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Review

Anti-diabetic drugs and weight loss in patients with type 2 diabetes

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ABSTRACT

Introduction: Obesity is frequently a comorbidity of type 2 diabetes. Even modest weight loss can significantly improve glucose homeostasis and lessen cardiometabolic risk factors in patients with type 2 diabetes, but lifestyle-based weight loss strategies are not long-term effective. There is an increasing need to consider pharmacological approaches to assist weight loss in the so called *diabesity* syndrome. Aim of this review is to analyze the weight-loss effect of non-insulin glucose lowering drugs in patients with type 2 diabetes.
Material and methods: A systematic analysis of the literature on the effect of non-insulin glucose lowering drugs on weight loss in patients with type 2 diabetes was performed. For each class of drugs, the following parameters were analyzed: kilograms lost on average, effect on body mass index and body composition.
Results: Our results suggested that anti-diabetic drugs can be stratified into 3 groups based on their efficacy in weight loss: metformin, acarbose, empagliflozin and exenatide resulted in a in a mild weight loss (less than 3.2% of initial weight); canagliflozin, ertugliflozin, dapagliflozin and dulaglutide induces a moderate weight loss (between 3.2% and 5%); liraglutide, semaglutide and tirzepatide resulted in a strong weight loss (greater than 5%).
Conclusions: This study shows that new anti-diabetic drugs, particularly GLP1-RA and Tirzepatide, are the most effective in inducing weight loss in patients with type 2 diabetes. Interestingly, exenatide appears to be the only GLP1-RA that induces a mild weight loss.

1. Introduction

Obesity is frequently a comorbidity of type 2 diabetes (T2D) and up to an 85.2% of people with T2D are overweight or obese [1] and by 2025, more than 300 million of people will have T2D associated with obesity [2]. In most cases it is not possible to understand these pathologies separately, so that some authors consider them as a unique entity termed as "diabesity"[3], which therefore also needs to be treated as a single entity to maximize the benefits of the therapies received by these patients [4]. Weight-loss has clinically meaningful implications in T2D and patients with T2D who lose weight are more likely to avoid the burden of morbidity and early mortality associated with a diagnosis of diabetes and obesity [5]. Weight-loss of 5–10%, not only improves glycemic control, but also influences cardiovascular risk factors, such as hypertension and dyslipidemia [6,7]. More pronounced weight-loss (>15%) is associated with decreased mortality and other clinical benefits, with reduction of sleep apnea and of non-alcoholic steatohepatitis [8]. Weight-loss is difficult to accomplish or maintain; indeed, meta-analyses of clinical trials on non-pharmacological strategies for weight loss have reported a reduction of 1–6 kg, which are difficult to be maintained [9]. Lifestyle-based weight-loss strategies, i.e. diet, exercise, and behavior change, may be initially successful, but after an early

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phase of weight-loss, there is a plateau at around 6 months, followed by a progressive weight gain over the following months [10]. The average weight reductions with the formerly used drugs, like sibutramine and orlistat, was nearly 3–5 kg, but with some adverse events that limited their use on daily basis [11]. Bariatric surgery has been demonstrated to reduce long-term mortality in obese patients, but the usefulness of these interventions, for large patient populations, are limited by the safety risks and the high-costs amount [12]. In consideration of the extent of the epidemiological entity of the *diabesity* syndrome and the low efficacy of most of the therapeutic approaches available, there is an increasing need to consider new pharmacological approaches to facilitate weight-loss in patients with the *diabesity* syndrome. Aim of this review is to analyze the weight-loss effect of all different non-insuline glucose lowering drugs in overweight patients with T2D. Thiazolidinediones were also excluded from our discussion due to their known effect of increasing body weight.

1.1. Metformin

Metformin is the first-line glucose-lowering medication recommended by almost all international guidelines [13]. Several studies demonstrated that metformin has a positive impact on body weight according to the specific mechanism of action of this drug. The main mechanism by which metformin induces weight-loss is the reduction of appetite with consequent decreased caloric intake (Fig. 1). The impact on appetite regulation depends on a directly central effect of the drug and indirectly on its gastrointestinal side effects, such as nausea, bloating, diarrhea and dysgeusia [14]. The mechanism by which metformin acts on appetite centers are different, including: the lactate-mediated, mild, metabolic acidosis, that may drive a central appetite suppression [15]., the increased secretion of the weight-loss promoting incretin glucagon like peptide 1 (GLP-1) [16] and of the anorectic hormone peptide YY (PYY), the suppression of orexogenic hypothalamic Agouti related protein (AgRP) neurons via AMP-activated protein kinase (AMP) suppression [17], and the reduced bile acid absorption through interaction with farnesoid X receptor, that is thought to promote the appetite suppressing neuropeptides [18]. The effect of metformin on body weight in randomized, controlled trials in patients sub-optimally controlled by diet was variable, with about half of studies demonstrating significant reductions in body weight with metformin [5]. However, Stumvoll and colleagues, firstly showed that the drug had a modest effect on weight. In the aforementioned study, patients lost an average of 2.8% of the initial weight (-2.7 kg in absolute value) despite the absence of change in resting energy expenditure or self-reported physical activity, with a decrease in body fat mass which accounted for about 88% of the weight-loss, whereas lean body mass did not change [19]. A non-statistically significant difference in the weight-loss between metformin and placebo was demonstrated by the Metformin Study Group (nearly 1 kg) [20]. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin was again similar to diet therapy as far as weight changes, which was a weight-gain in this case of nearly 1.7% of the initial weight (-1.5 kg in absolute value). The subsequent addition of metformin to sulphonylurea treatment in a subgroup of patients in this trial did not result in a significant weight change [21]. The group of Kahn and colleagues compared the effect on weight of three antidiabetic drugs, metformin, rosiglitazone and glyburide over a period of 5 years and they observed a weight-loss in the metformin group of 3.2% of the initial weight (-2.9 kg in absolute value CI, −3.4 to −2.3), while there was a weight gain in the rosiglitazone (change from baseline, 4.8 kg; 95% CI, 4.3–5.3) and in the glyburid (1.6 kg; 95% CI, 1.0–2.2) groups [22]. Most of the studies suggested that metformin may prevent the weight-gain associated with insulin treatment, with few

