Combatting the dual burden: therapeutic targeting of common pathways in obesity and type 2 diabetes

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SHORT TITLE

Dual therapy of obesity and diabetes

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SUMMARY

The increasing prevalence of obesity markedly triggers the current epidemics of type 2 diabetes (T2DM). Abdominal adiposity, a feature of ectopic fat syndrome, is associated with silent inflammation, abnormal hormone secretion and various metabolic disturbances that

contribute to insulin resistance and insulin secretory defect, resulting in T2DM, and induce a toxic pattern leading to cardiovascular disease, liver pathologies and cancer. Despite the importance of weight control strategies in the prevention and management of T2DM, long-term results are generally disappointing with lifestyle or drug interventions. Furthermore, most of the classical glucose-lowering agents are accompanied by weight gain rendering even more challenging the management of most overweight/obese individuals with T2DM. Many anti-obesity pharmacological agents targeting central control of appetite were withdrawn from the market because of safety concern. The gastrointestinal lipase inhibitor orlistat remained the only anti-obesity medication available until the recent launch (US but not Europe) of phentermine-topiramate CR and lorcaserin. The recent better knowledge of bodyweight regulation opens new perspectives with the potential use of peptides derived from the gut or the adipose tissue. Most probably, combination therapy would be necessary to avoid compensatory mechanisms and potentiate initial weight loss while avoiding weight regain. New glucose-lowering therapies, especially glucagon-like peptide-1 receptor agonists and sodium glucose cotransporter-2 inhibitors, offer advantages over traditional antidiabetic agents by promoting weight loss while improving glucose control. . The present review will explore the overlapping pathophysiology and also how the various therapies can, alone or in combination, combat the 'dual burden' of obesity and T2DM.

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Key words: obesity, type 2 diabetes, body weight, glucose control, drug therapy, cardiovascular risk

Introduction

The dramatic rise of the twin epidemics, type 2 diabetes (T2DM) and obesity, is associated with increased mortality and morbidity and represents one of the most important public health challenges worldwide[1].T2DM is a complex disease where genetic and epigenetic factors interact with a toxic environment that promotes the development of obesity[2]. Environmental risk factors include the consumption of high-calorie, high-fat foods, inadequate physical activity and recently proposed alternative mechanisms (see panel), creating a chronic energy imbalance[3]. Especially abdominal adiposity is associated with markedly increasing risk for T2DM, and overall 80% of people with T2DM are overweight or obese. Striking parallel increases in the prevalence of obesity and T2DM reflect the importance of body fatness as a contributing factor to diabetes incidence and complications[4]. Furthermore, adipose tissue is as an active endocrine and immune organ whose dysfunction (adiposopathy or "sick fat") is promoted by excessive caloric balance. Thus, targeting adiposopathy and not only body weight excess should be considered as a main objective in the management of the obese patient with T2DM[5].

Both obesity and T2DM carry with them many medical complications, especially cardiovascular (CV) disease[6], substantially increasing global medical costs[1]. Aggressive treatment, in particular preventing weight gain and ideally facilitating weight reduction, can minimize and reduce diabetes-associated complications[7]. However, weight loss and maintenance are challenging in the obese population without diabetes, even more in obese people with T2DM[8].

The close link between T2DM and excess body weight highlights the need to consider the weight effects of different treatment regimens, besides their effects on glucose homeostasis[9]. A paradigm shift from a glucocentric to a weight-centric management of T2DM may be proposed, emphasising the urgent need for new treatment strategies[10, 11]. Some glucose-lowering drugs cause weight loss and some (albeit fewer) anti-obesity drugs improve glucose tolerance; thus, the present review will explore the overlapping pathophysiology of obesity and T2DM and also how the various therapies can, alone or in combination, combat the “dual burden”. We will focus on lifestyle and drug therapy, whereas the marked success of bariatric/metabolic surgery in combating the dual burden obesity-T2DM has been covered elsewhere[12].

Panel

Main contributors to the pathophysiology of obesity and T2DM

- *Genetic predisposition and unhealthy lifestyle (sedentarity. overeating)*
- *Adipose tissue dysfunction leading to ectopic fat deposition*
- *Excess visceral fat ("adiposopathy" associated with silent inflammation)*
- *Insulin resistance leading to β-cell burden and progressive B-cell dysfunction/defect*
- *Dysfunction in neurohumoral pathways (interrelationships between brain, endocrine pancreas, adipose tissue and gastrointestinal tract)*
- *Potential role of environmental pollutants*
- *Potential interference of intestinal microbiome*

Search strategy and selection criteria

We searched Medline, PubMed, the Cochrane library, and Google Scholar for mainly original research articles published between 1973 and November 2013, and focused on the dual treatment of obesity and T2DM. The main search terms used were "obesity", "type 2 diabetes", "glucose-lowering", "antidiabetic", "anti-obesity", "weight loss" We identified full-text papers without imposing any language restriction. Reference lists of original studies, narrative reviews and previous systematic reviews and meta-analyses were also carefully examined. Criteria used to include or exclude studies were randomised controlled trials and meta-analyses (see restrictions in the legends of the various tables).

Complex interplay between obesity and T2DM

Impact of weight changes on T2DM

The excess risk for diabetes with even modest weight gain is substantial and absolute weight gain throughout adulthood is a significant independent risk factor for T2DM[7]. Intentional weight loss is associated with reduced insulin resistance and a subsequent reduction in glucolipotoxicity, improving overall glucose homeostasis[4, 13]. In both the Finnish and US Diabetes Prevention Program (DPP), weight loss gradually reduces the risk of

diabetes, and even modest weight loss can significantly reduce the incidence of T2DM, an effect persisting in the long-term[14, 15]. In the recent Look AHEAD (Action for Health in Diabetes) trial in overweight/obese patients with T2DM, weight loss was greater in the intensive lifestyle intervention group than in the control group throughout the study, and this was accompanied by greater reductions in HbA1c, allowing a lower use of insulin in the intervention group than in the control group[16].

Impact of glucose control on body weight regulation

Reaching and maintaining acceptable body weight is more difficult in overweight/obese patients with T2DM[17]. Among other factors, hyperinsulinaemia may contribute to this phenomenon via the antilipolytic and anabolic effects of the hormone[8]. For a given weight loss during a very-low calorie diet, the decrease in adiposity per unit weight loss was attenuated in T2DM subjects, possibly due to the anti-lipolytic effect of hyperinsulinaemia[18.] Furthermore, improvement in glucose control results in decreased glucosuria and thereby limitation of energy wasting[8]. Thereby, losing weight and fat mass is challenging in patients with T2DM[7, 19].

