diabetesresearchandclinicalpractice199(2023)110669

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Perspectives in weight control in diabetes – SGLT2 inhibitors and GLP-1–glucagon dual agonism

Nayyar Iqbal [a,*], Philip Ambery [b], Jennifer Logue [c], Ashwini Mallappa [a], C. David Sjöström [b]

[a] Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gaithersburg, MD, USA
[b] Late-Stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden
[c] Early-stage Development, Cardiovascular, Renal, and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Cambridge, UK

ARTICLE INFO

Keywords:
Organ protection
Normalization of metabolism
Cardio-renal outcomes
Metabolic correction
Modification of catabolism
Increased energy expenditure

ABSTRACT

Treatment of people with type 2 diabetes mellitus (T2D) and obesity should include glycemic control and sustained weight loss. However, organ protection and/or risk reduction for co-morbidities have also emerged as important goals. Here, we define this combined treatment approach as 'weight loss plus' and describe it as a metabolic concept where prolonged periods of energy consumption is central to outcomes. We suggest there are currently two drug classes – sodium-glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1)–glucagon dual agonists – that can facilitate this 'weight loss plus' approach. We describe evidence supporting that both classes address the underlying pathophysiology of T2D and facilitate normalization of metabolism through increased periods with a catabolic type of energy consumption, which effect other organ systems and may facilitate long-term cardio-renal benefits. These benefits have been demonstrated in trials of SGLT2is, and appear, to some degree, to be independent of glycemia and substantial weight loss. The combined effect of caloric restriction and metabolic correction facilitated by SGLT2i and GLP-1–glucagon dual agonists can be conceptualized as mimicking dietary restriction and physical activity, a phenomenon not previously observed with drugs whose benefits predominantly arise from absolute weight loss, and which may be key to achieving a 'weight loss plus' approach to treatment.

1. Introduction

Type 2 diabetes mellitus (T2D) is a chronic, complex disease that is often comorbid with obesity [1]. Moreover, obesity, specifically a body-mass index $\geq$30 kg/m^2, is a known critical risk factor for development of T2D [2]. Up to 90% of adults with T2D can be classified as having overweight or obesity, and people with obesity are 7-times more likely to develop T2D than those without obesity [3]. As such, weight management is an essential part of T2D control, with weight loss having beneficial effects on glycemic control [4] and potentially preventing the progression to overt T2D in at-risk individuals with obesity [5].

Obesity is an adiposity-based chronic metabolic disorder of energy homeostasis, and there are many proposed drivers for its development, including genetics, epigenetics, and the gut microbiome [6]. In addition, there are behavioral, environmental, developmental and hormonal factors that may promote increased energy intake and decreased energy expenditure, promoting a sustained net positive energy balance and exacerbating the effect of genetic variants linked to body weight [7]. Metabolic adaption to obesity over time can also mean that the body adapts to a higher body weight, and then actively works to maintain this higher weight through counter-regulatory mechanisms that promote weight regain [8–10]. This can make maintenance of weight loss difficult to achieve, as the body responds to weight loss by decreasing metabolism or increasing appetite, to maintain resting energy expenditure. As such, the use of pharmacotherapies and surgical approaches that reduce body weight over a longer duration may help people with obesity to maintain weight loss in the longer term.

Treatment guidelines for T2D from the American Diabetes Association (ADA) recommend that people with obesity or overweight may gain a benefit from modest (~3–7% of baseline weight) as well as large (>10% of baseline weight) magnitudes of weight loss to support the treatment of T2D [11]. The following strategies, in a shared decision-making model, are suggested: nutrition changes, physical activity, behavioral counselling, pharmacologic therapy, medical devices, and bariatric surgery [11]. These guidelines further clarify that among people with T2D and overweight/obesity, modest and sustained weight

* Corresponding author.
E-mail address: Nayyar.Iqbal@astrazeneca.com (N. Iqbal).

https://doi.org/10.1016/j.diabres.2023.110669
Received 31 March 2023; Accepted 9 April 2023
Available online 17 April 2023

loss improves glycemia, blood pressure, lipids, and/or other obesity-related conditions, and may reduce the need for additional medications to control these risk factors. Aside from addressing glucose- and weight-control, the guidelines also highlight the importance of considering other co-morbidities of T2D, such as cardio-renal and hepatic disorders, and state that clinicians should be striving to achieve long-term improvements in overall health and patient well-being for the reduction and prevention of complications [12]. For example, the joint treatment algorithm from the ADA and the European Association for the Study of Diabetes suggests specific treatments for patients at higher risk for cardio-renal complications, including cardiovascular disease, heart failure and chronic kidney disease [1,12].

