Impact of Newer Medications for Type 2 Diabetes on Body Weight

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Abstract Most patients with type 2 diabetes (T2DM) struggle with excess body weight. Many management strategies for achievement of euglycemia in T2DM are associated with weight gain, which worsens insulin resistance over time, increases health risk associated with obesity, and is associated with poor compliance with treatment. This review will discuss a host of new medications for management of hyperglycemia that have emerged and are emerging which are weight neutral, or facilitate weight loss. Incretin therapies are reviewed, including DPP-4 inhibitors which are weight neutral, and GLP-1 receptor agonists which can facilitate weight loss. SGLT-2 inhibitors, anticipated to become available soon, facilitate modest weight loss. Pramlintide can improve glycemic control and facilitate weight loss in T2DM patients on concomitant insulin therapy. The bile acid sequestering agent colesevelam, more recently approved for management of T2DM, modestly improves glycemic control and is weight neutral. The advent of these newer therapies makes it increasingly possible to optimize concomitant management of type 2 diabetes and obesity.

Keywords Type 2 diabetes mellitus · Obesity · Weight loss · Incretins · GLP-1 · Sodium glucose transporter 2 · Amylin · Liraglutide · Exenatide · Sitagliptin · Saxagliptin · Linagliptin · Vildagliptin · Dapagliflozin · Canagliflozin · Pramlintide · Colesevelam · Newer medications · Body weight

Introduction

There is a rising global prevalence of type 2 diabetes (T2DM), such that it has become one of today's most challenging health

issues. In the United States, it is estimated that 8.3 % of the population has T2DM, with an additional 35 % of American adults having prediabetes [1].

The rise in T2DM parallels the increasing prevalence of obesity, with 35.7 % of American adults being obese, and another 1/3 of adults being overweight [2]. Ninety percent of patients with T2DM are overweight or obese, and over 60 % of cases of type 2 diabetes can be attributed directly to excess body weight [3]. Outcomes are significantly worse in type 2 diabetic patients who are also obese, including an increased risk of cardiovascular disease and all-cause mortality of 44 % and 71 %, respectively [4].

Many management strategies that have traditionally been available for the management of hyperglycemia in T2DM have been accompanied by weight gain as an unwanted side effect [5•]. This creates a paradox in management, in that with weight gain, insulin resistance worsens, and while diabetes control may initially improve, the underlying insulin resistance progresses, potentially paving the way for an increased need for diabetes medications in the future [6]. Each 1 lb increase in body weight has been associated with a 2 % increased odds of progression of diabetes [7]. Patients' desire to avoid weight gain may also compromise compliance with treatment [8].

In the last several years, a host of new diabetes medications have emerged and are being developed to address this gap in diabetes care, designed to help to control hyperglycemia without causing weight gain. This review summarizes currently available and anticipated to soon become available treatment strategies for management of hyperglycemia in T2DM that do not result in weight gain (Table 1).

Traditional Antihyperglycemic Agents: Effect on Body Weight

Several traditionally available agents for the management of T2DM result in weight gain as an unwanted side effect. A

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Table 1 Newer agents for glycemic control in type 2 diabetes mellitus that do not cause weight gain

Medication class	Mechanism	A1C reduction	Typical effect on weight	Mode of administration
DPP 4 Inhibitors	prolongation of endogenous GLP-1 activity, leading to increased postprandial insulin release, glucagon suppression	−0.5 to −0.9 %	neutral	oral
GLP-1 Receptor Agonists	pharmacologic levels of GLP-1 activity, leading to increased postprandial insulin release, glucagon suppression, slowing of gastric emptying, central satiety stimulation	−0.8 % to −1.5 %	−3 kg to −5 kg weight loss	subcutaneous
SGLT-2 Inhibitors*	block renal glucose reabsorption	−0.5 to −0.8 %	−2 kg to −3 kg weight loss	oral
Pramlintide	pharmacologic levels of amylin activity, leading to suppression of glucagon, slowing of gastric emptying, central satiety stimulation	−0.5 % to −1.0 %	−1.5 kg weight loss	subcutaneous
Colesevelam	unclear; increased glycolytic disposal of oral glucose	−0.3 to −0.5 %	neutral	oral