While reduction of hyperglycaemia remains the foremost goal in the pharmacological treatment of T2DM, the avoidance of weight gain may be a clinically important secondary goal[20]. Except metformin, traditional glucose-lowering medications for T2DM (sulphonylureas, glitazones, insulin) can further increase weight in overweight/obese patients[21] and this may undermine the benefits of improved glycaemic control [7]. Even if a link between drug-induced weight gain and increased CV risk has not been established yet, pharmacological approaches that do not cause weight gain or promote weight loss, for example those that target the gut (incretin-based therapies)[22] or the kidneys (sodium glucose cotransporter-2 or SGLT-2 inhibitors)[23], may represent a valuable alternative in selected patients despite their higher cost [21].

Comorbidities shared and magnified by both obesity and diabetes

Adipose tissue releases many bioactive mediators that influence body weight homeostasis, insulin resistance, lipids, blood pressure, coagulation, fibrinolysis and inflammation, which together contribute to oxidative stress, endothelial dysfunction and atherosclerosis[6]. Therefore, obesity is not only a major risk factor for the development of T2DM but also predisposes individuals to co-morbidities including hypertension,

dyslipidaemia and sleep apnoea. Together, obesity and its comorbid conditions increase the risk for CV disease, the major cause of morbidity and mortality in T2DM [see below]. Conversely, moderate weight loss (>5% initial bodyweight), which has been associated with improvements in glycaemic parameters, also reduces the presence of other comorbidities, including dyslipidaemia and hypertension, culminating in a reduced risk of CV disease[24]. For all new medications developed as anti-obesity drugs (or as antidiabetic agents), their impact on CV risk factors (and ideally CV outcomes) is important to analyze, besides their specific weight-loss or glucose-lowering benefits[5].

Nonalcoholic fatty liver disease (NAFLD) is also commonly associated with (abdominal) adiposity, dyslipidaemia and insulin resistance. T2DM is an additional risk factor for progressive liver disease and liver-related death in patients with NAFLD. Nonalcoholic steatohepatitis (NASH) is present in approximately 10% of patients with T2DM and is associated with an increased risk for the development of cirrhosis, hepatocellular carcinoma and liver-related death[25].

There is a growing body of evidence to support a connection between T2DM, obesity and cancer[26]. Multiple meta-analyses of epidemiological data show that people with T2DM are at increased risk of developing many different types of cancers, along with an increased risk of cancer mortality. A number of common risk factors, including obesity, may be behind the association between diabetes and cancer. Abdominal adiposity, as part of the ectopic fat syndrome, has been shown to play a role in creating insulin resistance and a systemic pro-inflammatory environment, which could result in the development of both diabetes and cancer[26].

Obstructive sleep apnoea is a highly prevalent condition often associated with central obesity, which could contribute to worsen insulin resistance and lead to impaired glucose tolerance and T2DM[27]. Improvement of sleep apnoea with weight reduction can also improve insulin sensitivity and glucose profile.

As discussed, obesity is well known to worsen CV complications associated with diabetes [5, 6], but it may also be the case for microangiopathy. Obesity is an independent risk factor for kidney alterations, since it is associated with an increased risk of albuminuria and glomerulosclerosis, and worsens the course of chronic kidney disease[28]. T2DM persons with higher body mass index (BMI) and larger neck circumference are more likely to have diabetic

retinopathy and more severe stages of diabetic retinopathy[29]. Finally, CV autonomic neuropathy is common in persons with diabetes, and central obesity seems to play an important role in the early pathogenesis of this complication too[30].

Thus, targeting both obesity and diabetes will reduce the incidence and severity of most of these comorbid conditions, increasing patient's quality of life and lessening strain on health-care systems.

Pathophysiology and common therapeutic pathways

The common pathophysiology of obesity and T2DM is rather complex (Figure 1) and whether there is a "common soil", or whether obesity simply leads to T2DM, remains an open question. Genetic predisposition, epigenetic factors (programming in early life) and environmental exposure play a major role in the development of both obesity and T2DM[31, 32]. Even if epigenetic factors raised much interest in recent years, there is limited data to suggest that currently available interventions (lifestyle, drugs) may cause epigenetic modifications[32]. Overall, T2DM develops in obese people because of inadequate islet β-cell and adipose-tissue responses to chronic fuel excess, which results in so-called nutrient spillover, and metabolic stress that damages multiple organs[3, 13, 33]. Furthermore, environmental pollutants[34] and specific bacterial intestinal colonization[35] have recently been proposed as additional risk factors for obesity, β-cell dysfunction and T2DM development. Thus, reversal of overnutrition (contributing to weight loss), lessening of adipose tissue disturbances and protection/ healing of the β cells should be treatment priorities[5, 31].

Increasing evidence suggests that dysregulation in complex neurophysiological pathways (including hormonal secretions from adipocytes, pancreatic islets and the gastrointestinal tract) contributes to pathogenesis of obesity and T2DM (Figure 1). For instance, the neurohormonal control of body weight involves a complex interplay between long-term adiposity signals (e.g., leptin), and short-term satiation signals (e.g., amylin) [37]. The adipocyte-secreted leptin is known as a key appetite-regulating hormone, which effects on food intake, energy expenditure and behavior. Furthermore, leptin is not only a key player in controlling bodyweight but also affects the insulin-glucose axis. Dysfunction of the adipo-insular crosstalk plays a role in the development of hyperinsulinaemia and T2DM[36]. Amylin, an hormone co-secreted with insulin, exerts effects that complement those of insulin to regulate blood glucose concentrations, while it contributes to avoid weight gain and even promote weight loss[37]. Incretins, which are gut-derived hormones released in response to nutrient ingestion, may be perturbed in obesity and T2DM[38]. For example, glucagon-like

peptide-1 (GLP-1) can reduce food intake, via both central (hypothalamus) and peripheral (stomach) actions, but also markedly enhances insulin secretion, an effect that is essential in limiting postprandial hyperglycaemia[38]. These observations open new prospects for a better integrative management of obesity and T2DM[22].

Clinical challenges

The main clinical objectives in tackling the dual burden of obesity and T2DM may be : (i) in normoglycaemic overweight/obese patients, the primary prevention of T2DM, especially in patients at higher risk (those with impaired glucose tolerance for instance); (ii) in overweight/obese patients with T2DM, the reduction in bodyweight to facilitate glucose control (and reduce other risk factors) or at least avoid further weight gain; and (iii) the selection of effective treatments of both obesity and T2DM in the same patient while reducing associated CV risk factors and improving quality of life and life expectancy[19]. Similar to lifestyle changes, which positively influence both body weight and glucose control (Figure 2), other therapeutic interventions, especially pharmacological approaches, should ideally target both body weight and glucose regulation in an integrative approach[8, 19]. However, long-term head-to-head comparisons of the various treatment options on overall patient's prognosis are still lacking for most approaches. In particular, these is an urgent need for more data on young people, in whom the prevalence of obesity and type 2 diabetes is increasing.

