocolate cake, even though you might feel completely "full," your reward system overrides the homeostatic system, encouraging you to eat the cake.

Various factors control the different domains of energy expenditure influencing the basal metabolic rate, oxidation rate, and amount of physical activity. Individuals who are more likely to gain weight have lower basal metabolic rates and rates of fat oxidation35,36 and lower levels of physical activity.

2.3 | With weight loss

So what are the caloric equivalents of weight loss? Ultimately, weight change is caused by a long-lasting imbalance of food intake and energy expenditure. It was suggested that a cumulative energy deficit of 3500 kcal is required per pound (0.45 kg) of body weight loss,37 assuming exclusive loss of body fat. What this simplistic rule fails to consider are the physiological adaptations, which occur with altered body weight, specifically with changes in body composition. A potential confounder in achieving and sustaining weight loss is that energy expenditure decreases with weight loss. Coupled with a potentially heightened homeostatic and hedonic regulation of appetite, all of these biological mechanisms exert their effects preventing further weight loss and promoting weight regain.

During weight loss, loss of lean tissue/fat free mass (FFM) rather than fat mass may also exacerbate the gap between energy intake and energy expenditure. Although less energy is stored in lean tissue than in body fat (5-fold higher for fat),38 lean tissue consumes more energy than fat tissue and thus contributes more to total energy expenditure.39 An important objective during weight loss is to maximize the loss of body fat while minimizing the loss of metabolically active fat-free mass. When lean tissue is lost as opposed to fat, total energy expenditure decreases to a greater extent, making further weight loss more difficult. Hall et al have attempted to explain the large inter-individual variability in weight
change that occurs during a period of caloric restriction or energy deficit by mathematically modelling weight loss during a period of energy imbalance (specifically negative energy balance).30

Slowing of resting metabolic rate, beyond that expected from changes in body composition, is a known phenomenon in weight loss. It is a potentially adaptive mechanism to counterbalance weight loss and possibly contributes to weight regain over a sustained period. Measurement of resting metabolic rate (RMR) in participants of the American TV show, "The Biggest Loser" competition, demonstrated that those with the greatest weight loss also experienced the greatest slowing of RMR at the time, despite preservation of FFM.41 Interestingly, long-term follow-up (6 years) of the same participants showed that despite substantial weight regain in most subjects, a sustained metabolic slowing was seen.42 Rather counterintuitively, the degree of metabolic adaptation was not associated with weight regain, but those with a greater long-term weight loss had a greater ongoing metabolic slowing with no significant correlation with changes in hormonal signalling.

Alongside the wider health benefits of exercise, it might be expected to increase muscle mass43 and preserve RMR during weight loss,44 in particular with resistance training. In reality, long-term compliance to exercise is poor, and even when participants are monitored closely, limited studies have shown that exercise did not prevent a fall in RMR, despite relative preservation of FFM,44 with compensatory increases in energy intake commonly reported, although with high inter-variability.45

At the same time, metabolic inflexibility may be observed. Usually, during fasting conditions or high fat intake, there is a high rate of lipid oxidation (with high rates of fatty acid uptake) for energy production, while under insulin-stimulated or fed conditions, there is suppression of lipid oxidation, increased glucose uptake, oxidation, and storage.46 With metabolic inflexibility, we observe dual defects: under fasting conditions, diminished fatty acid oxidation leading to positive fat balance, while in the postprandial state (when glucose is the predominant fuel), an inability to switch to glucose metabolism. Metabolic inflexibility has been shown to predict future weight gain.55,56 Patients with obesity who then lose weight have lower rates of fat oxidation with those successful at maintaining weight loss long-term (responders) having higher oxidation rates than those experiencing weight regain (non-responders).47-49

During periods of negative energy balance and reduced energy stores (weight loss), attempts are made to maintain homeostasis through hormonal signalling (eg, leptin and insulin) and other afferent neuronal signals relaying information to the brain (hypothalamus) to stimulate appetite and promote weight gain. An important finding is that many of these hormonal alterations persist for 12 months or more after weight loss, even after weight regain.50 Coupled with a potentially heightened hedonic drive for consumption of highly palatable energy-dense food, this may completely overwhelm the homeostatic system driving further food intake even when there is no metabolic need, hampering long-term weight loss. Measuring eating behaviour and appetite can be challenging and inaccurate. Energy intake in the DIRECT study, comparing low fat versus low carbohydrate diets, was incorrectly believed to be unchanged based on a 24-hour recall and questionnaires leading to the assumption that bodyweight plateau and weight regain was a result of change in energy expenditure only.51 Using a validated mathematical modelling to determine energy intake, it can be clearly seen that the reductions in energy intake progressively subside,52 either through lack of compliance, or compensatory changes in appetite.