*Not yet in clinical use

recent meta-analysis examining the effect of noninsulin anti-diabetic drugs added to metformin therapy in T2DM found the weight gain associated with use of sulfonylurea, glinide, and thiazolidinediones to be increased compared to placebo, at 2.06 kg, 1.77 kg, and 2.08 kg, respectively [9]. Insulin therapy is long known to be associated with weight gain [10]. Alpha glucosidase inhibitors have been found to be weight neutral [9] to −1.0 kg weight negative [11] in meta-analyses. Metformin, the recommended first line therapy for T2DM [12–14] is slightly weight negative, with trials reporting a weight loss ranging from −0.6 kg to −2.9 kg [15–17].

Insulin, sulfonylureas, and glinides are additionally associated with an increased risk of hypoglycemia [11], episodes of which require immediate correction with oral carbohydrate. These unwanted calories may represent one mechanism by which these agents cause weight gain.

Incretin Therapies

There are two main incretin hormones known in human physiology, namely, glucagon like peptide − 1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP), with GLP-1 having the predominant effects.

GLP-1 is a peptide that is released from the L cells of the small intestine in response to the entry of nutrients into the intestine [18] via neuroendocrine mediators (acetylcholine, gastrin-releasing peptide, and GIP), and also in response to direct intraluminal contact between ingested nutrients and GLP-1 secreting cells [19]. GLP-1 stimulates insulin release from the beta cells of the pancreas in response to a meal, and is thought to account for 50–70 % of postprandial insulin secretion. In addition, GLP-1 suppresses glucagon release from alpha cells of the pancreas [20]. The insulintropic and glucagon suppressive effects of GLP-1 are only active in the presence of hyperglycemia; the clinical implication of this is that incretin therapies do not cause hypoglycemia.

Further, GLP-1 slows gastric emptying [21], and also promotes satiety by stimulating the central satiety center in the paraventricular nucleus of the hypothalamus [22]. It is by these latter two mechanisms that incretin therapies do not induce weight gain, and in the case of GLP-1 receptor agonists, can induce weight loss.

In patients with type 2 diabetes, it has been demonstrated that GLP-1 levels are significantly reduced compared to healthy controls [23]. There is additionally an element of impairment of the beta cell insulin secretory response to GLP-1 in type 2 diabetics [24]. Incretin therapies have been developed as a treatment for type 2 diabetes, in an attempt to counteract these pathophysiologic disturbances in GLP-1 physiology. The incretin therapies can be categorized into two subgroups, namely, DPP-4 inhibitors, and GLP-1 receptor agonists.

DPP-4 Inhibitors

The dipeptidyl peptidase type 4 (DPP-4) inhibitors are molecules that work by delaying the degradation of endogenous GLP-1. Shortly after its secretion, endogenous GLP-1 is rapidly degraded by the DPP-4 enzyme [25], such that the half life of endogenous GLP-1 is approximately 1–1.5 minutes [26]. By slowing degradation of endogenous GLP-1, the DPP-4 inhibitors provide prolongation of physiologic levels of GLP-1.

There are currently four DPP-4 inhibitors that are being utilized in clinical practice (though approval of specific medications varies by country): sitagliptin, saxagliptin, linagliptin, and vildagliptin. They are taken orally once daily, with the exception of vildagliptin, which is taken once daily with sulfonylurea, but twice daily together with metformin [27].

The DPP-4 inhibitors are viewed as weight neutral medications [28•], as found in an extensive meta-analysis [9]. The A1C reduction seen with DPP-4 inhibitors is equivalent

to that seen with other oral agents, ranging from -0.6% to -1.1% [29]. Overall, there appears to be no difference in terms of A1C reduction nor change in body weight amongst the DPP-4 inhibitors. In a head-to-head trial of saxagliptin 5 mg daily vs sitagliptin 100 mg daily, body weight reduction was small but equivalent in both groups (-0.4 kg) after 18 weeks of treatment [30]. Studies of linagliptin and vildagliptin have also evidenced weight neutrality [31–33].

GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1 RAs) take advantage of the incretin system by providing exogenous GLP-1 by way of subcutaneous injection. As they provide supraphysiologic GLP-1 activity, they are more potent than DPP-4 inhibitors, both in terms of A1C reduction (though this varies by agent) and in terms of weight loss. In the early phases of treatment, nausea may be experienced due to the effect of slow gastric emptying; the proportion of patients who experience this side effect varies by agent, but does tend to improve with time for most patients. The weight loss seen with GLP-1 RAs is independent of the nausea effect in most cases, and the weight loss is sustained despite resolution of nausea symptoms.

Exenatide was the first of the GLP-1 RAs to come into clinical use, receiving approval from the FDA in 2005. Exenatide is synthetic exendin-4, a naturally occurring component of the saliva of the Gila monster, sharing 53 % homology with human GLP-1. It is resistant to endogenous degradation by DPP-IV, and therefore has a prolonged half life of 2.4 hours [34].

In addition to achieving an average 1.0 % A1C reduction in patients with T2DM [35], a sustained weight lowering effect has been shown. A 30 week study of exenatide vs placebo found a dose dependent decrease in A1C (-0.4% and -0.8% for 5 mcg and 10 mcg twice daily, respectively, vs $+0.08\%$ on placebo) and weight (-1.6 kg and -2.8 kg respectively, vs -0.3 kg on placebo) [36]. In a two year long term extension of this study, all patients were placed on exenatide treatment, and a weight loss averaging about -5.4 kg at two years was observed, and was found to be unlikely to be driven by nausea [37]. The weight loss seen with exenatide was dependent on the starting BMI, with greater weight loss seen with a higher starting BMI.

Exenatide therapy is administered subcutaneously at an initial dose of 5 mcg twice daily, given within 60 minutes before the morning and evening meal. The dose can be increased to 10 mcg twice daily if well tolerated after four weeks, if additional glycemic control is needed.

Liraglutide is a GLP-1 analog, sharing 97 % homology with human GLP-1, that has been modified to non-covalently bind to serum albumin via a lipid side chain, resulting in slower degradation by DPP-IV. Liraglutide has a half life of

13 hours, and is therefore dosed once daily without regard to meals. A rodent study suggests that the effect of liraglutide to slow gastric emptying is not sustained over time, and that regulation of appetite signals in the brain is the main mechanism for liraglutide induced weight loss [38]. In contrast, this study showed that gastric emptying is slowed for a longer period of time with exenatide, suggesting that this mechanism may be more important for exenatide's effect to reduce weight.

Weight data from seven phase 3 randomized trials in the liraglutide development program for T2DM were recently evaluated in a meta-analysis [39]. The estimated weight loss seen with liraglutide 1.2 mg and 1.8 mg vs placebo over 26 weeks was -0.78 kg and -1.2 kg , respectively. However, the estimated weight loss seen with liraglutide 1.2 mg and 1.8 mg vs active comparator was -2.7 kg and -3.2 kg , respectively. A higher initial BMI was associated with slightly greater weight loss, and mean weight loss was slightly larger the longer gastrointestinal side effects persisted. While patients experiencing a higher degree of weight loss generally had greater A1C reduction, A1C change did not demonstrate a clear correlation with the amount of weight lost.

In a six month randomized controlled trial comparing liraglutide 1.8 mg daily vs exenatide 10 μg twice daily, liraglutide was found to be superior in terms of A1C reduction (-1.1% and -0.8% , respectively), but there was no significant difference in terms of weight loss, with weight loss of -3.2 kg and -2.9 kg , respectively [40]. While the proportion of patients affected by nausea was initially similar between the two groups at approximately 15 %, the nausea resolved more quickly in the liraglutide group. At 26 weeks, 2.5 % of the liraglutide group had persistent nausea, compared with 8.6 % of the exenatide group.

Liraglutide therapy is commenced at a dose of 0.6 mg subcutaneously once daily; if well tolerated after one week, the dose is increased to 1.2 mg. After another week, the dose can be further increased to 1.8 mg daily; both 1.2 mg and 1.8 mg daily are considered therapeutic doses.