It is, therefore, apparent that the optimal approach to the treatment of people with both T2D and obesity should include glycemic control and some degree of sustained weight loss, in combination with risk reduction for associated complications and organ protection, including the heart, kidneys, liver and pancreas. In this review, we define this treatment approach as 'weight loss plus' and describe it as a metabolic concept where the nature of energy release from cells, and increased time in a catabolic like metabolic state, are central to outcomes. 'Weight loss plus' is different from the more traditional 'absolute weight loss' concept, where an individual targets a specific number of kilograms or proportion of baseline body weight lost, without taking into account if the body is in a catabolic or anabolic state. Experience from weight loss trials suggest that targeting absolute weight loss will ultimately result in a physiological state of anabolic weight gain. In this state, despite absolute body weight being less than at the beginning of treatment, an individual will very likely start regaining body weight soon after reaching their weight loss nadir [13,14].

In the next section we describe the current guidance on therapeutics available for weight control in people with T2D, before focusing on two classes of drugs – sodium–glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1)–glucagon dual agonists – which we suggest are capable of facilitating the 'weight loss plus' approach.

2. Current management for weight control in people with T2D

For most people with T2D who have overweight or obesity, the ADA recommends an initial approach integrating nutrition, physical activity and behavioral therapy, targeting a $\geq$5% maintained weight loss [11]. Although this approach can improve glycemic control in some people, these interventions can be demanding to manage, meaning longer-term maintenance of weight loss can be challenging. Therefore, if an individual's glycemia is inadequately controlled on lifestyle interventions, additional pharmacotherapies such as GLP-1 receptor agonists and SGLT2is are recommended for people with T2D who might also benefit from weight reduction [12].

GLP-1 receptor agonists are known to suppress appetite, reduce food consumption, and ultimately promote weight loss. Their mechanism of action has been extensively described in the literature, and is therefore not the focus of this review. SGLT2is reduce the rate of glucose (and sodium) reabsorption in the kidneys, leading to glucosuria (calorie loss) and overall lower blood glucose levels, thereby improving glycemic control and reducing weight. SGLT2is work independently of insulin and are unaffected by the function of β cells or mechanisms of insulin resistance [15]. The effects of SGLT2is are discussed in more detail in the next section.

In addition to pharmacotherapies for T2D, there are also pharmacotherapies for obesity that may be used for people with T2D and obesity. The current FDA-approved pharmacotherapies are: phentermine/topiramate [16], naltrexone/bupropion [17], orlistat [18], liraglutide [19] and semaglutide once-weekly [20]. These therapies act through a number of mechanisms, including suppressing appetite and/or energy use, affecting satiety, or reducing gastrointestinal absorption/delaying gastric emptying [16–20]. At present it is unknown if these mechanisms can result in the long-term benefits associated with the 'weight-loss plus' approach introduced in the previous section.

A non-pharmacological option shown to be an effective long-term treatment for people with T2D and obesity is metabolic (or bariatric) surgery, where the capacity of the individual's stomach pouch is reduced with or without bypass of the proximal duodenum [11]. Due to the magnitude and rapidity of improvements in hyperglycemia and glucose homeostasis observed with metabolic surgery (which was an approach traditionally reserved for people with T2D and severe obesity), it is now recommended by the ADA for some patients with T2D and less severe obesity who have not achieved durable weight loss with other pharmacological treatments [11]. In people who have received metabolic surgery, improvements in insulin sensitivity have been observed within days/weeks of surgery, long before significant weight loss occurs [21–24]. In a study of people with obesity who underwent metabolic surgery, a significant increase in insulin clearance was observed within 1 week, alongside improvements in adipokine secretion [21]. Furthermore, hepatic insulin sensitivity was improved within 12 days of surgery [21]. Conversely, it has been shown that intrahepatic fat content does not respond as quickly, with reductions only observed over 1 month after surgery [25]. These data suggest that significant health benefits from metabolic surgery in people with T2D occur as a result of ongoing caloric restriction – and its subsequent catabolic effects on multiple metabolic pathways – rather than absolute weight loss [21].

3. The diverse effects of SGLT2 inhibition

3.1. *Effect on metabolism in relation to weight loss*

The glucosuria caused by SGLT2i has been suggested to mimic caloric restriction, with several studies showing an effect on metabolism, including a reduction in insulin resistance and a paradoxical increase in hepatic glucose production via a compensatory increase in glucagon secretion [26–29]. A study of the SGLT2i, dapagliflozin, in 18 people with T2D found that after 2 weeks of treatment, hepatic endogenous glucose production increased, and was accompanied by an increase in fasting plasma glucagon concentration [27]. Two randomized controlled trials of dapagliflozin found increased insulin-mediated whole body glucose uptake and increased endogenous glucose production indicating improved muscle insulin sensitivity, in addition to an increased acute insulin response to glucose [27,28]. Another study of dapagliflozin in people with T2D found that after 5 weeks there were major adjustments in metabolism, including increased fat oxidation, improved hepatic and adipose insulin sensitivity and improved 24-hour energy metabolism [30]. Increased endogenous glucose production, decreased tissue glucose disposal and a shift in fuel utilization towards fatty substrates has also been observed with empagliflozin, another member of the SGLT2i class [26].