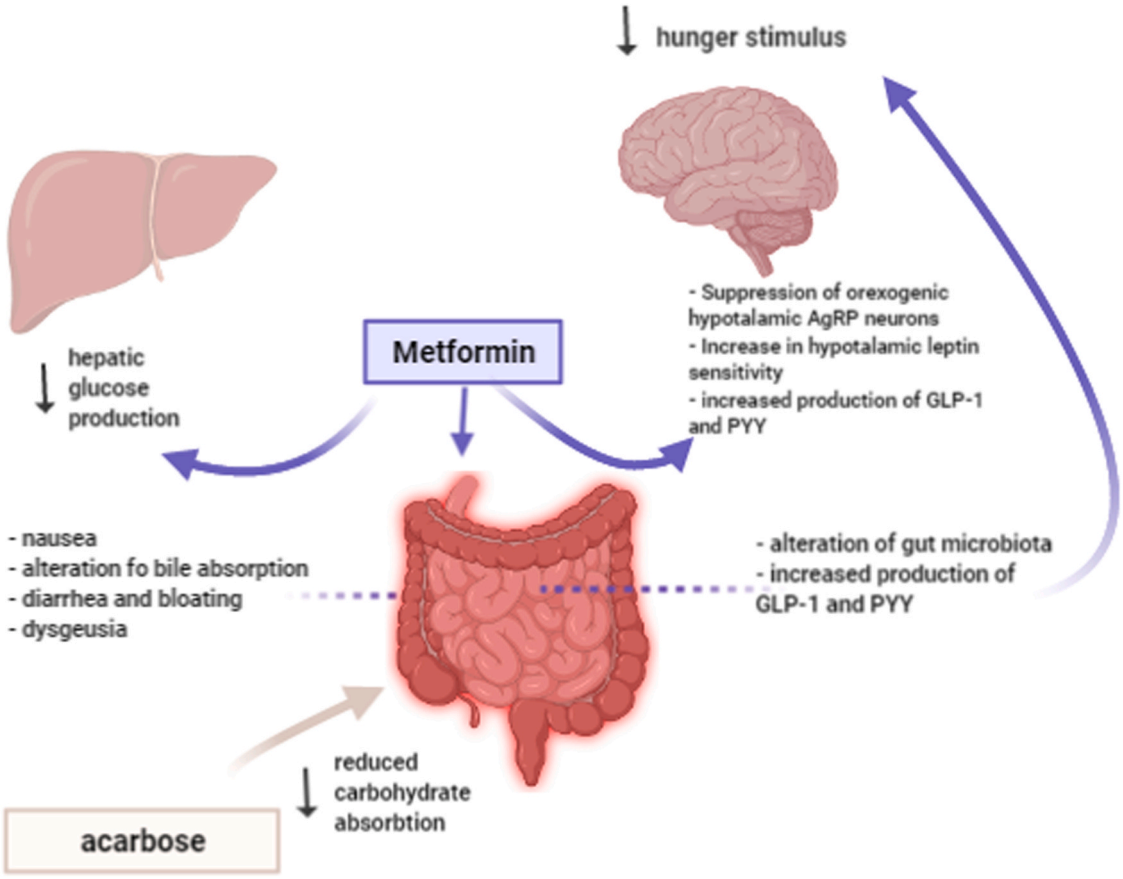

Fig. 1. Summary of weight loss mechanisms of metformin and acarbose.

showing no effects [23,24]. Douek et al. demonstrated that over 12 months, metformin was associated with less weight gain than placebo [mean 6.1 kg vs. 7.6 kg; P = 0.02] [25] and Kvapil et al. demonstrated in 341 patients with T2D a significant lower body weight increase in patients with T2D receiving insulin aspart plus metformin as compared to those receiving insulin aspart only (84 ± 13 vs. 89 ± 17 kg, p < 0.001) [26]. Few meta-analysis showed that, while metformin was superior to sulfonylureas as far as body weight, this was not evident with placebo [27]. Metformin has also been shown to have a positive effect on body composition in patients with T2D uncontrolled by diet, as it may reduce visceral fat mass and abdominal subcutaneous fat [28]. A summary of the mean weight-loss observed with metformin in different trials is shown in Table 1.