Exenatide q weekly (QW) is a once weekly preparation of exenatide, which utilizes biodegradable polymeric microspheres to provide an extended release at a controlled rate; steady state serum exenatide concentrations are achieved after 6–7 weeks of treatment [41]. In a 30 week study comparing exenatide weekly with twice daily exenatide, A1C reduction was superior on exenatide QW (-1.9% vs -1.5% for exenatide bid). Weight loss was not significantly different (-3.7 kg vs -3.6 kg , respectively), despite significantly less nausea being reported in the QW group (26 % vs 35 % respectively) [42]. Weight loss was observed in patients who reported no nausea throughout the trial (70 %) in both groups, though the weight loss seen was modestly greater in patients who reported at least one episode of nausea.

In an open label study of exenatide 2 mg QW versus liraglutide 1.8 mg, exenatide QW failed to meet noninferiority criteria for A1C reduction (-1.28 vs -1.48 %, respectively), and patients on exenatide had significantly less weight loss than those on liraglutide (-2.68 kg vs -3.58 kg, respectively) [43]. However, more patients in the liraglutide group discontinued the medication due to GI side effects (5.3 %) compared to exenatide QW (2.6 %).

Other GLP-1 RAs currently under development for the treatment of T2DM include once daily lixisenatide [44], and once weekly albiglutide [45] and semaglutide [46]. Patients utilizing GLP-1 RAs as part of their T2DM therapy have reported improved quality of life and satisfaction with treatment, particularly for the once daily and once weekly preparations [45, 47–49].

Combination Therapy with GLP-1 Receptor Agonists and Insulin

GLP-1 RAs can also improve glycemic control and facilitate weight loss (or minimize weight gain) in patients with T2DM on insulin therapy, a group in whom it is often quite difficult to effect weight loss due to the adipogenic qualities of insulin as well as the degree of insulin resistance manifested by these patients. A study compared the effect of adding exenatide twice daily vs placebo to patients on preexisting therapy with insulin glargine; insulin glargine was titrated to target glycemic control in both groups. After 30 weeks, a superior A1C reduction was seen with exenatide (-1.74 % vs -1.04 % in the placebo group), with an average insulin glargine dose increase of 13 units in the exenatide group compared to 20 units in the placebo group. Patients in the exenatide group lost -1.78 kg during the study, whereas patients in the placebo group gained $+0.96$ kg [50].

Liraglutide has also been studied in combination with insulin. A six month study was conducted, in which insulin detemir was added in a randomized fashion to T2DM patients who had not achieved A1C target of <7 % on metformin and 3 months of liraglutide (run-in phase), versus continuation without insulin detemir. After 26 weeks, weight decreased by -0.16 kg in the insulin group (in addition to -3.5 kg lost during the liraglutide run-in), vs -0.95 kg of weight loss without insulin detemir; A1C and body weight changes were sustained at 1 year [51, 52]. Thus, whereas insulin attenuated the liraglutide-induced weight loss to some extent, weight gain was not seen with addition of insulin therapy.

It is important to recognize that the efficacy of GLP-1 RAs to improve glycemic control in patients with T2DM on insulin is likely to depend in part on the amount of residual beta cell function. As one of the mechanisms by which GLP-1 RAs improve glycemic control is by stimulating

meal-induced insulin release, it follows that patients who require multiple dose intensive insulin therapy with basal and mealtime insulin are unlikely to have much endogenous beta cell function, and thus, this mechanism of GLP-1 RAs will not have a significant effect. However, the glucagon suppressive effect will still be relevant in these patients, and this, combined with the stimulation of satiety (inducing weight loss), can still have a significant impact to improve glycemic control, reduce insulin requirements, and facilitate weight loss in these patients.

Future Considerations: GLP-1 Receptor Agonists as Obesity Therapy?