These effects may result from glucosuria caused by SGLT2i promoting nutrient-deprivation signaling and restoring mitochondrial health and renewal, increasing nutrient oxidation and oxidative phosphorylation, and reducing the cytosolic accumulation of deleterious glucose and lipid by-products [31–33]. These changes in metabolic signaling pathways resemble those experienced in an individual after a prolonged fast. It may be that this 'normalization of metabolism', and potentially a shift towards ketone bodies as the metabolic substrate for the brain, heart and kidneys [31,34], helps facilitate the 'weight loss plus' benefits outlined in the previous section. This change in metabolic condition may also reflect that the glucosuria caused by SGLT2i drives consistent overnight periods of increased catabolism, thereby enabling the body to revert to diurnal metabolic rhythms, which may be disrupted in people with obesity [31]. An overview of the potential mechanism of benefit is provided (Fig. 1) [31–34], which suggests that periods of catabolism may eventually change mitochondrial morphology from a fission to a sustained fusion state.

Taken together, these data support the concept that SGLT2i provide ongoing caloric restriction and subsequent catabolic effects via multiple

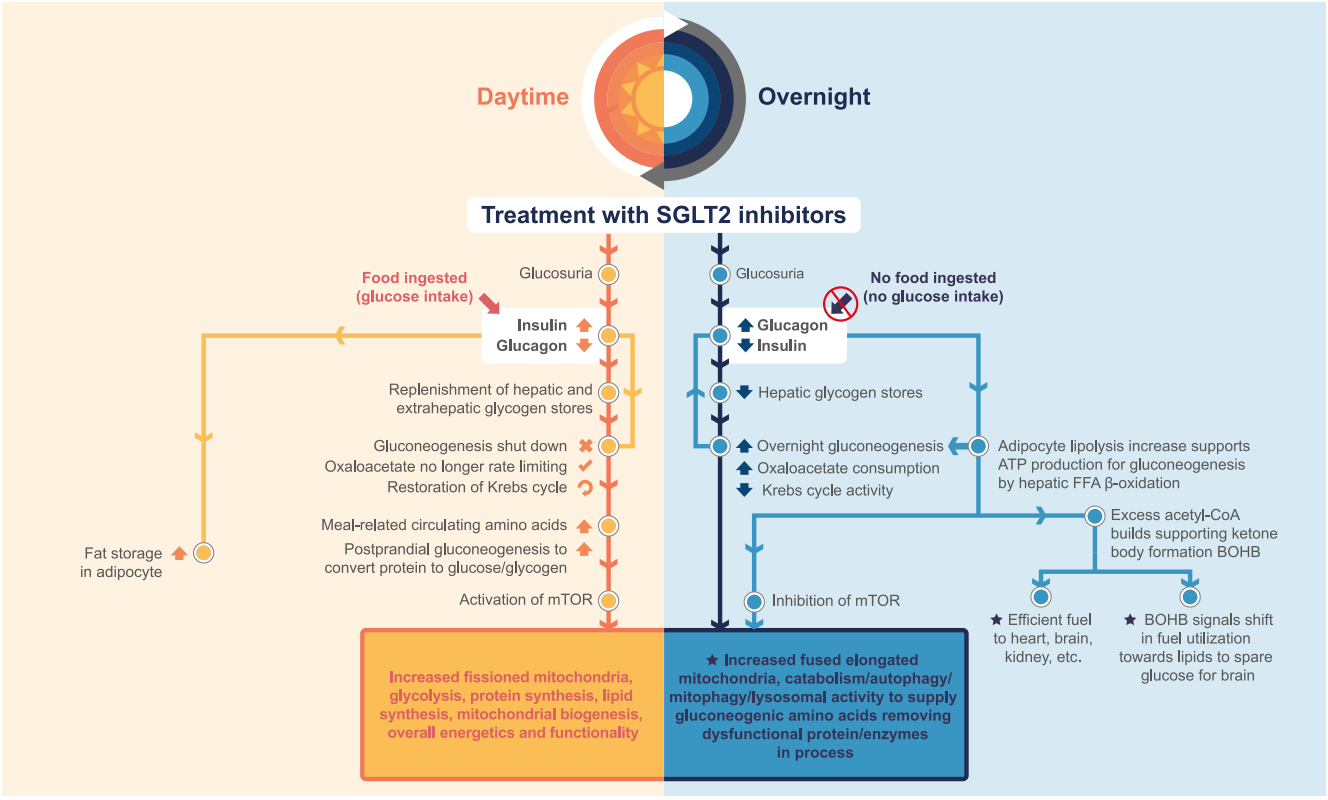

Fig. 1. Proposed metabolic mechanism of benefit with SGLT2 inhibition [31–34]. ATP = adenosine triphosphate; BOHB = β-hydroxybutrate; FFA = free fatty acid; mTOR = mammalian target of rapamycin; SGLT2 = sodium–glucose cotransporter-2.