Taken together, to accurately predict weight loss with any lifestyle or pharmacological intervention imposing an energy deficit, one must factor in initial body weight and body composition, differential mobilization of fat versus lean tissue with progressive weight change leading to dynamic changes in resting metabolic rate and substrate oxidation, and compensatory changes in appetite that may occur.

3 | RESPONDERS VERSUS NONRESPONDERS

The concept of “responders” and “non-responders” applies to any physiological outcome with any intervention, eg, change in HbA1c with glucose-lowering therapies, or changes in VO2 max with exercise training. Clinical trial data reporting mean weight loss as an outcome measure conceal the heterogeneity of weight change, with significant vs. absent/negligible weight loss giving rise to responder (defined as greater than or equal to 5% weight loss) vs. non-responder populations (defined as less than or equal to 5% weight loss). However, it should be recognized that the response is not dichotomous and usually follows a normal distribution curve that is shifted to the left or right depending on the intervention (Figure 2).

FIGURE 2 Graphical representation of potential weight loss variability achieved with a weight loss drug [Colour figure can be viewed at wileyonlinelibrary.com]
All recently approved weight loss medication labels apply "stopping rules" based on responder analyses, stipulating thresholds when pharmacotherapy should be discontinued if clinically relevant weight loss has not occurred (based on risk/benefit and cost). Several studies have attempted to explain the heterogeneity in weight change by stratification of weight loss: responders (greater than or equal to 5% weight loss) and non-responders (less than or equal to 5% body weight loss). Others have identified three levels of response: responders (more than 5% weight loss), non-responders (less than 5% weight loss), and those who gained weight. In such cases, additional phenotype (eg, early weight loss), psychological and physiological adaptations, were discussed but no firm conclusions were drawn.

Obesity represents a chronic disease, and the critical consideration during a weight loss intervention is not only the short-medium–term weight loss (3-6 months) but also longer-term maintenance of weight loss (1-2 years or more). After weight loss, rates of recidivism are universally high with many suggesting that there are compensatory mechanisms involved to defend a weight "set-point" and resist weight loss. Should physicians discontinue drug therapy in apparent non-responders, minimizing side effects from ineffective treatment and rationalizing scarce health resources more stringently, or is this an opportunity to intensify treatment? There is little consensus on how to treat patients who reached the initial milestones but later plateau or indeed gain weight. Further research is required to optimize long-term weight loss strategies, particularly in individuals with T2DM.

4 | TREATMENT VARIABILITY

A complex interplay of non-biological and biological factors may explain treatment variability (Figure 3).

The differential ways in which an, "obesogenic environment" may influence obesity-promoting behaviour (eg, eat more, do less) among individuals is not fully understood. An almost overwhelming number of non-biological factors in our circumstances and environment combine together to determine our health. Determinants of weight may include the social and economic environment (eg, income, education, and employment), the physical environment (eg, food availability and safe areas for physical activity), and access to healthcare. Could it be that "non-response" in some people is simply because of the obesogenic environment counteracting any therapeutic attempt of weight loss? Some individuals may be better than others at resisting such an environment. Implementation of policies that prioritize healthy food environments and systems is beyond the scope of this review but warrants significant consideration.

Compliance with the prescribed medication or the concomitant prescribing of multiple glucose-lowering agents, which counteract the desired weight loss should also be considered. There would be lesser weight loss in patients taking concomitant sulfonylureas, thiazolidinediones, and insulin, agents usually associated with weight gain, compared with those not taking such agents. For example, the relative efficacy of the weight loss effects observed with the SGLT2i dapagliflozin in real world evidence (approximately 6 kg) compared with a smaller effect in clinical trials (approximately 2-3 kg) in T2DM, may reflect lower real world use of agents associated with weight gain, such as sulfonylureas and/or insulin, and a higher relative use of metformin.