Some GLP-1 RA analogs are currently under study as treatments for obesity in the absence of T2DM. In a randomized controlled, open label trial, different doses of liraglutide were compared to orlistat and placebo, in addition to a -500 kcal per day energy reduced diet and exercise counseling [53]. In the initial 20 weeks, a dose dependent response to liraglutide was seen, with -7.2 kg of weight loss on the highest dose of liraglutide of 3.0 mg, compared with -4.1 kg on orlistat and -2.8 kg on placebo. During an extension of the study to 1 year, patients on liraglutide 3.0 mg experienced an overall -5.8 kg placebo-subtracted weight loss, and -3.8 kg more than those on orlistat. This weight loss was predominantly body fat, with a -15.4 % decrease in body fat and a -2.0 % decrease in lean tissue being observed [54]. Mean change in waist circumference was also significantly greater with liraglutide 2.4/3.0 mg compared to orlistat. Higher doses of liraglutide were associated with more nausea compared to lower doses, but most were transient and of mild or moderate intensity. The weight loss seen after 1 year on liraglutide 3.0 mg was higher (-10.0 kg) for those with nausea and/or vomiting than those without (-7.1 kg), but weight loss without nausea/vomiting was still -4.2 kg greater than placebo and -2.3 kg greater than orlistat.

Following a 1 year extension of this study, all patients were then switched to 2.4 mg liraglutide, then 3.0 mg liraglutide (based on 20 week and 1 year results, respectively) [54]. At 2 years, patients on liraglutide 2.4/3.0 mg for the full duration of the study maintained a weight loss of -7.8 kg, and almost 70 % of liraglutide 2.4/3.0 mg patients maintained weight loss of >5 % of screening weight at year 2. In this study, prediabetes was reduced by 52 %, and improvement in other cardiovascular risk factors was also observed.

Exenatide has been studied in two smaller trials to date as an obesity therapy. One study showed -5.1 kg of weight loss on exenatide vs -1.6 kg on placebo after 26 weeks of treatment in addition to lifestyle intervention, with significantly greater normalization of prediabetes in the exenatide group (77 % and 56 %, respectively) [55]. Another study of

41 obese women, conducted in a double blind, placebo controlled crossover fashion demonstrated that 16 weeks of exenatide 10 mcg bid without any lifestyle intervention resulted in an average of -2.5 kg weight loss compared with -0.4 kg on placebo, as well as a significant decrease in waist circumference [56]. While nausea was seen more commonly on exenatide than on placebo, the severity of nausea decreased with time and did not correlate with weight loss.

No GLP-1 RA is currently approved for use as a weight loss agent.

SGLT-2 Inhibitors

Glucose reabsorption in the kidney is mediated by sodium glucose cotransporters (SGLT) located in the proximal tubules. There are two types of SGLT; SGLT2 is responsible for 98 % of renal glucose reabsorption, whereas SGLT1 is responsible for only 2 % [57]. An emerging class of oral medications, known as SGLT2 inhibitors, block SGLT2 mediated glucose reabsorption, resulting in iatrogenic glucosuria [58, 59••]. It is by this mechanism that SGLT-2 inhibitors improve glycemic control and result in modest weight loss.

The SGLT-2 inhibitor dapagliflozin is anticipated to be in clinical use soon in Europe, as the Committee for Medicinal Products for Human Use recommended the granting of a marketing authorization in April 2012 [60]. In a trial of dapagliflozin vs placebo, dapagliflozin at a dose 10 mg daily resulted in an HbA1C reduction of -0.84 % and a placebo-subtracted weight loss of -2.0 kg at six months [61]. In a one year trial comparing dapagliflozin to glipizide, a weight reduction of -3.2 kg was seen in the dapagliflozin group, while the glipizide group gained $+1.2$ kg, with no significant difference in A1C reduction (0.5 % in both groups), and a significantly lower risk of hypoglycemia in the dapagliflozin group (3.5 % vs 40.8 % in the glipizide group) [62].

Another study comparing dapagliflozin to placebo in patients with T2DM evaluated changes in body composition using dual energy x-ray absorptiometry (DXA) in each group. In addition to finding a placebo-subtracted weight loss of -2.08 kg over six months with dapagliflozin therapy, they found that about 2/3 of the weight loss observed with dapagliflozin was attributable to reductions in fat (with the other 1/3 being a loss of lean body mass), compared to the weight loss in the placebo group being half fat, and half lean mass [63].