Blood glucose control becomes increasingly challenging in the obese patient with T2DM after failure of metformin monotherapy (a glucose-lowering medication that does not induce weight gain or hypoglycaemia)[11, 19]. Attempts to reach fasting/postprandial glucose or glycated haemoglobin (HbA_{1c}) targets with other therapies can lead to a higher risk of hypoglycaemia and/or weight gain, which can worsen overall prognosis[8]. Fear of hypoglycaemia and/or weight gain might favour physician's therapeutic inertia and reduce patient's compliance, contributing to the fact that targets are largely unmet worldwide. Relatively recently developed incretin-based therapies now offer some benefits regarding both weight changes and risk of hypoglycaemia[22]. Nevertheless, additional new strategies with low risk of hypoglycaemia and weight gain (and if possible with some weight loss) should be developed to better control glucose; ideally, such strategies should also improve also other CV risk factors[10, 22].

Worsening trends in obesity and T2DM raise a serious conundrum : how can blood glucose, blood pressure, and lipids be controlled when so many antidiabetic agents cause weight gain and thereby exacerbate CV risk factors ? Thus, a clear need exists for clinicians to

understand the risks and benefits of different therapeutic options in order to minimize CV risk in obese patients with T2DM[11]. In the next sections, we discuss evidence underlying treatments for obesity and diabetes that can help to inform the clinician as to the most appropriate strategy (lifestyle, monotherapy, or combination therapy) for each individual patient.

Lifestyle intervention in the management of obesity and T2DM

Diet alone

Obesity is mainly caused by an excess of caloric intake in relation to energy expenditure[3] so its treatment should primarily focus on healthy diet and increased physical activity, especially in presence of T2DM (Figure 2)[39]. Implementing and maintaining the lifestyle changes associated with weight loss can, however, be challenging for many patients[24]. Various weight-loss strategies with follow-up for at least 6 months have been evaluated in people with T2DM with variable results[40].

Nutritional interventions are most effective in promoting initial weight loss. Furthermore, energy restriction will improve glycaemic control within days of initiation, independent of weight loss. However, the net improvement of glucose profile is usually small 1 year after weight loss. Very-low-calorie diets lead to better initial weight loss and glycaemic control but yield no better long-term results than more moderate energy restriction treatment. Weight loss seems to be mediated via changes in energy intakes rather than diet composition[41]. Similarly, diet composition has little effect on glycaemic control independent of total calories[40]. However, recent data suggest that prebiotic and probiotic approaches may target gut microbiome and thereby improve host metabolism[42].

Physical activity alone

Exercise training that consisted of aerobic exercise, resistance training, or both combined significantly reduced HbA1c in patients with T2DM[43], but no significantly greater change in BMI was found when exercise groups were compared with control groups. Importantly, BMI might not be a very relevant measure in exercise studies: exercise can increase muscle mass while decreasing fat mass (a good thing for patient health), such changes are not necessarily reflected by a change in BMI. In another study, a 12-week aerobic exercise programme, without hypocaloric diet, reduced visceral adipose tissue, an effect that may improve overall metabolic profile[44].

Diet and physical activity combination

Lifestyle combining healthy hypocaloric diet and physical activity is the mainstay of management to improve the metabolic profile of overweight/obese individuals with prediabetes or T2DM. The clinical effectiveness of such an approach has been established from randomised controlled trials (RCTs) of structured interventions[14, 15]. However, translation into routine practice has generally less effect on T2DM risk reduction[45]. In a meta-analysis of randomised controlled trials, HbA1c changes in patients with T2DM corresponded to those in bodyweight and both changes were overall rather small[46]. However, while the overall improvements are limited from a population standpoint, some individuals may achieve substantial improvements in multiple metabolic parameters.

It must also be mentioned that lifestyle might not be sufficient to reduce CV risk in patients with T2DM. The recent Look Ahead trial examined whether an intensive lifestyle intervention for weight loss would decrease CV morbidity and mortality among overweight/obese patients with T2DM. After a median follow-up of 9.6 years and despite significant improvements in bodyweight and various CV risk factors and a partial remission of T2DM[47], there was no difference in the primary outcome, a composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina[16]. An insufficient weight reduction in the intervention group versus the control group or progressive better medical management of CV risk factors in routine medical care might be possible explanations for the lack of significant difference in the rate of CV events between groups[16].

To date, no controlled study is available showing that lifestyle intervention alone is able to reduce the incidence and the severity of diabetes-related complications.

Anti-obesity agents with positive effects on diabetes

Although the obesity epidemic is constantly expanding at very high costs for health care systems, the currently available options for the pharmacotherapy of obesity are very limited because of a poor efficacy/safety profile of the majority of the antiobesity drugs developed up to now. Nevertheless, several antiobesity drugs have demonstrated potential in the prevention and management of T2DM[48, 49], although the long-term health benefits remain unclear.

Most medications used as anti-obesity agents were withdrawn because of safety issues[50]. Nevertheless these drugs supported the proof-of-concept that pharmacological

approaches to promote weight loss may contribute to improve blood glucose control and attenuate other CV risk factors in patients with T2DM, and that part of these metabolic effects occur independent of weight loss. This was first the case for fenfluramine and its stereoisomer dexfenfluramine although these drugs, mainly acting by releasing serotonin, were only evaluated in small-size short-term clinical trials in patients with T2DM,[48] and are not reviewed here.

In 2012, the US Food and Drug Administration (FDA) approved two new medications, lorcaserin and phentermine-topiramate ER, which may help in combating the dual burden of obesity and T2DM [24, 51]. However, these two medications did not receive approval from the European Medicine Agency (EMA) so that it seems that the overall political environment against anti-obesity drug therapy is different in the US and in Europe[52]. Although head-to-head comparison trials are not available, lorcaserin is likely less effective but better tolerated than phentermine/topiramate ER in obese patients with or without T2DM. CV outcome data will be invaluable in determining the place of both drugs in the therapy in overweight/obese patients with T2DM[53].

Sibutramine

Sibutramine inhibits the reuptake of both norepinephrine and serotonin. It induces dose-dependent weight loss in overweight/obese patients, with improvement of some CV risk factors, especially lipid profile (increased HDL cholesterol)[54] and glucose profile[55]. In obese subjects with T2DM[56], the reduction in bodyweight, waist circumference, fasting blood glucose and HbA_{1c} levels were significantly greater after sibutramine (10-20 mg/day) than after placebo (see references in Table 1, upper part). However, the overall effect size on HbA_{1c} was rather modest (-0.28% , 95% CI 0.13 to 0.42; P =0.0002), with some heterogeneity among studies[57]. Because sibutramine may increase heart rate and blood pressure, concern has been raised about its CV safety[58]. The Sibutramine Cardiovascular OUTcomes (SCOUT) trial in overweight/obese subjects with preexisting CV disease, T2DM, or both (84% with T2DM) showed a significantly higher risk of a primary CV outcome event in the sibutramine group than in the placebo group[59]. However, greater weight loss was associated with reduced overall CV risk in both groups[60].Sibutramine was withdrawn from the market due to an uncertain benefit-risk balance, even in patients with T2DM.