Biological determinants of weight loss response can be broadly split into genetic and non-genetic factors. Given the high heritability of obesity (approximately 40%-70%), this field has attracted much interest. Genetic predisposition in most people is polygenic, with each individual genetic variant having only subtle effects; although cumulatively the effect on BMI is much greater. It seems logical to consider genetics in the context of response to treatments and weight loss. One example comes from the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, in which carriers of the fat mass and obesity-associated gene (FTO) variant risk allele lost weight
more successfully on a high-protein than on a low-protein diet.\textsuperscript{59} Despite promising advances in the pharmacogenomics of T2DM, some results have been conflicting, with difficulty translating findings to suggest any specific genetic polymorphisms are associated with a differential clinical effect at this stage.\textsuperscript{60} Response to pharmacotherapy may vary due to a number of broader characteristics such as demographics (age, gender, ethnicity, body mass index), psychological traits, or comorbidities.\textsuperscript{61-64} Despite this, patients with apparently similar phenotypes do not always achieve the same weight change.

5 | GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted from the L-cells in the small intestine, increasing pancreatic β-cells’ insulin secretion (in a glucose dependent manner) and inhibiting hepatic glucose production via reduced α-cell glucagon secretion.\textsuperscript{65,66} GLP-1 is a physiological regulator of appetite and food intake via the central GLP-1 receptors, mediating reduced appetite and weight loss.\textsuperscript{67,68} Administration of GLP-1 to rats into key mesolimbic structures (ventral segmental area and nucleus accumbens) resulted in decreased motivated behaviour for sucrose in rats, eg, reduction in how hard the rat was willing to work for a sweet reward.\textsuperscript{69} Conversely, blocking the GLP-1 receptor increases food intake in satiated rats.\textsuperscript{70}

Currently, available GLP-1 RAs in Europe include exenatide b.d. and weekly, liraglutide; and more recently, lixisenatide and dulaglutide.

A meta-analysis of 21 trials of patients who were overweight or with obesity, with or without T2DM, treated with a GLP-1 RA (exenatide twice daily, exenatide once weekly, or liraglutide up to 1.8 mg) showed a weighted mean difference in body weight of −2.9 kg, achieved with the highest dose of GLP-1 RAs compared with the control treatment (placebo, oral antidiabetic drugs, or insulin).\textsuperscript{71} Weight loss in the GLP-1 RA groups for patients without diabetes (−3.2 kg, −4.3 to −2.1; three trials) as well as patients with diabetes (−2.8 kg, −3.4 to −2.3; 18 trials) was demonstrated.

More recently, liraglutide 3.0 mg, tested as an adjunct to a reduced calorie diet and increased physical activity, has been studied in pre-diabetes and people with diabetes in the Satiety and Clinical Adiposity Liraglutide Evidence in (SCALE) phase III studies. Depending on the study, participants experienced a dose-dependent weight loss ranging between 5.7% and 9.2% (6.0-8.8 kg), whereas subjects treated with placebo (on diet and exercise alone) had a mean weight loss between 0.2% and 3.1% (0.2-3.0 kg).\textsuperscript{20,72} Liraglutide 3.0 mg once daily, combined with diet and exercise, also was able to significantly enhance the weight loss achieved with a low calorie diet (LCD), an estimated further reduction of 6% of body weight versus an LCD alone (with placebo).\textsuperscript{73} Semaglutide, a novel once weekly injectable GLP-1 RA has been studied in people with diabetes in a series of SUSTAIN studies, with marked dose-dependent weight loss observed.\textsuperscript{74-77} In a phase II trial in patients with obesity only, doses of 0.2 mg day\textsuperscript{−1} or more resulted in clinically meaningful weight loss compared with placebo and higher than liraglutide 3.0 g day\textsuperscript{−1}; 0.4 mg day\textsuperscript{−1} of once daily semaglutide was associated with a weight loss of −15.15 kg (estimated percentage weight loss change −13.8%) from a baseline of 113.2 kg.\textsuperscript{78}