metabolic pathways. Similar to the previously described findings that the significant improvements in glucose control observed with bariatric surgery are mainly due to early metabolic processes – as opposed to absolute weight loss [21] – there is also evidence that this is the case with SGLT2i. In a *post-hoc* regression analysis in people with T2D receiving dapagliflozin, the attained absolute weight loss (~2 kg) only contributed to 6% of the observed reduction in HbA_{1c} [35].

3.2. *Effect on ectopic fat and the liver in relation to weight loss*

Studies have shown that weight loss with SGLT2i is associated with changes in body composition and loss of total body fat mass, including reductions in both visceral and subcutaneous adipose tissue [36,37]. Excess energy storage at visceral sites results in increased ectopic fat, a crucial risk factor for T2D which is also implicated in liver damage [38]. This occurs because ectopic fat within the liver can cause liposomes in hepatocytes to increase in size, and the resulting pathogenic state is described as non-alcoholic fatty liver disease (NAFLD) [39]. If not identified early or if ineffectively monitored or managed, NAFLD can progress to non-alcoholic steatohepatitis (NASH) and further adverse liver-related outcomes including mortality [40].

There is a strong bidirectional association between T2D and NAFLD, with a meta-analysis of 24 studies involving 35,599 people with T2D finding that 20,264 patients also had NAFLD; the resulting pooled prevalence was 60% [41]. This bidirectional relationship between T2D and NAFLD is complex and is well described in the literature. In brief, NAFLD may promote the insulin resistance that drives T2D, while T2D can contribute to fat accumulation, inflammation, and subsequent deterioration in liver function – this apparent relationship can propagate a patient's morbidity [42,43]. Ectopic fat in the liver is also a risk factor for other morbidities such as heart failure and other cardiovascular disorders, further highlighting the extensive impact that ectopic fat accumulation, and the importance of weight loss, on multiple organ systems beyond T2D [44,45].

3.3. *Effect on the cardio-renal system and organ protection in relation to weight loss*

While SGLT2i have been shown to improve glycemic control and reduce body weight, they have also demonstrated a number of other cardio-renal and organ protective effects, which appear (at least to some degree) to be independent of glycemia and weight loss.

Cardio-renal benefits have been described across several outcome studies and real-world reports [46–57]. In the DECLARE-TIMI58 trial of people with T2D who had, or were at risk for, atherosclerotic cardiovascular disease, dapagliflozin was associated with a significantly lower rate of cardiovascular death or hospitalization for heart failure (4.9% vs 5.8%; HR: 0.83 [95% CI: 0.73–0.95]; p = 0.005) and a numerically lower rate of renal events (4.3% vs 5.6%) compared with placebo [46]. Similar findings were observed in the EMPA-REG OUTCOME trial, which evaluated empagliflozin in patients with T2D who were at high risk for cardiovascular events [47]. Empagliflozin reduced the risk for a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 14% compared with placebo (10.5% vs 12.1%; HR: 0.86 [95% CI: 0.74, 0.99]; p = 0.04) and also reduced the risk for hospitalization for heart failure (2.7% vs 4.1%; HR: 0.65 [95% CI: 0.50, 0.85]; p = 0.002) [47] Slower kidney disease progression and lower rates of clinically relevant renal events were also observed with empagliflozin compared with placebo [48]. These improved cardiac outcomes were also observed when assessed in patients with heart failure in the DAPA-HF trial of dapagliflozin and in the EMPEROR-Reduced and -Preserved trials of empagliflozin [49–51]. Improved renal outcomes were also observed with dapagliflozin in the DAPA-CKD study and with empagliflozin in the EMPA-KIDNEY study, in people with

chronic kidney disease (with or without T2D) [52,53]. Beneficial cardiorenal outcomes have also been seen using real-world data, with the CVD-REAL study of 309,056 people with T2D who had been newly prescribed an SGLT2i or an alternative glucose-lowering drug finding significantly lower rates of hospitalization for heart failure (HR: 0.61 [95% CI: 0.51–0.73]), death (HR: 0.49 [95% CI: 0.41–0.57]), and hospitalization for heart failure or death (HR: 0.54 [95% CI: 0.48–0.60]) with the use of SGLT2i ($p<0.001$ for all) [54].