Rimonabant

Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves CV and metabolic risk factors in non-diabetic overweight/obese patients[61]. Rimonabant 20 mg/day produced a clinically meaningful reduction in bodyweight and improved HbA_{1c} and various CV and metabolic risk factors in patients with T2DM inadequately controlled with various glucose-lowering therapies (see references in table 1, lower part). In a pooled efficacy analysis, rimonabant produced weight loss and significant improvements in multiple cardiometabolic risk factors such as waist circumference, HbA_{1c}, HDL cholesterol, triglycerides and blood pressure, and some of these effects were partly independent of weight loss[62]. However, rimonabant increased the risk of psychiatric adverse events[63]. The CV outcome study CRESCENDO (Rimonabant for prevention of cardiovascular events) was stopped prematurely because of a higher risk of suicide in the rimonabant 20 mg group compared to placebo[64], leading to the withdrawal of the drug from the market.

Orlistat

Following the withdrawal of (dex)fenfluramine, rimonabant and sibutramine, orlistat, which acts via a peripheral rather than central mechanism, remains the only approved anti-obesity drug for long-term therapy in most countries. Orlistat, a gastrointestinal lipase inhibitor, has been evaluated in combination with a mildly reduced-calorie reduced-fat diet in overweight/obese patients with[49] or without T2DM[65]. Orlistat (120 mg 3x/day) has proven its efficacy and tolerability in 6-12-month placebo-controlled RCTs in overweight/obese patients with various background therapies (see references in Table 2). Orlistat is a useful adjunctive treatment for producing weight loss and reduction in waist circumference and improving glycaemic control, β-cell function and insulin resistance indices, serum lipid levels, inflammatory markers, and in some trials, blood pressure. More orlistat- than placebo-treated patients improved from diabetic status to normal or impaired glucose tolerance. In a 4-year RCT, orlistat plus lifestyle changes produced slightly greater weight loss and resulted in a greater reduction in the incidence of T2DM (hazard ratio : 0.627, 95% CI 0.455–0.863; P=0.0032) in obese patients, compared with lifestyle changes alone. The preventive effect was essentially explained by the difference in subjects with impaired glucose tolerance[66]. Orlistat tolerance profile is acceptable although mild to moderate, most often transient, gastrointestinal events were reported.

A retrospective analysis of pooled data suggested that orlistat improves glycaemic control more than would be predicted by weight loss alone[67], in agreement with an indirect

comparison between orlistat and sibutramine[57]. Postulated mechanisms underlying this intrinsinc effect of orlistat on glucose control include improvement of insulin sensitivity, incomplete digestion of dietary fat, reduction of postprandial plasma non-esterified fatty acids, decreased visceral adipose tissue, and partial stimulation of GLP-1 secretion[67].

Phentermine plus topiramate

Topiramate, a sulfamate-substituted monosaccharide whose complex mechanism of action remains poorly known, is approved as a treatment for migraine headaches, bipolar disease and seizure disorders. Although known to facilitate weight loss, an effect confirmed in RCTs in obese individuals[68], topiramate monotherapy does not have a regulatory indication as an anti-obesity agent. Nevertheless, RCTs investigated topiramate (96 mg or 192 mg/day) in overweight/obese patients with T2DM (see reference in Table 3). Topiramate significantly reduced bodyweight and HbA1c in a dose-dependent manner, with a HbA_{1c} reduction more than predicted from observed weight loss. However, topiramate 96 mg twice daily did not significantly increase insulin-stimulated glucose uptake, despite reductions in body weight, body fat and HbA_{1c} levels[69]. Using the new controlled release formulation of topiramate ER (extended release [ER]) confirmed significant reductions in bodyweight and HbA1c in patients with T2DM (Table 3). However, the central nervous system and psychiatric adverse event profile of topiramate makes it unsuitable for the treatment of obesity and T2DM as monotherapy.

Phentermine, a well known sympathomimetic amine acting as stimulant and appetite-suppressant, was combined with topiramate ER as a fixed-dose combination (FDC) to further decrease appetite and increase satiety[70]. Several RCTs demonstrated it to be effective in losing weight and improving adiposopathy-associated metabolic diseases, including dysglycaemia[71]. The efficacy and safety of two doses of phentermine plus topiramate ER combination (7.5 plus 46 mg and 15 plus 92 mg) as an adjunct to lifestyle for weight loss and metabolic risk reduction were assessed in individuals who were overweight/obese, with two or more risk factors (hypertension, dyslipidaemia, diabetes or prediabetes, or abdominal obesity)[72]. At 56 weeks, changes in bodyweight were significantly greater with both combinations than with placebo. The higher dose was associated with a slight increase in depression- and anxiety-related adverse events[72]. In a subanalysis, metformin-treated T2DM patients reported greater weight loss and reductions in HbA1c with both doses of phentermine plus topiramate than with placebo (Table 3). Among individuals without diabetes at baseline,

fewer patients progressed to T2DM ; the relative risk (*vs* placebo) was 0.78 (95% CI 0.40–1.50) with phentermine 7.5 mg plus topiramate 46 mg, and 0.47 (95% CI 0.25–0.88) with phentermine 15 mg plus topiramate 92 mg. These positive results were confirmed in a two-year extension period (see reference in Table 3). In subjects with T2DM at baseline, HbA1c did not change in the placebo group (despite net increases in glucose-lowering medications), whereas treatment with low and high strengths of the FDC led to significant HbA1c reductions (Table 3). In subjects without T2DM at baseline, the favourable effects of weight loss on insulin sensitivity and glycaemia were associated with decreased progression to T2DM (-54%, P=0.1514 with the lower dosage and -76%, P=0.0078 with the higher dosage) after 104 weeks. Finally, in overweight subjects with prediabetes and/or metabolic syndrome, phentermine plus topiramate ER produced significant weight loss and markedly reduced progression to T2DM, accompanied by improvements in multiple cardiometabolic disease risk factors[73].

Lorcaserin

Oral lorcaserin, a selective serotonin 5-HT2C receptor agonist resulting in decreased food intake and increased satiety, is indicated in the US as an adjunct to diet and exercise in the chronic weight management of obese (BMI ≥30 kg/m²) adults, or overweight (BMI ≥27 kg/m²) adults with at least one weight-related comorbidity (e.g. dyslipidaemia, hypertension, T2DM)[74]. In a systematic review and meta-analysis of one-year RCTs in obese adults, weight loss of 3.23 kg was observed with lorcaserin (10 mg once or twice daily) compared with placebo[75]. In comparison to placebo, lorcaserin decreased waist circumference, blood pressure, cholesterol and triglycerides, without affecting heart rate. Adverse events were headache, nausea and dizziness[74, 75].