2. α-Glucosidase inhibitors

Acarbose is a competitive inhibitor of intestinal α-glucosidase, which exerts its activity in the gastrointestinal tract. By reversibly inhibiting the enzymatic cleavage of complex carbohydrates to simple absorbable sugars, treatment with acarbose results in a reduction in post-prandial blood glucose [29]. In consideration of the reduced carbohydrate absorption and consequently of the reduced caloric intake, acarbose is an anti-diabetic drug that has been hypothesized to reduce body weight. A randomized, double-blind, placebo-controlled, trial conducted on 354 patients with T2D, acarbose induced after 1 year of follow up a loss of 0.4 ± 0.3 kg, which appeared higher than the placebo (weight-loss of 0.3 ± 0.5 kg, p = 0.02). The authors concluded that long-term acarbose therapy results in a small weight-loss, which is due partly to the reduced doses of other agents and insulin and partly due to energy loss for the increased colonic fermentation, while there are no effects on energy or nutrient intakes [30]. A summary of the mean weight-loss observed with α-Glucosidase Inhibitors in different trials is shown in Table 1.

3. SGLT-2 inhibitors

The sodium-dependent glucose cotransporter proteins 1 and 2 (SGLT1/2) regulate renal glucose reabsorption in the proximal renal tubule of the kidney. SGLT2 transporter induces approximatively the 90% of reabsorption, while the remaining 10% is reabsorbed in the distal segment thank to SLGT1 transporter [31]. Through the inhibition of these co-transporters, a large amount of glucose, ranging from 50 to 100 g daily, and the corresponding caloric equivalent (200–400 kcal/die) are pharmacologically forced into urinary excretion, so the whole-body metabolism must undergo adaptive changes involving glucose fluxes, hormonal responses, fuel selection, and energy expenditure [32] (Fig. 2). In particular, SGLT2 inhibitors induce an increased glucagon/insulin ratio causing an increased lipid mobilization. Furthermore, SGLT-2i reduce serum leptin and increase adiponectin concentration, which are mechanisms contributing to lipolysis, weight loss and reduction of adipose accumulation in the myocardium [33]. There are currently four SGLT2 inhibitors available for use in Europe: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Pharmacological blockade of renal glucose reabsorption reduces fasting and postprandial glycemia both acutely and chronically without causing hypoglycemia, with improvement of both β cell function and insulin sensitivity [34]. In the long-term deficit of glucose oxidation induced an increase in lipid oxidation, thereby maintaining energy balance, with reduction in fat mass [35]. The use of SGLT2-inhibitors does not result in reduced energy expenditure and weight-loss is less than predicted probably because it stimulates calories intake and endogenous glucose production [36].

Table 1
Main studies related to weight loss in diabetic patients treated with metformin and α-glucosidase inhibitors.

Drug	Study	Dose (mg)	Average weight loss (Kg)	% weight loss vs. baseline	Observation interval (weeks)
Metformin	Stumvoll et al.	2550 per day	-2.7 ± 1.3	-2.8%	16
	Kahn et al.	500 per day	-2.9 (CI −3.4; −2.3)	-3.2%	260
	Defronzo et al.	2550 per day	-0.6 ± 0.3	-0.6%	29
	Holman et al.	2550 per day	+1.5 (no CI provided)	+1.7%	312
Acarbose	Wolever et al.	200 three times per day	-0.4 ± 0.3	-0.4%	52

3.1. Canagliflozin

Among the various subtypes of SGLT2-I, canagliflozin has been extensively shown to induce a significative weight-loss drug compared to placebo. Stenlöf et al. demonstrated a significant weight-loss with canagliflozin of 2.2% of the initial weight (-2.0 kg in absolute value) and 3.3% of the initial weight (- 3.0 kg in absolute value) respectively with the 100 and 300 mg dose [37]. In the CANVAS Program, which integrated data from two trials involving a total of 10,142 participants with T2D and high cardiovascular risk, participants were randomly assigned to receive canagliflozin 100 mg daily or placebo and were followed for a mean of 188 weeks. In the aforementioned study a mean difference of 1.8% of the initial weight (1.6 kg in absolute value, 95% CI, −1.70 to −1.51) (P < 0.001) was evident in patients treated with Canagliflozin as compared to those who received placebo [38]. Canagliflozin reduced body weight in patients previously treated with other oral antidiabetic drugs as well. In a study conducted by Rosenstock et al. in 2012, 451 subjects inadequately controlled with metformin monotherapy were randomized to canagliflozin 50, 100, 200, or 300 mg once daily or 300 mg twice daily, sitagliptin 100 mg daily, or placebo. Body weight reductions were seen in all canagliflozin groups as compared to placebo, with a reduction in weight from baseline of 2.6% (−2.0 kg in absolute value) with 100 mg per day and 3.4% (−3.2 kg in absolute value) with 300 mg per day at week 12, while a minor reduction was seen in placebo and sitagliptin treatment groups (−0.8 and −0.4 kg from baseline, respectively). Weight-loss appeared to be greatest in subjects in the canagliflozin 300 mg groups and it was progressive during the 12-week treatment period without apparently reaching a plateau [39].