At present, we cannot confidently or quantitatively separate the contribution of weight loss with SGLT2i from other concurrent beneficial effects on disease drivers. However, we do know that the benefits observed in the above-mentioned cardio-renal studies occurred in conjunction with the modest amount of weight loss that is characteristic of SGLT2 inhibition. For example, in DAPA-HF, patients treated with dapagliflozin experienced a relatively modest mean weight loss of ~0.9 kg over the study period [49]. These cardio-renal benefits may somewhat relate to the osmotic diuresis associated with SGLT2i treatment, but we suggest that they also relate to ongoing catabolic effects on metabolism. Indeed, modest weight loss (resulting in improved insulin sensitivity and decreased sympathetic nervous system activity) has been shown to normalize blood pressure, without individuals reaching a predescribed 'ideal' weight [58]. However, maintenance of weight-loss has been shown to be of key importance with respect to these outcomes. For example, in a study of post-bariatric surgery patients, it was demonstrated that a given weight regain in the later part of the study had almost twice as large an absolute impact on final blood pressure as: i) the same degree of weight loss in the beginning of the study, or ii) a corresponding difference in absolute weight at inclusion in the study [59].

Taken together, these studies provide evidence that a large weight loss is not required to achieve a beneficial effect on cardio-renal outcomes, and supports the 'weight loss plus' approach that pharmacotherapies that offer modest sustained weight loss can improve cardio-renal outcomes and in turn provide long-term organ protection.

4. GLP-1–glucagon dual agonism may also facilitate a 'weight loss plus' approach

Various combination approaches, with co-agonism of multiple gastric hormone signaling axes, are currently being evaluated for the treatment of people with T2D and obesity or other metabolic disorders. GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual agonism is now approved for the treatment of T2D, and early-phase trials of GLP-1, glucagon and GIP receptor tri-agonism and GLP-1 and glucagon dual agonism have also been performed [60]. In the remainder of this section we will focus on the dual agonism of the GLP-1 and glucagon axes.

GLP-1 modulates glucose homeostasis through stimulation and suppression of insulin and glucagon release, respectively, which result in suppressive effects on appetite and food consumption, and are also partially responsible for the feeling of postprandial satiety [61]. As glucagon receptor activation drives hepatic glucose production and lipolysis and increases energy expenditure [60,62], combining this approach with GLP-1 receptor agonism may offer a two-pronged approach for caloric restriction. The benefit of this type of dual agonism has been shown by the effect of oxyntomodulin, an endogenously secreted dual agonist of the GLP-1 and glucagon receptors, the secretion of which increases after metabolic surgery and is thought to contribute to subsequent weight loss and improved glycemic control [63]. Furthermore, a systematic review and meta-analysis of the GLP-1–glucagon dual agonist, cotadutide, has demonstrated that in people with T2D significant improvements in body weight, HbA_{1c}, glucose area under the curve and fasting plasma glucose were observed versus placebo [64].

However, we suggest that the benefits of GLP-1–glucagon dual agonism could potentially go beyond quantitative decreases in glycemia and weight, and that similar to the SGLT2 inhibition described in the previous section, normalization of metabolism may be achieved with this dual agonism that may in turn facilitate 'weight loss plus' benefits in people with T2D [64,65]. We propose that this is achieved by appetite suppression conferred by GLP-1 mimicking a caloric restriction diet, in combination with glucagon increasing liver glycogen usage and stimulating lipolysis and hepatic ketogenesis, driving liver fat loss in a similar manner to that observed with physical activity [62,66–68]. As such, people with T2D who undergo GLP-1–glucagon dual agonism, may experience changes and benefits as if they were in effect undergoing caloric restriction and physical activity.

In a study of cotadutide in people with T2D and overweight/obesity, significant and sustained weight loss was observed over 41 days, with patients experiencing a reduction in subcutaneous and visceral adipose tissues [69]. Furthermore, cotadutide promoted a significant reduction in liver fat over the short study period, which surpassed what would have been expected through absolute body weight loss alone [69] In a longer 54-week study of cotadutide in people with T2D and overweight/obesity, cotadutide significantly decreased HbA_{1c} and body weight compared with placebo [70]. Interestingly, cotadutide had similar effects on glycemic control to the GLP-1 mono-agonist, liraglutide, but was associated with significantly larger improvements in aspartate and alanine transaminase levels and with a trend for larger improvements in triglycerides [70]. Indeed, for a given amount of weight loss, cotadutide led to removal of glycogen and liver fat to an extent that was not observed with liraglutide [70,71]. Data from a phase II study in people with T2D and chronic kidney disease also suggest a benefit with cotadutide on urinary albumin-to-creatinine ratios, with a reduction in albuminuria that again was more pronounced than would be expected with GLP-1 mono-agonism [72]. Preclinical data also suggest that cotadutide can increase mitochondrial turnover and improve mitochondrial oxidative capacity through direct stimulation of glucagon receptor signaling [73].