The 1-year BLOOM-DM (Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus) study evaluated lorcaserin in T2DM patients treated with metformin, a sulfonylurea or both. Weight loss was amplified, more patients lost ≥5% bodyweight, while HbA1c and fasting glucose reductions were greater with the two doses of lorcaserin (10 mg once or twice daily) than with placebo (see reference in Table 3). Slightly more patients taking lorcaserin than placebo decreased the overall use of oral antidiabetic medications while fewer patients taking lorcaserin increased the total daily dose of glucose-lowering agents. Insulin resistance index was more markedly reduced with lorcaserin compared to placebo, but no significant between-group differences were observed

regarding lipid profile, blood pressure or inflammatory markers. Symptomatic hypoglycaemia occurred slightly more frequently with lorcaserin than with placebo.

Antidiabetic agents with positive effects on obesity

Pramlintide

Pramlintide is an analogue of the pancreatic hormone amylin, which is relatively deficient in patients with T2DM[37]. Through mechanisms similar to those of amylin, pramlintide (120-240 microg 3 times daily) improves overall glycaemic control and reduces bodyweight in patients with T2DM (Figure 3, Table 4). Besides reducing postprandial glucose levels, pramlintide treatment is also associated with improvements in markers of oxidative stress and CV risk. Pramlintide has been shown to increase satiety and, therefore, decrease caloric intake via a central mechanism[37]. It is generally well tolerated, with the most frequent treatment-emergent adverse event being transient nausea.

Preliminary trials assessing the use of pramlintide for weight loss in obese patients without diabetes have demonstrated weight loss of up to 8 kg after 1 year. However, current trials were limited by inconsistent study design, dosing, and patient population[76]. Newer research is focusing on weight loss effects with a combined peptide approach in obese individuals (see below)[37, 77].

GLP-1 receptor agonists and DPP-4 inhibitors

Incretin-based therapies exploit the insulinotropic actions of GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 for the treatment of T2DM (Figure 3, Table 4). They include GLP-1 receptor agonists (GLP-1RAs) and inhibitors of dipeptidyl peptidase-4 (DPP-4), the enzyme that inactivates these two incretin hormones in the body[38]. Weight neutrality of DPP-4 inhibitors (also called gliptins) while improving glucose control[78] may be an advantage in the management of overweight/obese patients with T2DM compared with other glucose-lowering agents known to promote weight gain (see above)[21]. Furthermore, these new compounds do not expose patients to hypoglycaemia (except when added to insulin or sulphonylureas)[78] and may also exert favourable effects on various CV risk factors[79]. Similar positive effects are observed with GLP-1RAs[80] , with the add-on value of promoting weight loss in obese patients with T2DM[22]. Furthermore, GLP-1RA effects on bodyweight are also apparent in non-diabetic obese individuals, offering a potential for use in the treatment of obesity[81].

According to a systematic review of RCTs in overweight/obese patients with or without T2DM, treatment with GLP-1RAs (as monotherapy or combination therapy : exenatide twice daily, exenatide once weekly, or liraglutide once daily) results in greater weight loss than control groups (placebo, oral antidiabetic drugs, or insulin). Weight loss was recorded in the GLP-1RA groups for patients with diabetes (-2.8 kg, 95% CI -3.4 to -2.3) and without diabetes (-3.2 kg, 95% CI -4.3 to -2.1). In T2DM patients, GLP-1RAs had beneficial effects on blood pressure, plasma cholesterol, and glycaemic control (see reference in Table 4). GLP-1RAs were associated with nausea, diarrhoea, and vomiting, a slight increase in pulse rate, but not with hypoglycaemia. In a post-hoc analysis of 26-week data from seven RCTs assessing liraglutide (1.2-1.8 mg once daily) in T2DM, liraglutide-treated subjects experienced additional HbA1c reduction beyond that which induced by weight loss[82].

In patients with T2DM not well controlled on oral glucose-lowering therapies (mainly metformin and/or sulfonylurea) and compared with insulin glargine[83], the addition of GLP-1RAs showed almost similar (or better) blood glucose control but with a lower incidence of hypoglycaemia and less weight gain (conversely a significant weight loss was recorded). The combination of a GLP-1RA (mainly targeting postprandial hyperglycaemia) and basal insulin (mainly targeting fasting hyperglycaemia) may also be highly effective for optimal glucose control, while limiting weight gain, an adverse effect typically associated with insulin therapy in patients with T2DM[84].

Liraglutide[85, 86] appears also to have promising effects on bodyweight in overweight/obese adults without T2DM. Monotherapy with liraglutide at a higher dose of 2.4-3.0 mg once a day induced significant and sustained weight loss, improved certain obesity-related risk factors (especially blood pressure), and reduced the incidence of prediabetes and metabolic syndrome over 1-2 years[85, 86]. Of interest, results were more favourable with liraglutide than with orlistat (120 mg three times a day orally) used as an active comparator.

Several studies investigated whether weight loss with GLP-1RAs corresponds to fat loss and which mechanisms might be implicated (see references in Table 5). Overall, studies demonstrated significant reductions in waist circumference, total fat and visceral fat, proportional to weight loss; this effect resulted from decreased appetite and reduced energy intake (with some changes in food preference), with almost no or only a slight increase in energy expenditure.

Finally, GLP-1RAs were shown to improve various CV risk factors in overweight/obese T2DM patients, especially blood pressure, postprandial lipid profile,

endothelial dysfunction, inflammatory markers and oxidative stress[80]. All these pleiotropic effects may lead to improvement in CV prognosis, although this hypothesis remained to be confirmed in ongoing large prospective RCTs[80].

SGLT-2 inhibitors

SGLT-2 inhibitors (dapagliflozin, canagliflozin, empagliflozin) increase glucose excretion, independent of insulin secretion or action, by inhibiting the renal reabsorption of glucose[87]. Dapagliflozin (5 or 10 mg) has been approved in Europe for the treatment of T2DM as an adjunct to diet and exercise, in combination with other glucose-lowering medicinal products, including insulin, and as a monotherapy for metformin-intolerant patients[88] while canagliflozin was approved by the US Food and Drug Administration in April 2013 and is undergoing evaluation by the European Medicines Agency[89]. Other SGLT-2 inhibitors (especially empagliflozin) are currently in late phase of clinical development.