3.2. Dapagliflozin

Trials on dapagliflozin showed efficacy on weight-loss; particularly a study conducted by Ferrannini showed a body weight reduction of 3.2% of the initial weight (−3.3 kg in absolute value) and 3.4% of the initial weight (−3.2 kg in absolute value) with Dapagliflozin 5 mg and 10 mg respectively, without however reaching a statistical difference as compared to the placebo [40]. In the DECLARE study, 17,160 patients with T2D, including 10,186 who had or were at risk for atherosclerotic cardiovascular disease, were randomly assigned to receive either dapagliflozin or placebo and followed for a median of 4.2 years. Difference between the groups as far as body weight reduction was 1.8 kg (95% CI, 1.7–2.0) in favor of dapagliflozin [41]. In another study evaluating the efficacy of three different doses of dapagliflozin versus placebo in patients inadequately controlled on metformin, a sustained significative weight-loss from 1.6% to 1.8% of the initial weight at 102 weeks was shown, whereas increases were noted in placebo-treated patients [42]. Bolinder et al. conducted a double-blind, placebo-controlled study in patients with T2D inadequately controlled on metformin over 102 weeks, observing a loss of 4.9% of the initial weight (−4.5 kg in absolute value), of waist circumference of 5.0 cm and of fat mass of

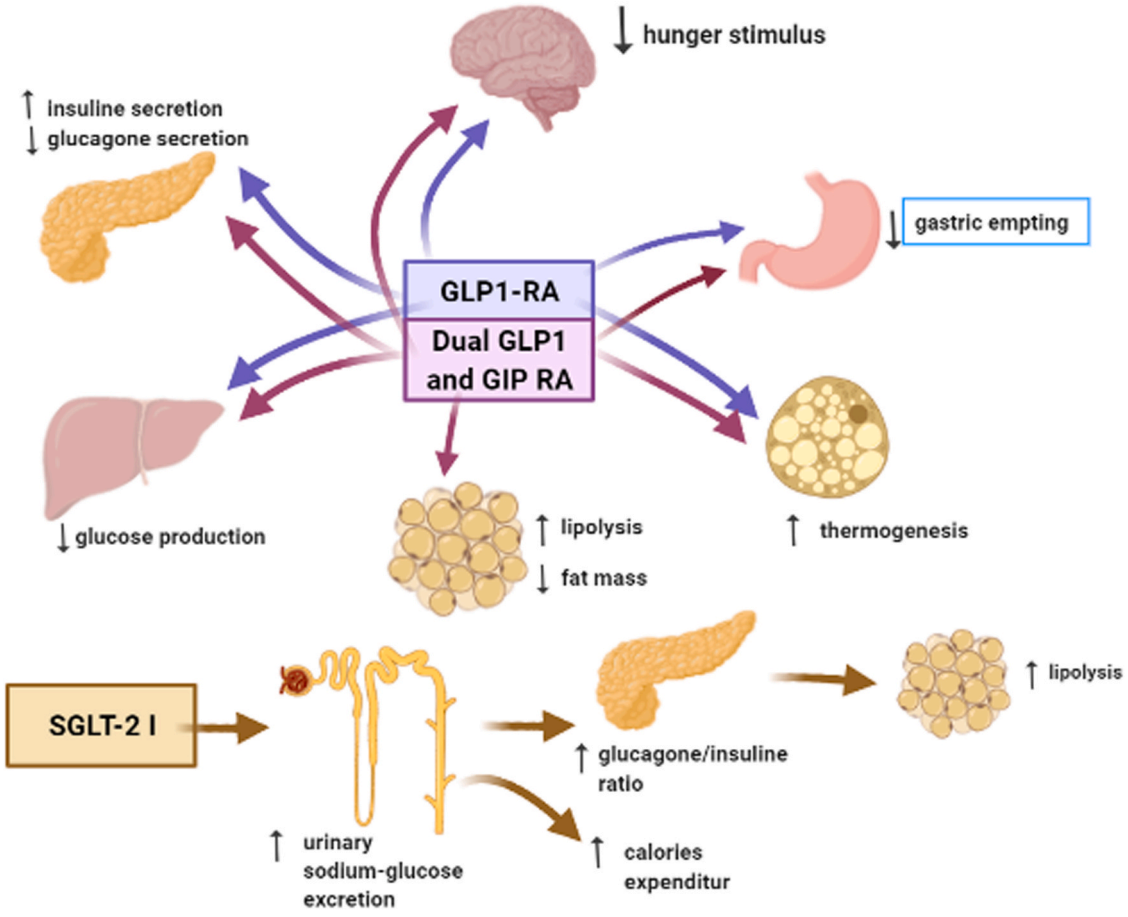

Fig. 2. Summary of weight loss mechanisms of GLP1-RA, dual GLP1/GIP-RA and SGLT-2 I.

2.8 kg [35]. In another randomized study, patients with T2D with poor metabolic control treated with metformin received dapagliflozin or glipizide for 18 weeks and a greater weight-loss (3.2 kg) was observed as compared to with glipizide (1.2 kg) [43].

3.3. Empagliflozin

The benefit of empagliflozin over metformin was extensively evaluated in the EMPA REG study. Empagliflozin 10 and 25 mg for 24 weeks as add-on to metformin therapy significantly reduced weight with placebo with differences of adjusted means versus placebo of 1.9% of the initial weight (- 1.6 kg in absolute value, 95% CI −2.1 to −1.2) for empagliflozin 10 mg and 2.5% of the initial weight (−2.0 kg in absolute value 95% CI −2.5 to −1.5] for empagliflozin 25 mg. The decreases in body weight with empagliflozin 10 and 25 mg were accompanied by significant reductions in waist circumference (−1.5 cm [0.2 cm] and −1.6 cm [0.2 cm], respectively) as compared to placebo (−0.5 cm [0.2 cm]) [44]. In the EMPA-REG PIO™ trial, 168 patients with HbA1c between 7% and 10% were randomized and treated with empagliflozin 10 mg or 25 mg or placebo as add-on to pioglitazone and metformin for 24 weeks. Adjusted mean changes in weight were − 1.6/1.5 kg with empagliflozin 10 mg and 25 mg, respectively, as compared to +0.3 kg with placebo [45].