Collectively, these data highlight the potential of targeting GLP-1–glucagon dual agonism in people with T2D to provide benefits beyond improvements in glycemic control and body weight reductions. Until longer-term cardiovascular outcomes data are available, however, we can only speculate if GLP-1–glucagon dual agonists will have protective effects on other organ systems, as has been observed with SGLT2 inhibition.

5. Conclusion

Weight loss is essential in the management of people with T2D and overweight/obesity and guidelines recommend at least moderate weight loss, with use of pharmacotherapies suggested for those with comorbidity risk factors. Importantly, it is now widely accepted that the goal of T2D treatment should not solely be glucose control and weight loss, but instead should be centered on sustained improvements in long-term outcomes, organ protection, and extending the years of quality-of-life benefits that accompany such improvements. We propose that this 'weight loss plus' approach can be realized by addressing the underlying pathophysiology of T2D and targeting normalization of metabolism. We have described how the modification of catabolism that occurs with SGLT2i appears to drive other metabolic processes, such as lipolysis and ketogenesis in the liver, which ultimately have effects on other organ systems and can facilitate organ protection and long-term cardio-renal benefits. Furthermore, we suggest that these metabolic processes will also be central to organ protection in future trials with GLP-1–glucagon dual agonists. The mechanism of action of these therapies has the potential to keep the body in a catabolic or exercise-like state over longer periods of time, a phenomenon that has not been observed with drugs whose benefits predominantly arise from absolute weight loss.

Declaration of Competing Interest

As all authors are employees (and own stock in) AstraZeneca, this

could appear to influence the work reported in this paper.

Acknowledgements

The authors wish to acknowledge Alexander Jones and Róisín O'Connor, inScience Communications, Springer Healthcare, for assistance with medical writing, which was funded by AstraZeneca. They would also like to acknowledge Sudha Shankar, AstraZeneca, for valuable input into discussions.

Author Disclosures:

NI, PA, JL, AM and CDS are employees of, and own stock in, AstraZeneca. Within the past 36 months, JL has also received grants/contracts from National Institute of Health Research, consulting fees from Novo Nordisk, and participated in a data safety monitoring board or advisory board for Novo Nordisk.