Despite the considerable efficacy, there is considerable heterogeneity in their weight-lowering effect. Perhaps not surprisingly, early weight loss in treatment has been identified as a key predictor of success with the variable response to GLP-1 RA apparent as early as 4 weeks in some trials.\textsuperscript{55} In the weight management programme scale less than or equal to 4% weight loss (responder) at week 16, with liraglutide 3.0 mg, was a strong predictor of clinically meaningful weight loss after 1 year. Early responders without T2DM achieved mean weight loss of 10.8% (11.2 kg) compared with early non-responders (less than 4% weight loss from baseline at W16) without T2DM, losing 3.0% (3.2 kg) at week 56. Early responders with T2DM achieved mean weight loss of 8.5% (9.0 kg) at week 56, while early non-responders with T2DM only lost 3.1% (3.2 kg) at week 56.\textsuperscript{53}

5.1 | Potential biological mechanisms underpinning weight loss heterogeneity with GLP-1 RAs

5.1.1 | Effect of gender and baseline weight

In the liraglutide 3.0 mg clinical development programme, weight loss and glycaemia improvement were dose-dependent with higher doses required for maximum weight reduction.\textsuperscript{20,72} There was a tendency for greater weight loss in females versus males, and less weight loss in subjects with a BMI > 40 kg m\textsuperscript{2}.

5.1.2 | Pharmacokinetic factors

Limited head-to-head studies of GLP-1 RAs suggest that semaglutide and liraglutide are most effective for weight loss, whereas weight loss is somewhat less with albiglutide,\textsuperscript{12-16,19,21,79-81} perhaps because the albumin component of this drug limits its ability to reach the central nervous system.\textsuperscript{21}

Population pharmacokinetic analysis of liraglutide up to 3.0 mg in non-diabetic and diabetic people have demonstrated a clear exposure-response relationship between liraglutide and body weight reduction, suggesting that differences in response to treatment may be associated with differences in exposure.\textsuperscript{82-84} Body weight and sex were relevant factors for the exposure level of liraglutide.\textsuperscript{82,83} Higher body weight was associated with decreased liraglutide exposure. Liraglutide exposure was 32% higher in females than in males of comparable body weight.\textsuperscript{82} Women had greater weight loss than men at similar exposures, although the absolute weight loss in all subgroups was clinically meaningful with increasing exposure associated with increasing weight loss.\textsuperscript{84}

5.1.3 | Polymorphisms in the GLP-1 receptor

Pharmacogenetic studies on GLP-1 RA are limited. Genetic variability in GLP-1 receptor has been demonstrated to be associated with inter-individual differences in weight lowering potential with liraglutide in
T2DM (gene variant: rs6923761)\(^8^5\) and in women with obesity and PCOS (gene variant: rs10305420).\(^8^6\) Among these genetic variants, the T2DM associated variants in TCF7L2 (gene variant: rs7903146) and WFS1 (Wolfram Syndrome 1) have been shown to affect the response to exogenous GLP-1, while variants in KCNQ1 (gene variants: rs151290, rs2237892, and rs2237895) have been reported to alter endogenous GLP-1 secretion.\(^8^7\)-\(^8^9\)

5.4.1 Variability of CNS food-related responses to GLP-1 RA action

Using functional magnetic resonance imaging (fMRI) several studies in individuals with obesity have demonstrated increased activation in appetite- and reward-related brain areas (eg, amygdala, nucleus accumbens, insula, and orbitofrontal cortex) in response to viewing food cues,\(9^0\) and this increased food cue responsiveness predicted weight gain.\(9^1\) Interestingly, GLP-1 receptor activation reduces brain response (ie, in insula, amygdala, putamen, and orbitofrontal cortex) to food cues in subjects with obesity, with and without T2DM, correlating with reductions in food intake.\(9^2\)

These findings are useful when considering response to treatment in clinical practice, but they do not look at the differences in response to understand the weight change variability between weight responders and non-responders to treatment. Attempts to dissect the homeostatic and hedonic components of appetite would be helpful to define how GLP-1 RAs affect each, and which component is "resistant" in patients who do not lose weight. Further human functional neuroimaging studies, before and after GLP-1 RA therapy, determining whether there are differential effects of GLP-1 RAs on the ability to modulate CNS food-related responses in responders vs. non-responders after short- to medium-term treatment, may provide insight into the biological mechanisms underlying weight loss variability with treatment.