In patients with T2DM, SGLT-2 inhibitors reduced HbA1c (-0.5% to -1.5%) when used as either monotherapy or combined therapy with any other glucose-lowering agent, including insulin, with a weight loss of up to 3 kg (Figure 3) and a low incidence of hypoglycaemia. Cardiometabolic benefits included a reduction in systolic blood pressure and triglycerides (see reference in Table 4). Because of side effects (urinary tract and genital infections), a potential risk of dehydration (elderly patients on diuretics) and a reduced glucose-lowering activity in subjects with renal impairment, appropriate patient selection and close monitoring will be important. Further clinical studies should demonstrate the effect of SGLT-2 inhibitors on diabetic complications and CV events as well as their long-term tolerability/safety profile.

So far, SGLT-2 inhibitors are the only oral glucose-lowering agents also promoting significant weight loss[23]. Dapagliflozin induced weight loss, predominantly by reducing fat mass, visceral and subcutaneous adipose tissue in patients with T2DM inadequately controlled with metformin[90]. Experimental data in rodents suggested, however, that the persistent urinary glucose excretion induced by dapagliflozin was accompanied by compensatory hyperphagia[91]. These animal observations are in agreement with findings in humans showing a lower weight loss than that predicted by the recurrent waste of calorie through sustained increased glucosuria. Therefore, gliflozin-induced weight loss might also require dietary intervention or other adjunct therapies limiting food intake.

The future for pharmacology of T2D and obesity

Novel pharmacological therapies are currently under investigation as potential treatments for obesity and T2DM[50]. There are two main avenues of investigation: the first targets the central nervous system to reduce food intake (with drugs including naltrexone plus bupropion, tesofensine and zonisamide) but again with the risk of frequent adverse events[92]; the second is more innovative and targets complex interrelated hormonal pathways (brain, gut, adipose tissue) involved in weight regulation and glucose homeostasis (Figure 1)[93, 94].

Naltrexone sustained release plus bupropion sustained release

The efficacy of current centrally-acting obesity pharmacotherapies is limited by compensatory mechanisms that mitigate weight loss and by potential side effects, paving the route for combined therapies. Opioid receptor antagonism (naltrexone) plus pro-opiomelanocortin activation (bupropion) causes greater weight loss than monotherapy with either agent or placebo[95], an effect confirmed in overweight/obese patients with comorbid T2DM, hypertension or hyperlipidaemia[96, 97]. Overall, placebo-subtracted mean weight loss averaged 4.7% (range 3.2-5.2%) with naltrexone/bupropion after 1 year, with a higher proportion of patients achieving ≥5-10% weight loss and improvement of waist circumference, triglycerides, high-density lipoprotein, fasting insulin, and insulin resistance compared with placebo. Reductions in body fat mass and visceral adipose tissue were proportional with weight loss[98]. In patients with T2DM, naltrexone/bupropion therapy significantly decreased HbA1c 0.5% more than placebo (see reference in Table 3). Because systolic blood pressure and pulse rate were higher compared with placebo, further studies are necessary to determine the effect of naltrexone/bupropion on CV outcomes. It is not approved as an anti-obesity therapy yet[99].

Leptin and leptin-related synthetic peptide analogues

Leptin not only controls food intake and energy expenditure, but also modulates the insulin-glucose axis[36]. Consequently, leptin replacement therapy raised hope in obesity and T2DM[100]. Unfortunately, results with recombinant human leptin were rather disappointing, especially in overweight/obese patients with T2DM[101]. Metreleptin, an analogue of human leptin, improved insulin sensitivity, hypertriglyceridaemia and hyperglycaemia in patients with lipodystrophy[102]. In obese patients with T2DM, however, metreleptin did not alter body weight or circulating inflammatory markers and reduced HbA1c only marginally[103]. New

approaches in the development of anti-obesity and anti-diabetes pharmacophores are now focused on utilizing leptin-related synthetic peptides as leptin receptor antagonists or leptin-related synthetic peptide analogues or mimetics[104].

Peptide hormone combination therapies

Experimental data suggest that leptin and amylin, two hormones involved in satiation control (see above), have additive effects[105]. In a proof-of-concept RCT in overweight/obese subjects, combination treatment with pramlintide/metreleptin led to significantly, early and sustained, greater weight loss than treatment with pramlintide or metreleptin alone. Although pramlintide/metreleptin combination was promising as novel, integrated neurohormonal approach to obesity pharmacotherapy with or without T2DM[106, 107], the latest RCT was recently stopped due to safety concerns[108].

Finally, instead of using two or more agonists for the treatment of obesity and T2DM, another promising option may be the use of single co-agonists. As examples, GLP-1-glucagon and GLP-1-amylin co-agonists may be of potential interest[109]. Although substantial progress has been achieved in preclinical studies, the putative success and safety of co-agonist therapy for the treatment of patients with obesity and T2DM remains uncertain and requires extensive additional clinical validation[110]. Another potential future option is a SGLT-2 inhibitor/GLP1-RA combination in an attempt to weaken the compensatory "overeating" mechanism observed with SGLT-2 inhibition[91].

Conclusion

The management of the obese diabetic patient remains challenging, but, in any case, weight reduction should be considered as a key objective. Lifestyle intervention to lose weight is recommended in most T2DM patients to improve glycaemic control and reduce associated risk factors for complications. Even modest weight loss can significantly improve glucose homeostasis and lessen cardiometabolic risk factors, although achieving and especially maintaining 5-10% weight reduction remains difficult for many patients, and these surrogate endpoints are not always strengthened by hard outcome data. There is a growing concern that the weight gain induced by some diabetes medications diminishes their clinical benefits. New glucose-lowering agents (incretin-based therapies, SGLT-2 inhibitors) are associated with some weight reduction and improvement of various CV risk factors.

However, the long-term benefit-risk profile of these new compounds remains to be determined in large prospective studies. Finally, the place of anti-obesity agents in the management of overweight/obese patients with T2DM was limited by rather poor efficacy and safety concern. A better understanding of weight-regulating mechanisms has led to the identification of new targets for anti-obesity agents. Especially, peptide hormones control body weight and glucose homeostasis by engaging peripheral and central metabolic signalling pathways responsible for the maintenance of body weight and euglycaemia. Notably, therapeutic attempts to normalize body weight and glycaemia with single agents alone have generally been disappointing paving the route for using combined therapies in the future.

Individualized therapy in the management patients with T2DM will become increasingly important with (and perhaps a consequence of) the increasing number of drugs available and the presence of obesity may certainly influence the physician's choice of the best pharmacological approach.

Author contributions

Both authors contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafted or revised the paper; and approved the final version to be published.

Conflict of interest statement

The Authors declare no conflict of interest.
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Figure 1 : Illustration of the complex pathophysiology of obesity and T2DM, involving genetics, epigenetics and environment burdens interfering with various target organs that are interconnected via complex hormonal pathways (↔) . GLP-1 : glucagon-like peptide-1. GIP : glucose-dependent insulinotropic polypeptide. NEFA : non esterified fatty acids.