References

[1] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2022;65(12):1925–66.
[2] Schnurr TM, Jakupović H, Carrasquilla GD, Ängquist L, Grarup N, Sørensen TIA, et al. Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. Diabetologia 2020;63(7):1324–32.
[3] Grant B, Sandelson M, Agyemang-Prempeh B, Zalin A. Managing obesity in people with type 2 diabetes. Clin Med (Lond) 2021;21(4):e327–1231.
[4] Wilding JP. The importance of weight management in type 2 diabetes mellitus. Int J Clin Pract 2014;68(6):682–91.
[5] Sjostrom CD, Peltonen M, Wedel H, Sjostrom L. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. Hypertension 2000;36(1):20–5.
[6] Schwartz MW, Seeley RJ, Zeltser LM, Drewnowski A, Ravussin E, Redman LM, et al. Obesity pathogenesis: an endocrine society scientific statement. Endocr Rev 2017;38(4):267–96.
[7] Martin WP, le Roux CW. Obesity is a disease. In: Haslam D, Malhotra A, Capehorn MS, editors. Bariatric Surgery in Clinical Practice. Cham: Springer International Publishing; 2022. p. 23–8.
[8] Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. Lancet 2022;399(10322):394–405.
[9] Rose KL, Evans EW, Sonneville KR, Richmond T. The set point: weight destiny established before adulthood? Curr Opin Pediatr 2021;33(4):368–72.
[10] Berthoud HR, Seeley RJ, Roberts SB. Physiology of energy intake in the weight-reduced state. Obesity (Silver Spring, Md) 2021;29(Suppl 1):S25–30.
[11] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of care in diabetes—2023. Diabetes Care 2023;46:S128–39.
[12] ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes—2023. Diabetes Care 2022;46(Supplement_1):S140–57.
[13] Franz MJ, VanWormer JJ, Crain AL, Boucher JL, Histon T, Caplan W, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007;107(10):1755–67.
[14] Machado AM, Guimarães NS, Bocardi VB, da Silva TPR, Carmo ASD, Menezes MC, et al. Understanding weight regain after a nutritional weight loss intervention: systematic review and meta-analysis. Clinical nutrition ESPEN 2022;49:138–53.
[15] Tsushima Y, Lansang MC, Makin V. The role of SGLT-2 inhibitors in managing type 2 diabetes. Cleve Clin J Med 2021;88(1):47.
[16] Garvey WT, Ryan DH, Bohannon NJ, Kushner RF, Rueger M, Dvorak RV, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. Diabetes Care 2014;37(12):3309–16.
[17] Hollander P, Gupta AK, Plodkowski R, Greenway F, Bays H, Burns C, 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):4022–9.
[18] Berne C. Orlistat Swedish Type 2 diabetes Study G. A randomized study of orlistat in combination with a weight management programme in obese patients with Type 2 diabetes treated with metformin. Diabet Med 2005;22(5):612–8.
[19] Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjoth TV, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314(7):687–99.
[20] Davies M, Faerch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397(10278):971–84.
[21] Flynn CR, Tamboli RA, Antoun J, Sidani RM, Williams B, Spann MD, et al. Caloric restriction and weight loss are primary factors in the early tissue-specific metabolic changes after bariatric surgery. Diabetes Care 2022;45(8):1914–6.
[22] Bojsen-Møller KN, Dirksen C, Jørgensen NB, Jacobsen SH, Serup AK, Albers PH, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after roux-en-Y gastric bypass. Diabetes 2014;63(5):1725–37.
[23] Wickremesekera K, Miller G, Naotunne TD, Knowles G, Stubbs RS. Loss of insulin resistance after Roux-en-Y gastric bypass surgery: a time course study. Obes Surg 2005;15(4):474–81.
[24] Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg 1995;222(3):339–50; discussion 50-2.
[25] Johansson L, Roos M, Kullberg J, Weis J, Ahlström H, Sundbom M, et al. Lipid mobilization following Roux-en-Y gastric bypass examined by magnetic resonance imaging and spectroscopy. Obes Surg 2008;18(10):1297–304.
[26] Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, et al. Shift to fatty substrate utilization in response to sodium-glucose cotransporter 2 inhibition in subjects without diabetes and patients with type 2 diabetes. Diabetes 2016;65(5):1190–5.
[27] Merovci A, Solis-Herrera C, Daniele G, Eldor R, Fiorentino TV, Tripathy D, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124(2):509–14.
[28] Mudaliar S, Henry RR, Boden G, Smith S, Chalamandaris AG, Duchesne D, et al. Changes in insulin sensitivity and insulin secretion with the sodium glucose cotransporter 2 inhibitor dapagliflozin. Diabetes Technol Ther 2014;16(3):137–44.
[29] Bonner C, Kerr-Conte J, Gmyr V, Queniat G, Moerman E, Thevenet J, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21(5):512–7.
[30] Op den Kamp YJM, de Ligt M, Dautzenberg B, Kornips E, Esterline R, Hesselink MKC, et al. Effects of the SGLT2 inhibitor dapagliflozin on energy metabolism in patients with type 2 diabetes: a randomized, double-blind crossover trial. Diabetes Care 2021;44(6):1334–43.
[31] Esterline RL, Vaag A, Oscarsson J, Vora J. MECHANISMS IN ENDOCRINOLOGY: SGLT2 inhibitors: clinical benefits by restoration of normal diurnal metabolism? Eur J Endocrinol 2018;178(4):R113–25.
[32] Packer M. SGLT2 inhibitors: role in protective reprogramming of cardiac nutrient transport and metabolism. Nat Rev Cardiol 2023. https://doi.org/10.1038/s41569-022-00824-4. PMID: 36609604. Online ahead of print (https://europepmc.org/article/med/36609604).
[33] Zannad F, Ferreira JP, Butler J, Filippatos G, Januzzi JL, Sumin M, et al. Effect of empagliflozin on circulating proteomics in heart failure: mechanistic insights into the EMPEROR programme. Eur Heart J 2022;43(48):4991–5002.
[34] Cowie MR, Fisher M. SGLT2 inhibitors: mechanisms of cardiovascular benefit beyond glycaemic control. Nat Rev Cardiol 2020;17(12):761–72.
[35] Sjostrom CD, Hashemi M, Sugg J, Ptaszynska A, Johnsson E. Dapagliflozin-induced weight loss affects 24-week glycated haemoglobin and blood pressure levels. Diabetes Obes Metab 2015;17(8):809–12.
[36] Sakamoto M, Goto Y, Nagayama A, Yano M, Sato S, Tajiri Y, et al. Two-year administration of sodium-glucose co-transporter 2 inhibitor brought about marked reduction of body fat independent of skeletal muscle amount or glycemic improvement in Japanese patients with type 2 diabetes. Diabetol Int 2022;13(1):117–23.
[37] Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, 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. J Clin Endocrinol Metab 2012;97(3):1020–31.
[38] Sattar N, Gill JMR. Type 2 diabetes as a disease of ectopic fat? BMC Med 2014;12(1):123.
[39] Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376(3):254–66.
[40] Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328–57.
[41] Dai W, Ye L, Liu A, Wen SW, Deng J, Wu X, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. Medicine (Baltimore) 2017;96(39):e8179.
[42] Muzica CM, Sfarti C, Trifan A, Zenovia S, Cuciureanu T, Nastasa R, et al. Nonalcoholic fatty liver disease and type 2 diabetes mellitus: a bidirectional relationship. Can J Gastroenterol Hepatol 2020;2020:6638306.
[43] Lee C-H, Lui DT, Lam KS. Non-alcoholic fatty liver disease and type 2 diabetes: an update. J Diab Investig 2022;13(6):930–40.
[44] Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. J Hepatol 2016;65(3):589–600.
[45] Mantovani A, Petracca G, Csermely A, Beatrice G, Bonapace S, Rossi A, et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals. Gut 2023;72(2):372–80.
[46] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347–57.
[47] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117–28.
[48] Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375(4):323–34.
[49] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995–2008.