3.4. Ertugliflozin

Ertugliflozin is the newest of the class and it was reported to have a significant weight-reducing effect as compared to placebo [46]. In the VERTIS SITA2 study, 5 mg of ertugliflozin added to metformin and sitagliptin over 52 weeks of treatment induced a significant placebo-adjusted reduction in body weight [average weight reduction: −1.3 kg (−1.8, −0.9) in placebo group, −3.4 kg (−3.8, −2.9) in Ertugliflozin group] [47]. In another randomized, double-blind, multicentric study (VERTIS FACTORIAL), the efficacy of Ertugliflozin 5 and 15 mg were compared to sitagliptin 100 mg. At week 26 a significantly greater reduction in body weight was observed for Ertugliflozin 5 mg, with an average loss of 3.0% of the initial weight (−2.7 kg in absolute value, CI −3.1, −2.2), and 15 mg, with an average loss of 4.2% of the initial weight (−3.7 kg in absolute value, CI −4.2, −3.3), compared to sitagliptin 100 mg [−0.7 kg (−1.1, −0.2)] [48]. A summary of the mean weight-loss observed with SGLT2 inhibitors in different trials is shown in Table 2.

4. GLP1 and GLP-1/GIP receptor agonist

GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide) are natural incretin released by the gut during meals; they maintain a normal blood glucose level by stimulating glucose-dependent insulin secretion, thereby driving insulin-mediated glucose disposal to the muscle and fat cells. Moreover, GLP1–1/GIP inhibited postprandial glucagon secretion and hepatic glucose production. In healthy individuals, the insulin surge after meals rapidly leads to a reduction in glucose plasma levels. In people with T2D, the incretin effect is markedly diminished, resulting in higher and sustained glucose plasma concentration after ingestion of carbohydrates [49]. GLP1–1/GIP agonists increase the sense of satiety, with reduction of food intake, and, consequentially, body weight. GLP1–1/GIP have a direct effect on pancreas, but while GLP-1 induces increase of insulin secretion and reduction of glucagon release, GIP causes increasing of both these hormones. Only GLP-1 has a variety of other effects,

Table 2
Main studies related to weight loss in diabetic patients treated with SGLT2-inhibitors.

Drug	Study	Dose (mg)	Average weight loss (Kg)	% weight loss vs. baseline	Observation interval (weeks)
Canagliflozin	Stenlöf et al.	100 per day	-1.9 ± 0.3	-2.2%	26
		300 per day	-2.9 ± 0.7	-3.3%	26
	CANVAS study	100 per day	-1.6 ± 0.1	-1.8%	188
	Rosenstock et al.	100 per day	-2.3 (no CI provided)	-2.6%	12
		300 per day	- 3.0 (no CI provided)	-3.4%	12
Dapagliflozin	Ferrarini et al.	5 per day	-2.8 ± 0.5	-3.2%	24
		10 per day	-3.2 ± 0.5	-3.4%	24
	Nauck et al.	10 per day	-3.2 ± 0.4	NA	52
	DECLARE study	10 per day	-1.8 ± 0.2	NA	218
	Bailey et al.	5 per day	-2.9 ± 0.5	-3.4%	24
			-1.5 ± 0.2	-1.8%	102
		10 per day	-2.7 ± 0.5	-3.1%	24
			-1.4 ± 0.3	-1.6%	102
	Bolinder et al.	10 per day	-4.5 ± 0.9	-4.9%	52
Empagliflozin	EMPA-REG Study	25 per day	-2.0 ± 0.5	-2.5%	24
		10 per day	-1.6 ± 0.4	-1.9%	24
	EMPA-REG PIO trial	25 per day	-1.5 ± 0.2	NA	24
Ertugliflozin	VERTIS SITA2 study	5 per day	-3.4 ± 0.4	NA	26
		15 per day	-3.0 ± 0.4	NA	26
	VERTIS FACTORIAL	5 per day	-2.7 ± 0.4	- 3.0%	26
		15 per day	-3.7 ± 0.4	- 4.2%	26

including slowing the gastric emptying, improving insulin sensitivity and reducing hepatic glucose production and ectopic lipid accumulation [50]. GIP has direct effects on subcutaneous white adipose tissue, improves insulin sensitivity and lipid buffering capacity, blood flow and storage capacity, while it reduces proinflammatory immune cell infiltration [51,52]. In this way, GIP indirectly also reduces the dietary triglycerides. In consideration of the effect of these hormones, GLP-1 receptor agonist (GLP-1 RA) drugs and, lately, the combined GLP-1 and GIP receptor agonists (GLP-1/GIP RA) have been studied in many trials for their anti-diabetic and weight-loss effect (Figs. 2, 3).

4.1. Exenatide

Exenatide is a short acting GLP-1 RA which has been demonstrated to have a positive effect on body weight in patients with T2D. A meta-analysis of 25 trials of patients with overweight or obesity, with or without T2DM, treated with exenatide or liraglutide showed a mean difference of 2.7% of the initial weight (−2.7 kg in absolute value), achieved with the highest dose of GLP-1 RAs compared as compared to controls [53]. Apovian et al. found that adding exenatide to an intensive lifestyle modification program, consisting of 600 kcal/day deficit and physical activity of at least 2.5 h/week, induces greater weight-loss than lifestyle program and placebo (−6.2 ± 0.5 vs. −4.0 ± 0.5 kg) [54]. Patients with T2D failing to achieve glycemic control with metformin and treated with exenatide display progressive dose-dependent weight-loss (−2.8 kg) as compared to placebo [55]. A similar effect on body weight was also observed in patients with T2D poorly controlled by sulfonylurea as monotherapy, with a dose-dependent progressive weight loss of 1.7% of the initial weight (−1.6// ± 0.3 kg in absolute value) from baseline in the group treated with exenatide [56].