6 SODIUM-GlUCOSE CO-TRANSPORTER 2 INHIBITORS (SGLT2i)

It is widely accepted that the sodium-dependent glucose co-transporter proteins 1 and 2 (SGLT1/2) regulate renal glucose reabsorption in the proximal renal tubule of the kidney: approximately 90% by SGLT2 with the SGLT1 transporter, in the distal segment, responsible for the remaining 10%.\(^9^3\) In T2DM, there is paradoxically excessive renal glucose reabsorption exacerbating hyperglycaemia.\(^9^4\)-\(^9^5\) Potentially because of upregulation of SGLT2 or SGLT1 or both.\(^9^5\)-\(^9^6\) Further understanding of this is needed in order to maximize glucosuria, but SGLT1 drugs inhibit glucose reabsorption, promoting approximately 75 g of urinary glucose excretion with an associated caloric loss (approximately 300 kcal day\(^{-1}\)), explaining the weight loss.\(^9^7\) There are currently four SGLT2i available for use within Europe, namely canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

Clinical trial data suggest SGLT2i produces a mean weight loss of approximately 2 to 3 kg in patients with T2DM, irrespective of the background therapy (monotherapy,\(2^2\)-\(^2^4\) as add-on therapy to other oral agents, eg, metformin,\(2^5\)-\(^2^6\) sulfonylureas,\(2^7\)-\(^2^9\) glitins,\(1^0^0\) and insulin\(^1^0^1\)).

In patients with chronic kidney disease (CKD), HbA1c-lowering effects of SGLT2 inhibition are consistently reduced because of the attenuation of glycosuria in the setting of CKD; urinary glucose excretion is about 50% lower in patients with T2DM, with CKD3 treated with dapagliflozin, compared with patients with normal/mildly impaired renal function. There is no evidence that variation in urinary glucose excretion (UGE), independent of renal function, is a factor in determining weight loss.

Phase II trials have considered SGLT2i in subjects who are overweight or with obesity without diabetes (SGLT2i are not currently licensed for this indication). Weight loss observed over 12 weeks in one randomized controlled trial (RCT) was relatively modest but significant (placebo-subtracted changes for all canagliflozin doses, percent body weight change less than 2%). Canagliflozin 50, 100, and 300 mg produced approximately 2 to 3 kg of weight loss compared with baseline, and approximately 1 to 1.5 kg of weight loss compared with placebo.\(^1^0^2\)

In real-world data, one observational study in primary care demonstrated a mean weight loss of 2.6 kg (95% CI, 2.3-2.9) 14 to 90 days after starting dapagliflozin and 4.6 kg (95% CI, 4.0-5.2) beyond 180 days.\(^1^0^3\) Weight loss with SGLT2i generally plateaus after 26 weeks of treatment in patients with T2DM despite sustained UGE.\(^2^6\)-\(^2^7\)-\(^2^9\)

6.1 Possible adaptations to SGLT2i therapy that limit weight loss

There is great interest as to why SGLT2i therapy is not associated with more pronounced weight loss considering the caloric loss/energy deficit (300 kcal day\(^{-1}\); approximately 1,300 kJ) accompanying the enhanced glucose excretion (75 g of daily urinary glucose excretion).\(^9^7\) As an energy deficit of 15 MJ week\(^{-1}\) would be expected to be associated with a 0.5 kg loss of body weight per week (using the "static weight loss rate"), the expected weight loss over 24 weeks treatment with SGLT2i would be approximately 7 kg (assuming no compensatory changes in energy balance or diuresis).