[50] Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413–24.
[51] Butler J, Filippatos G, Jamal Siddiqi T, Brueckmann M, Böhm M, Chopra VK, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-preserved trial. Circulation 2022;145(3):184–93.
[52] Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436–46.
[53] The E-K-C-G, Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023;388(2):117–27.
[54] Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). Circulation 2017;136(3):249–59.
[55] Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16):1451–61.
[56] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644–57.
[57] Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295–306.
[58] Mertens IL, Van Gaal LF. Overweight, obesity, and blood pressure: the effects of modest weight reduction. Obes Res 2000;8(3):270–8.
[59] Sjostrom CD, Peltonen M, Sjostrom L. Blood pressure and pulse pressure during long-term weight loss in the obese: the Swedish Obese Subjects (SOS) Intervention Study. Obes Res 2001;9(3):188–95.
[60] Jepsen MM, Christensen MB. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. Expert Opin Emerg Drugs 2021;26(3):231–43.
[61] Andersen A, Lund A, Knop FK, Vilsbøll T. Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol 2018;14(7):390–403.
[62] Kleinert M, Sachs S, Habegger KM, Hofmann SM, Müller TD. Glucagon regulation of energy expenditure. Int J Mol Sci 2019;20(21).
[63] Hope DCD, Vincent ML, Tan TMM. Striking the balance: GLP-1/glucagon co-agonism as a treatment strategy for obesity. Front Endocrinol 2021;12:735019.
[64] Ali MM, Hafez A, Abdelgalil MS, Hasan MT, El-Ghannam MM, Ghogar OM, et al. Impact of Cotadutide drug on patients with type 2 diabetes mellitus: a systematic review and meta-analysis. BMC Endocr Disord 2022;22(1):113.
[65] Parker VER, Robertson D, Wang T, Hornigold DC, Petrone M, Cooper AT, et al. Efficacy, safety, and mechanistic insights of cotadutide, a dual receptor glucagon-like peptide-1 and glucagon agonist. J Clin Endocrinol Metab 2019;105(3):803–20.
[66] Muller TD, Finan B, Clemmensen C, DiMarchi RD, Tschop MH. The new biology and pharmacology of glucagon. Physiol Rev 2017;97(2):721–66.
[67] van der Windt DJ, Sud V, Zhang H, Tsung A, Huang H. The effects of physical exercise on fatty liver disease. Gene Expr 2018;18(2):89–101.
[68] Cigrovski Berkovic M, Bilic-Curcic I, Mrzljak A, Cigrovski V. NAFLD and physical exercise: ready, steady, go! Front Nutr 2021;8:734859.
[69] Ambery P, Parker VE, Stumvoll M, Posch MG, Heise T, Plum-Moerschel L, et al. MEDI0382, a GLP-1 and glucagon receptor dual agonist, in obese or overweight patients with type 2 diabetes: a randomised, controlled, double-blind, ascending dose and phase 2a study. Lancet 2018;391(10140):2607–18.
[70] Nahra R, Wang T, Gadde KM, Oscarsson J, Stumvoll M, Jermutus L, et al. Effects of cotadutide on metabolic and hepatic parameters in adults with overweight or obesity and type 2 diabetes: A 54-week randomized phase 2b study. Diabetes Care 2021;44(6):1433–42.
[71] Ambery P. GLP-1 – glucagon combination at the INCSG Symposium: GLP-1 dual and multi-agonist peptides: which additional activities to dial in? In: 58th European Association for the Study of Diabetes Annual Meeting 19–23 September 2022. Sweden and Online: Stockholm; 2022.
[72] Parker VER, Hoang T, Schlichthaar H, Gibb FW, Wenzel B, Posch MG, et al. Efficacy and safety of cotadutide, a dual glucagon-like peptide-1 and glucagon receptor agonist, in a randomized phase 2a study of patients with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2022;24(7):1360–9.
[73] Boland ML, Laker RC, Mather K, Nawrocki A, Oldham S, Boland BB, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist Cotadutide via modulating mitochondrial function and lipogenesis. Nat Metab 2020;2(5):413–31.