4.2. Liraglutide

Liraglutide is a glucagon-like peptide-1 with 97% homology to human glucagon-like peptide-1 and it is approved for the treatment of T2D. Weight-loss due to this drug is mediated by central appetite reduction with consequent decreased energy intake rather than by increased energy expenditure [57]. The effect of Liraglutide on weight is dose-dependent, as demonstrated in the SCALE study, in which patients experienced a dose-dependent weight-loss ranging from 6.0 to 8.8 kg, whereas subjects treated with placebo (on diet and exercise alone) had a mean weight-loss between 0.2 and 3.0 kg. In the same study, adding liraglutide 3 mg once daily to diet and exercise, resulted in an additional weight-loss of 6% versus lifestyle intervention only [58]. Davies et al. observed a significant weight-loss in obese patient with T2D treated with two different doses of Liraglutide; indeed after 12 weeks, the mean weight-loss was 4.7% of the initial weight (−5 kg in absolute value) and 6.0% of the initial weight (−6.4 kg in absolute value) with 1.8 and 3 mg respectively of liraglutide as compared to a weight loss of 2.2% (−2.2 kg in absolute value) with placebo [59]. Interestingly, an early weight loss in treatment with liraglutide has been identified as a key predictor of a late successful response to the drug [60].

4.3. Dulaglutide

Dulaglutide an once-weekly injectable GLP-1 RA has a positive effect in terms of reduction of body mass index and waist circumference [61], but most of the authors describe a modest effect on weight-loss which is dependent on the administered dose. An interesting study compared the effect of two different doses of dulaglutide, exenatide and placebo in patients with T2D. The mean weight change from baseline to 26 weeks was a loss of 1.4% of the initial weight (−1.3 ± 0.3 kg in absolute value) for dulaglutide 1.5 mg, a gain of 0.2% of the initial weight (0.2 ± 0.3 kg in absolute value) for dulaglutide 0.75 mg, a loss of 1.1% (−1.1 ± 0.3 kg in absolute value) for exenatide, and a gain of 1.3% (1.2 ± 0.4 kg in absolute value) for placebo [62]. The effect on body weight with different doses of dulaglutide was also demonstrated by Nauck et al. who showed that changes in body weight from baseline to 52 weeks were significantly greater for dulaglutide 1.5 mg, with a loss of 3.4% of the initial weight (−3.0 ± 0.2 kg in absolute value) and dulaglutide 0.75 mg, with a loss of 3.0% of the initial weight (−2.6 ± 0.2 kg in absolute value) as compared to sitagliptin, that induces a weight loss of 1.6% (−1.5 ± 0.2 kg in absolute value) [63].

4.4. Semaglutide

Semaglutide is a novel once-weekly injectable or oral GLP-1 RA, which has been studied in a series of SUSTAIN studies in patients with T2D. In the SUSTAIN-1 trial, a double-blind, randomized, placebo-controlled phase 3a trial, including patients with T2D, showed a

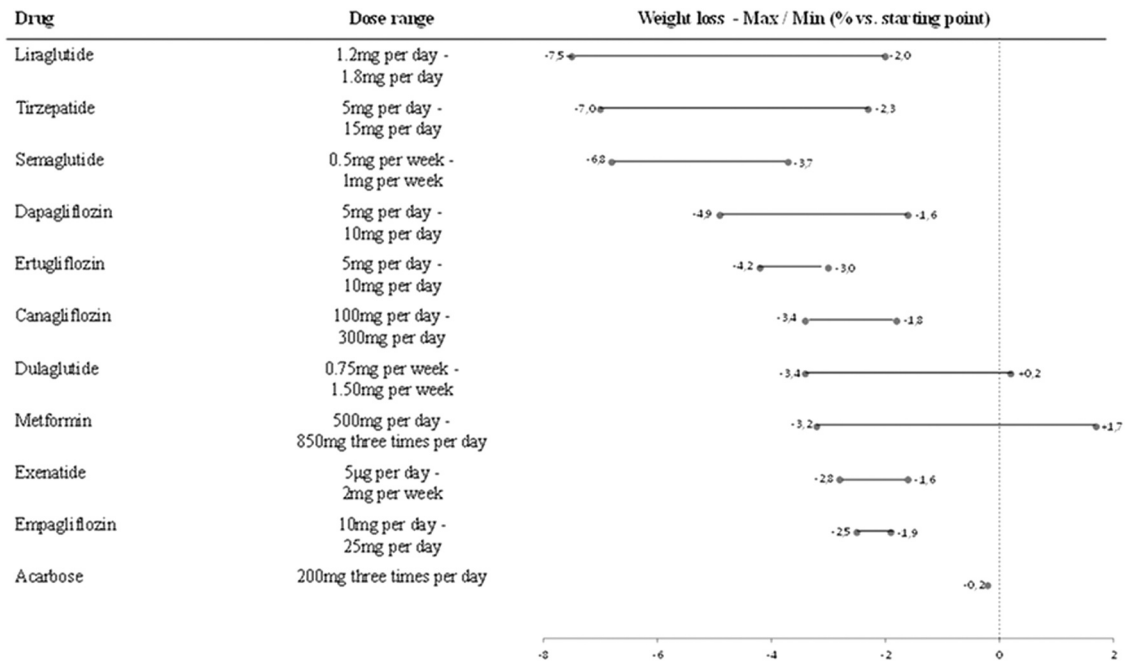

Fig. 3. Summary of weight loss for the most common antidiabetic drugs.