6.1.1 Compensatory hyperphagia

It has been speculated that the discrepancy between observed and expected weight loss with SGLT2i may arise because of compensatory increases in energy intake and changes in energy expenditure that act to attenuate the energy imbalance. In rodent models, SGLT2 deletion or chronic treatment with the SGLT2i dapagliflozin resulted in a compensatory increase in caloric intake.\(^1^0^4\)-\(^1^0^5\) Rats with dietary obesity lose weight when treated with dapagliflozin (approximately 4%), but this is associated with a 30% increase in energy intake. Furthermore, weight loss was four times larger when animals were pair-fed as compared with ad-libitum diet.\(^1^0^5\) Studies using alternative SGLT2i in
animals have not demonstrated the same increase in energy intake (approximately 4%).

Mathematical models based on studies of SGLT2i in patients with T2DM predict that energy intake after weight loss because of urinary glucose excretion (UGE) may exceed adaptions in energy expenditure, contributing to difficulties with sustained weight loss. In one study, weight loss was less than a third of that predicted by the model, with the majority of the difference accounted for by an increase in energy intake (13%), with a small contribution for diet-induced thermogenesis.\textsuperscript{108}

Considering the hormonal and metabolic adaptations that occur with weight loss (from any intervention) that tries to limit weight gain and restore body weight back to its previous "set point," the compensatory hyperphagia reported with SGLT2i therapy is in many ways entirely appropriate.

6.1.2 Changes in energy expenditure/substrate utilization

There are a paucity of human interventional data on whole body metabolic changes occurring secondary to increased urinary glucose excretion with SGLT2i. Several publications have shown that the increased urinary glucose excretion following SGLT2 inhibition is associated with a paradoxical increase in endogenous (hepatic) glucose production\textsuperscript{108-110} possibly caused by a compensatory release of glucagon from the \( \alpha \)-cells in the pancreatic islets.\textsuperscript{111} This will partially negate the SGLT2i effect on glucose concentration, but would not necessarily modify weight loss.

In SGLT2 knockout, mice food intake was greater, physical activity increased, energy expenditure was higher, and respiratory quotient fell, consistent with a shift from carbohydrate to fat metabolism.\textsuperscript{105} Human studies have demonstrated that chronic (4 weeks) administration of empagliflozin causes a shift in fuel utilization from carbohydrate towards fatty substrates to cause loss of fat mass and weight loss, but no changes were seen in resting or post-prandial energy expenditure as measured by indirect calorimetry, implying that energy intake is increased to explain the discrepancies in weight loss seen.\textsuperscript{108}

The development of euglycaemic ketoacidosis in T2DM subjects treated with SGLT2i has been reported. While the underlying mechanism is poorly understood, it is suggestive of complex metabolic adaptations taking place. Changes in substrate utilization from glucose to lipid provides an explanation for increased ketogenic production with SGLT2i.\textsuperscript{108}

6.1.3 Genetic polymorphisms

A large number of genetic polymorphisms have been described affecting the response to treatment with other oral hypoglycaemic agents. This may explain the inter-individual response to SGLT2i and there is an emergence of data regarding genetic variability. In a population pharmacokinetic model of canagliflozin in diabetic and non-diabetic individuals, Hoeben at al reported UGT1A9*3 among several other covariates to influence the drug's elimination rate.\textsuperscript{112} Carriers of reduced function variants UGT1A9*3 had increased plasma concentrations of canagliflozin, although the clinical significance of this is presumably small. Nonsense and missense mutations in the SCL5A2 gene coding for the glucose transporter SGLT2 cause familial renal glycosuria, characterized by urinary glucose excretion in the presence of low-normal glucose levels.\textsuperscript{113} Interestingly, these individuals appear to have normal growth and are asymptomatic.\textsuperscript{114} The presence of normal blood glucose concentrations, despite significant glycosuria, highlights that potentially counter-regulatory mechanisms are being activated to compensate for the urinary loss.

7 COMBINATION THERAPY WITH SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS (SGLT2I)

As discussed previously, the anticipated weight loss with SGLT2i is less than expected, possibly explained by a compensatory increase in food intake. It therefore seems logical to combine SGLT2i with anorexigenic drugs.