Figure 2 : Main mechanisms controlling bodyweight (upper panel A) and blood glucose (lower panel B) and crucial role of lifestyle (before considering pharmacological interventions : see figure 2). Bodyweight changes influence glucose control while glucose control may influence bodyweight changes in patients with type 2 diabetes. Besides lifestyle, genetics may also play a role in controlling appetite and energy expenditure (resting metabolic rate, thermogenesis, energy metabolism).

Figure 3 : Multiple pharmacological approaches used to control hyperglycaemia in type 2 diabetes with special focus on drug's effect on bodyweight. (*) Modest effect. GLP-1 RA : glucagon-like peptide-1 receptor agonist. DPP-4 : dipeptidyl peptidase-4 inhibitor. SGLT-2 : sodium glucose cotransporter-2.

Table 1 : Mean effects of sibutramine and rimonabant on bodyweight, HbA1c, fasting plasma glucose, blood pressure and total cholesterol in placebo-controlled trials in overweight/obese patients with T2DM. Only trials that randomised at least 50 patients per arm with a follow-up of at least 16 weeks were considered (no such trials were reported with fenfluramine./dexfenfluramine). * References available in appendix. $ p-value < 0.05 compared with placebo or control. **[A: without p values or CIs, it is not possible for the reader to determine which trials showed a real difference between groups. Thus, for columns highlighted here and in other tables, please note which differences were significant, perhaps just by applying a symbol. I added as example for weight, but please confirm the additions are correct.]**

References*	Back-ground therapy	Duration Weeks	Drug : N	BMI kg/m²	BW kg	Δ Weight kg	HbA1c %	Δ HbA1c %	FPG mmol/l	Δ FPG mmol/l	Δ SBP/DBP mmHg	Δ [OK?]Total cholesterol mmol/l
SIBUTRAMINE												
Kaukua et al 2004[111]	Diet	52	Pbo : 122 Sibu 15 mg : 114	35.6 35.7	98.1 100.8	- 2.6 - 7.1$	NA NA	+ 0.3 - 0.2	NA NA	NA NA	+ 4.1/- 0.2 + 3.6/+ 1.7	NA NA
Serrano-Rios et al 2002[112]	SU	26	Pbo : 65 Sibu 15 mg : 69	37.3 35.5	94.2 92.0	- 1.7 - 4.5$	9.5 9.0	- 0.68 - 0.78	9.9 9.3	- 0.3 - 0.8	+ 0.5/NA - 1.1/NA	0 + 0.1
McNulty et al 2003[113]	Metformin	52	Pbo : 64 Sibu 15 mg : 68 Sibu 20 mg : 62	36.2 36.3 37.5	100.7 103.5 104.3	- 0.2 - 5.5$ - 8.0$	9.73 9.75 9.14	- 0.22 - 0.56 - 0.32	9.1 9.5 9.2	+ 0.2 - 0.3 - 0.1	- 0.2/+ 0.5 + 4.4/+ 3.3 - 1.5/+ 0.4	- 0.2 - 0.1 0
Fujioka et al 2000[114]	Met/SU	24	Pbo : 86 Sibu 5-20 mg : 89	33.8 34.1	98.2 99.3	- 0.4 - 3.7$	8.3 8.4	+ 0.27 + 0.17	9.9 10.2	+ 1.0 + 0.6	+ 2.4/+ 1.4 + 3.9/+ 2.6	+ 0.09 + 0.13
RIMONABANT												
Rosenstock et al 2008[115]	Diet	26	Pbo : 140 Rimo 20 mg : 138	34.6 34.4	96.3 96.6	- 2.8 - 6.7$	7.9 7.9	- 0.3 - 0.8	8.7 9.0	+ 0.1 - 0.9	NA/NA NA/NA	+ 0.10 - 0.08

Scheen et al 2006[116]	Met or SU	52	Pbo : 348 Rimo 20 mg : 339	34.2 34.1	96.0 95.7	- 1.4 - 5.3$	7.2 7.3	+ 0.10 - 0.60	8.2 8.5	+ 0.33 - 0.64	+ 1.6/- 0.7 - 0.8/- 1.9	+ 0.10 + 0.04
Hollander et al 2010[117]	Insulin	48	Pbo : 187 Rimo 20 mg : 179	34.25 34.98	95.3 97.6	+ 0.13 - 2.49$	9.12 9.13	- 0.24 - 0.89	11.03 11.40	- 0.63 - 1.85	NA/NA NA/NA	+ 0.02 + 0.11

SU : sulphonylurea. Met : metformin. Pbo : placebo. Sibu : sibutramine. Rimo : rimonabant. BMI : body mass index. BW : body weight. HbA1c : glycated haemoglobin. FPG : fasting plasma glucose. SBP : systolic blood pressure. DBP : diastolic blood pressure. Δ : change versus baseline. NA : not available.

Table 2 : Mean effects of orlistat (120 mg 3x/day) on bodyweight, HbA1c, fasting plasma glucose, blood pressure and total cholesterol in placebo-controlled trials in overweight/obese patients with T2DM. Note that orlistat treatment reduced the requirement for anti-diabetic medication more than placebo. Only trials that randomised at least 50 patients per arm with a follow-up of at least 16 weeks were considered. * References available in appendix.

References*	**Back-ground therapy**	**Duration Weeks**	**N**	**BMI kg/m²**	**BW kg**	**Δ Weight kg**	**HbA1c %**	**Δ HbA1c %**	**FPG mmol/l**	**Δ FPG mmol/l**	**Δ SBP/DBP mmHg**	**Δ Total cholesterol mmol/l**
Shi et al 2005[118]	Newly diagnosed	24	P : 124 O : 125	NA NA	78.7 79.4	- 2.4 - 5.4	7.3 7.3	- 0.6 - 1.0	8.0 8.1	- 0.5 - 1.3	- 3.8/- 3.5 - 5.6/- 3.7	+ 1.20 - 6.50
Halpern et al 2003[119]	Diet	24	P : 174 O : 164	34.5 34.6	89.5 89.7	- 2.58 - 4.24	8.49 8.37	- 0.22 - 0.61	11.50 11.05	- 0.01 - 1.00	NA/NA NA/NA	- 0.03 - 0.40
Hollander et al 1998[120]	SU	57	P : 159 O: 162	34.0 34.5	99.7 99.6	- 4.31 - 6.19	8.20 8.05	+ 0.18 - 0.28	9.09 8.85	+ 0.54 - 0.02	NA/NA NA/NA	+ 0.39 - 0.08
Miles et al 2002[121]	Metformin	52	P : 254 O : 249	35.2 35.6	101.1 102.1	- 1.8 - 4.7	8.79 8.87	- 0.41 - 0.75	11.1 11.6	- 0.7 - 2.0	- 0.4/NA - 2.1/NA	+ 0.06 - 0.27
Berne et al 2005[122]	Met or Met + SU	52	P : 109 O : 111	32.9 32.6	95.7 95.3	- 1.7 - 4.8	7.6 7.6	- 0.2 - 1.1	10.9 11.2	- 0.3 - 1.9	- 3.1/- 1.9 - 3.2/- 2.4	+ 0.10 - 0.20
Kelley et al 2002[123]	Insulin (± Met/SU)	52	P : 269 O: 266	35.6 35.8	101.8 102.0	- 1.27 - 3.89	8.99 9.01	- 0.27 - 0.62	11.16 10.91	- 1.08 - 1.63	- 0.9/- 1.0 - 1.2/- 2.3	+ 0.08 - 0.30