significant weight-loss at week 30 of 4.1% of the initial weight (−3.7 kg (95% CI −4.5 to −2.9) with 0.5 mg semaglutide, of 4.9% of the initial weight (−4.5 kg (−5.3 to −3.7) with 1.0 mg semaglutide and a non-significant weight-loss of 1.4% (−1.0 kg (−1.8 to −0.1) with placebo [64]. The efficacy of semaglutide in patients with T2D was also demonstrated as add-on to other oral antidiabetic agents (e.g.; metformin, thiazolidinediones and sitagliptin) in the SUSTAIN-2 study: body weight reduced by 4.8% of the initial weight (−4.3 kg in absolute value) with semaglutide 0.5 mg and 6.8% of the initial weight (−6.1 kg in absolute value) with semaglutide 1.0 mg [65]. In the SUSTAIN-3 study once-weekly semaglutide 1.0 mg s.c. was compared with exenatide extended release 2.0 mg s.c. in patients with T2D. Mean body weight was reduced by 5.8% of the initial weight (−5.6 kg in absolute value) with semaglutide and 2.1% of the initial weight (−1.9 kg in absolute value)with exenatide [32]. In the SUSTAIN-4, semaglutide 0.5 and 1.0 mg achieved weight losses of //3.7% (−3.5 kg in absolute value)// and 5.6% of the initial weight (−5.2 kg in absolute value) respectively, versus a weight gain of 1.3% of the initial weight (−1.1 kg in absolute value) with insulin glargine [66]. //The significant weight loss founded in SUSTAIN-4 study was also observed in SUSTAIN-6 study, where authors reported an average weight loss of 3.9% of the initial weight (−3.6 kg in absolute value) with semaglutide 0.5 mg and of 5.3% of the initial weight (−4.9 kg in absolute value) with semaglutide 1 mg [67]. A comparative study of the efficacy of semaglutide compared to liraglutide showed that weight reductions with semaglutide 1.6 mg were greater than those with liraglutide 1.8 mg (−2.6 kg), but adverse events and withdrawals occurred more frequently [68]. The effect of semaglutide on body composition compared to canagliflozin was assessed in a subset of participants in the SUSTAIN-8 study. Authors observed an improvement in body composition (including fat mass, lean mass and visceral fat mass) after 52 weeks with both treatments, with a reduction of fat mass by 3.4 kg and 2.6 kg with semaglutide and canagliflozin, respectively. Although total lean mass was also reduced by 2.3 kg and 1.5 kg with semaglutide and canagliflozin, respectively, the proportion of lean mass (baseline 59.4%) increased by 1.2%- and 1.1%-point, respectively [69,70]. The weight-lowering effect of semaglutide was also demonstrated for the oral formulation: in the PIONEER 6 study comparing the effect of oral semaglutide versus placebo the authors found a reduction in body weight of 4.8% of the initial weight (−4.2 kg in absolute value) at the end of the study (190 weeks) compared to − 0.8 kg with placebo [71].

4.5. Tirzepatide

Tirzepatide (LY3298176) is a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist that is being developed for the treatment of T2D [66]. In a recent double-blind, randomized, phase 2 study published in 2018 by Frias et al., patients with T2D were randomly assigned to receive either once-weekly subcutaneous Tirzepatide (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. From the comparative analysis of the six groups of patients emerged that changes in mean body weight ranged from −0.9 kg to −11.3 kg for LY3298176, as compared to −0.4 kg for placebo and −2.7 kg for dulaglutide. The weight-loss was dose-dependent, with patients who received 10 mg or 15 mg LY3298176 losing the most weight (mean differences in body weight: 2.3% of the initial weight (−2.1 kg in absolute value) for 5 mg, 4.7% of the initial weight (−4.4 kg in absolute value) for 10 mg, and 7.0% of the initial weight (−6.2 kg in absolute value) for 15 mg) (Table 3). More patients treated with 5 mg, 10 mg, and 15 mg LY3298176 reached weight targets (≥5%, ≥10%, and ≥15% weight loss from baseline) than did those treated with placebo and dulaglutide. Changes in waist circumference ranged from −2.1 cm to −10.2 cm for LY3298176, as compared to −1.3 cm for placebo and −2.5 cm for dulaglutide. At week 26, mean waist circumference decreased with the 5 mg, 10 mg, and 15 mg doses of LY3298176 [72]. A summary of the mean weight-loss observed with GLP-1 RA and Tirzepatide in different trials is shown in Table 3.

5. Conclusions

Diabesity is an increasingly widespread clinical condition characterized by the coexistence of diabetes and obesity [2]. Weight-loss has an important role in patients with T2D both to improve glycemic control and to prevent complications of this pathology. The weight-loss strategies currently available have some limitations; for instance lifestyle changes, after an early phase of weight loss, show a progressive recurrence of weight gain [10]. Drugs currently approved for the treatment of obesity have important adverse events, which lead to poor complicity in

Table 3
Main studies related to weight loss in diabetic patients treated with GLP1 receptor agonists and Tirzepatide.