With phentermine

Results of a phase II trial of the combination of phentermine 15 mg (an appetite suppressant) with canagliflozin 300 mg in individuals without diabetes showed greater weight loss with combination therapy than with use of either agent alone.\textsuperscript{115} Over 26 weeks, placebo, canagliflozin, phentermine, and canagliflozin/phentermine groups had mean percentage changes in body weight of \(-0.6\%\), \(-1.9\%\), \(-4.1\%\), and \(-7.5\%\), respectively. It will be interesting to see whether this combined therapeutic approach is also effective in individuals with diabetes, although phentermine is not currently licensed for use in Europe.

With GLP1-RAs

On the basis of the known distinct and complementary mechanisms of action of SGLT2i and GLP-1 RAs, and in particular the observations that GLP-1 RA can both potently inhibit appetite and reduce hepatic (endogenous) glucose production,\textsuperscript{116} co-administration of these two agents could overcome the two potentially (mal)adaptive compensatory responses that attenuate the weight loss occurring with SGLT2i alone. Support for this approach with respect to hepatic glucose production comes from the findings of Rosenstock et al.,\textsuperscript{117} who noted that the combination of a DPP-IV inhibitor with an SGLT2i may suppress the latter's pro-glucagogenic effects.

DURATION-8, a 28-week randomized controlled trial, considered the efficacy and safety of combination therapy with dapagliflozin and Exenatide QW in T2DM, inadequately controlled by metformin.\textsuperscript{118} There were significantly greater reductions in absolute weight change with exenatide plus dapagliflozin (\(-3.41\) kg) versus exenatide (\(-1.54\) kg) or dapagliflozin (\(-2.19\) kg) alone. While the weight loss with
combination of therapy is not additive, rather synergistic, this study supports the co-initiation of dapagliflozin and exenatide weekly. More recently, the AWARD-10 study demonstrated greater weight loss with the sequential addition of dulaglutide 1.5 mg to patients treated with SGLT2i (with or without metformin). SGLT2i and GLP-1 RAs are already frequently used concomitantly in clinical practice, and in the future, use of the combination will likely increase. Undoubtedly, real-world evidence will emerge on the efficacy of this exciting combination.

8 FUTURE CLINICAL AND RESEARCH DIRECTIONS

Why some patients lose a significant amount of weight with any intervention and others lose none at all remains unanswered. Is it that the intervention in question will always work for group A and never for group B with identifiable biological predictors explaining this? Or is it that the individual non-responder will almost never respond to any treatment with the primary driver being environmental and social factors? Studies dissecting the responses seen in weight responders and non-responders to treatment may help further target treatment approaches. With regards to regulation of appetite, it is not known whether non-responders to weight loss interventions have a maintained hyper-activation of the reward system to explain weight change variability and weight regain and whether this mal (adaptive) response can be "re-set."

There is considerable interest in the mechanisms through which bariatric surgery mediates long-term weight loss and its wider health benefits. Efforts to mimic the changes in circulating gut hormones and neuroendocrine signalling pharmacologically are much sought after. GLP-1 is just one product of the preproglucagon gene others, including oxyntomodulin and glucagon, also have anorectic effects. There is an array of other gut hormones (cholecystokinin [CKK], peptide YY [3-36], and pancreatic polypeptide [PP]) and co-peptides that act on multiple receptors to control appetite on the horizon. Combination therapies and co-peptides that work on multiple receptors seem likely to improve the clinical outcomes. Phase II studies are beginning to investigate hybrid molecules, which are mostly aimed at three key peptide hormone receptors: GLP-1, glucagon, and glucose-dependent insulinotropic polypeptide (GIP) receptors. Results of a Phase II trial with a dual GIP-GLP-1 RA (LY3298176) demonstrated clinically meaningful reductions in HbA1c and weight change (~11.3 kg for 15 mg LY3298176) in people with T2DM when compared with placebo and dulaglutide (~0.4 kg for placebo, ~2.7 kg for dulaglutide). Metabolic compensations are clearly capable of modifying the outcome of any weight loss intervention, but this will likely vary between individuals with data suggesting that it only partially explains weight loss variability and weight regain. If metabolic compensation, eg, appetite and energy expenditure does offset a negative energy balance, interventions to stop this would be beneficial, thereby limiting weight regain.

CONFLICTS OF INTEREST

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