Dapagliflozin has been studied in combination with insulin, with evidence to suggest that dapagliflozin can facilitate weight loss and improve glycemic control in these patients. A 26 week study evaluated the effect of adding dapagliflozin to patients on pre existing insulin therapy, compared with placebo [64]. Patients on dapagliflozin

10 mg experienced an A1C reduction (-0.57 %) compared with placebo group, despite a reduction in insulin requirement of -7 units compared to the placebo group. Body weight was reduced by -2.0 kg compared with placebo. An extension to this study is currently underway.

The American Food and Drug Administration (FDA) has not yet approved dapagliflozin, due to concerns regarding an increased incidence of breast and bladder cancers, as well as hepatotoxicity [65].

Canagliflozin, another SGLT-2 inhibitor currently under study, has been shown to provide similar improvements in glycemic control and weight reduction [66].

Pramlintide

Pramlintide is an analog of the hormone amylin, a peptide that is stored in pancreatic beta cells and co-secreted with insulin. Amylin is deficient in patients with type 1 diabetes, and low in patients with T2DM who are later in the natural history of the disease where beta cell function is relatively low, as evidenced clinically by the need for exogenous insulin therapy [67]. Amylin affects glycemic control via several mechanisms, including suppression of postprandial glucagon and slowing the rate of gastric emptying. The anorectic effect of amylin and the gastric emptying effects appear to be mediated by stimulation of the area postrema of the hindbrain [68]. Contrary to the actions of GLP-1, amylin does not increase postprandial insulin release.

Amongst type 2 diabetics, pramlintide has been shown to improve glycemic control as well as facilitate weight loss, with the largest weight reductions being observed in more obese patients [69]. A 16 week study of pramlintide vs placebo added to therapy in T2DM patients treated with basal insulin with or without oral agents showed that pramlintide resulted in a greater A1C reduction (-0.7 % vs -0.36 % on placebo) and significant weight loss (-1.6 kg vs $+0.7$ kg on placebo) [70]. In a 6 month study where T2DM patients with inadequate control on basal insulin with or without oral agents were randomized to the addition of mealtime insulin vs pramlintide, patients on pramlintide maintained weight while patients on mealtime insulin gained an average of $+4.7$ kg, with similar improvements in glycemic control in each group (-1.1 % and -1.3 % in the pramlintide and mealtime insulin groups, respectively) [71].

In the US, pramlintide is indicated for use in type 1 diabetics, and in type 2 diabetics who require mealtime insulin [72]. In type 2 diabetics, the recommended initial dose is 60 mcg administered subcutaneously with meals, titrated to 120 mcg as tolerated with meals. Mealtime insulin doses must be reduced with the initiation of pramlintide therapy to avoid insulin-induced

hypoglycemia. As pramlintide slows gastric emptying, nausea can occur with initiation of therapy, but this usually dissipates after 4 weeks of treatment. There are inadequate data to support the use of pramlintide with GLP-1 analog therapy in T2DM.

Pramlintide was under study with metreleptin as a combination therapy for the management of obesity, but this program was halted in 2011 [73].

Colesevelam

Colesevelam is a weight-neutral bile acid sequestering agent that lowers LDL cholesterol, which has also been shown to have a modest effect on glycemic control in T2DM, reducing A1C by -0.3 to -0.5 % [74–76]. Available for several years for management of dyslipidemia, colesevelam was approved for treatment of T2DM by the FDA in 2008 [77]. The mechanism by which colesevelam improves glycemia is unclear, but appears to involve increased glycolytic disposal of oral glucose without a change in endogenous glucose production [78].

Conclusions

With the advent of several new therapies in our toolbox to manage glycemia in type 2 diabetes, it is becoming increasingly possible to manage type 2 diabetes with less iatrogenic weight gain, or while simultaneously facilitating weight loss. Not only does this result in a lesser degree of insulin resistance over time, it also results in a lower risk of obesity-mediated health complications over time, with early evidence to suggest improved quality of life and therefore the potential for improved patient compliance with treatment. As the availability and use of these agents are anticipated to broaden in parallel with increasing knowledge and experience with these medications, it is anticipated that the optimal concomitant management of T2DM and obesity will continue to improve as well.

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Sanofi, BMS; has performed research studies of new DM or obesity medications for Novo Nordisk, Eli Lilly, Boehringer, Johnson&Johnson, Sanofi, BMS.

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