Drug	Study	Dose (mg)	Average weight loss (Kg)	% Weight loss vs. baseline	Observation interval (weeks)
Exenatide	Vilsbøll et al.	10 μg per day	-2.8 ± 1–3	NA	20
	Buse et al.	10 μg per day	-1.6 ± 0.3	- 1.7%	26
	De Fronzo et al.	10 μg per day	-2.8 ± 0.5	- 2.8%	30
		5 μg per day	-1.6 ± 0.4	- 1.6%	26
Liraglutide	Vilsbøll et al.	1.2 per day	-2.2 ± 1.3	NA	20
	Wadden et al.	3.0 per day	-8.4 ± 7.3	- 7.5%	56
	Davies et al.	3.0 per day	-6.4 (No CI provided)	- 6.0%	56
		1.8 per day	-5.0 (No CI provided)	- 4.7%	56
Dulaglutide	Wysham et al.	1.50 per week	-1.3 ± 0.3	- 1.4%	26
		0.75 per week	+0.2 ± 0.3	+ 0.2%	26
	Nauck et al.	1.50 per week	-3.0 ± 0.2	- 3.4%	52
		0.75 per week	-2.6 ± 0.2	- 3.0%	52
Semaglutide	SUSTAIN1	0.5 per week	-3.7 ± 0.8	- 4.1%	30
		1.0 per week	-4.5 ± 0.8	- 4.9%	30
	SUSTAIN2	0.5 per week	-4.3 (No CI provided)	- 4.8%	56
		1.0 per week	-6.1 ± 1.0	- 6.8%	56
	SUSTAIN3	1.0 per week	-5.6 (No CI provided)	- 5.8%	56
	SUSTAIN4	0.5 per week	-3.5 ± 0.4	- 3.7%	30
		1.0 per week	-5.2 ± 0.5	- 5.6%	30
	SUSTAIN6	0.5 per week	-3.6 (No CI provided)	- 3.9%	104
		1.0 per week	-4.9 (No CI provided)	- 5.3%	104
	PIONEER	14.0 daily	-4.2 (No CI provided)	- 4.8%	190
Tirzepatide	Frias et al.	5 per day	-2.1 (no CI provided)	- 2.3%	26
		10 per day	-4.4 (no CI provided)	- 4.7%	26
		15 per day	-6.2 (no CI provided)	- 7.0%	26

treatment and bariatric surgery can only be performed in limited cases due to the safety risks and the high costs amount [12]. In this work, we reviewed the effects of most common non insulin anti-diabetic drugs with positive effects on body weight and body composition in overweight/obese T2D patients. Our results suggested that anti-diabetic drugs can be stratified into 3 groups based on their efficacy in weight loss: we considered a mild effect a weight loss less than 3.2% of initial weight, a moderate effect a weight loss between 3.2% and 5%, and a strong effect a weight loss greater than 5%. Out of the major four classes of anti-diabetic drugs, metformin acts on weight-loss both through its gastrointestinal side effects, through a central appetite suppressing effect and through its insulin-sensitizing effect [14,15]. Studies on metformin do not fully agree on the effect of the drug on body weight [5]. Most of the authors found a mild reduction in body weight (less than 3.2% of initial weight in all studies) with metformin [19,22], with the advantage that adding this hypoglycemic agent to insulin therapy may reduce its negative effect on weight [24–26] Acarbose causes a reduction in the intestinal absorption of glucose, thus inducing a reduction in the daily caloric intake, however, the effect of body weight is mild [30]. SGLT-2 I induce increased urinary glucose excretion in a dose-dependent manner and produce a statistically significant reduction in body weight. Weight-loss observed with SGLT-2i is mainly due to loss of fat versus lean mass, with slightly greater loss of visceral versus subcutaneous fat in patients with T2D [35]. The effect of SGLT-2 I on weight loss is moderate, excluded of empagliflozin which induces a mild weight reduction. GLP1-RA are the class of anti-diabetic agents that have shown the greatest benefit in terms of weight reduction. The effect on weight of these drugs was mild for exenatide and modest for dulaglutide, while was strong for liraglutide, the only GLP1-RA approved for obesity, and semaglutide [73]. The dual GIP and GLP-1 receptor agonist, LY3298176, is a promising therapy from the point of view of weight reduction too, showing a significantly better efficacy than dulaglutide. This drug has also shown an interesting effect on reducing the waist circumference [72].

In conclusion, among anti-diabetics the new drugs, in particular the new molecules of the GLP-1 RA class, are the most effective in inducing weight reduction in patients with T2D. In these patients, weight-loss, combined with other extraglycemic and extrapancreatic effects, has a positive impact on cardiovascular risk, with a consequent reduction in mortality and morbidity of the disease [74].

CRediT authorship contribution statement

Elisa Lazzaroni, **Laura Montefusco**, **Laura Plebani**, **Antonio Rossi**, **Ida Pastore:** Conceptualization, Methodology. **Elisa Lazzaroni**, **Elio Ippolito**, **Cristian Loretelli**, **Moufida Ben Nasr:** Writing – original draft. **Elisa Lazzaroni**, **Elena Lunati**, **Andrea Mario Bolla**, **Luciana Vallone:** Visualization. **Paolo Fiorina**, **Elisa Lazzaroni:** Investigation. **Paolo Fiorina:** Supervision, Validation. **Elisa Lazzaroni**, **Cesare Berra**, **Gian Vincenzo Zuccotti**, **Francesca D'Addio:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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