SU : sulphonylurea. Met : metformin. P : placebo. O : orlistat. BMI : body mass index. BW : body weight. HbA1c : glycated haemoglobin. FPG : fasting plasma glucose. SBP : systolic blood pressure. DBP : diastolic blood pressure. Δ : change versus baseline. NA : not available.

Table 3 : Mean effects of topiramate, topiramate/phentermine, lorcaserin and naltrexone/bupropion on bodyweight, HbA1c, fasting plasma glucose, blood pressure and total cholesterol with T2DM in placebo-controlled trials in overweight/obese patients. Only trials that randomised at least 50 patients per arm with a follow-up of at least 16 weeks were considered. * References available in appendix.

References*	Back-ground therapy	Duration Weeks	Drug : N	BMI kg/m²	BW kg	Δ Weight kg	HbA1c %	Δ HbA1c %	FPG mmol/l	Δ FPG mmol/l	Δ SBP/DBP mmHg	Δ Total cholesterol mmol/l
TOPIRAMATE												
Stenlof et al 2007[124]	Diet	40	Pbo : 78 Topi 96 mg : 74 Topi 192 mg : 77	36.1 36.2 35.6	104.1 104.9 101.9	- 2.6 - 6.9 - 9.3	6.7 6.9 6.8	- 0.2 - 0.6 - 0.7	7.8 8.0 7.7	0 - 0.9 - 1.0	- 2.0/+ 0.8 - 6.3/- 3.3 - 7.6/- 3.2	NA NA NA
Toplak et al 2007[125]	Metformin	24	Pbo : 208 Topi 96 mg : 219 Topi 192 mg : 213	36.6 36.2 36.0	103.2 102.4 99.4	- 1.8 - 4.6 - 6.5	7.3 7.1 7.1	- 0.1 - 0.4 - 0.6	8.8 8.6 8.7	+ 0.11 - 0.45 - 0.92	- 0.4/- 0.4 - 4.8/- 1.4 - 4.4/- 1.4	+ 0.22 + 0.16 + 0.10
Rosenstock et al 2007[126]	Diet ± Met	16	Pbo : 57 Topi CR 175 mg : 54	37.7 38.1	109.7 106.0	- 2.5 - 6.0	7.4 7.6	- 0.4 - 0.9	9.2 9.3	- 0.6 - 1.9	- 4.2/- 1.6 - 10.2/- 5.3	- 0.08 - 0.32
Gadde et al 2011[127] **(**)**	Diet ± Met	56	Pbo : 157 Topi 46 mg + Phen 75 mg : 67 Topi 92 mg + Phen 15 mg : 164	NA NA NA	NA NA NA	- 1.9 (*) - 6.8(*) - 8.8(*)	6.8 6.8 6.8	- 0.1 - 0.4 - 0.4	7.6 7.5 7.3	- 0.31 - 0.54 - 0.66	NA/NA NA/NA NA/NA	NA NA NA
LORCASERIN												
O'Neil et al 2012[128]	Met and/or SU	52	Pbo : 248 Lorca 2 x 10 mg : 251 Lorca 1 x 10 mg : 96	35.9 36.1 36.1	102.3 103.5 106.1	- 1.6 - 4.5 - 4.7	8.0 8.1 8.1	- 0.4 - 0.9 - 1.0	8.89 9.09 8.77	- 0.66 - 1.52 - 1.58	- 0.9/- 0.7 - 0.8/- 1.1 + 0.6/+ 0.3	NA NA NA

NALTREXONE/BUPROPION												
Hollander et al 2010[129]	Any OAD	56	Pbo : 159 Nal/Bup : 265	36.0 36.0	105.0 106.4	- 1.9 - 5.3	7.99 7.97	- 0.14 - 0.63	9.11 8.89	- 0.22 - 0.66	NA/NA NA/NA	NA NA

(*) Change expressed in % of initial body weight instead of kg. (**) Analysis in a subgroup of patients with T2DM

SU : sulphonylurea. Met : metformin. OAD : oral antidiabetic drug. Pbo : placebo. Topi : topiramate. Phen : phentermine. Lorca : lorcaserin. Nal/Bup : naltrexone/bupropion. BMI : body mass index. BW : body weight. HbA1c : glycated haemoglobin. FPG : fasting plasma glucose. SBP : systolic blood pressure. DBP : diastolic blood pressure. Δ : change versus baseline. NA : not available.

Table 4 : Meta-analyses of randomised controlled trials with pramlintide, GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors in patients with T2DM : Mean effects on bodyweight, HbA1c, fasting plasma glucose, blood pressure and total cholesterol. Results are expressed as weighted mean differences versus placebo (95% confidence intervals). Results reported with the anti-obesity agent orlistat (the only anti-obesity drug available worldwide) are shown for the purpose of comparison. * References available in appendix.

Drug References*	**Trials N**	**Patients N**	**Δ Body Weight kg**	**Δ HbA1c %**	**Δ FPG mmol/l**	**Δ SBP mmHg**	**Δ DBP mmHg**	**Δ Total cholesterol mmol/l**
Anti-obesity agent								
ORLISTAT Norris et al 2005[49]	4	904	- 2.64 (- 3.17, - 2.11)	- 0.38 (- 0.51, - 0.25)	- 0.86 (- 1.32, - 0.40)	- 1.11 (- 2.91, + 0.69)	- 1.30 (- 2.99, + 0.39)	- 0.37 (- 0.47, - 0.29)
Glucose-lowering agents								
PRAMLINTIDE Sing-Franco et al 2011[130]	5	930	- 2.57 (- 3.44, - 1.70)	- 0.33 (- 0.51, - 0.14)	- 0.35 (- 1.39, + 0.68)	NA	NA	NA
GLP-1RAs Vilsboll et al 2012[131]	25 (22 in T2DM)	6411 (5817)	- 2.90 (- 3.59, - 2.22)	- 0.63 (- 0.80, - 0.46)	- 1.32 (- 1.35, - 1.29)	- 3.57 (- 5.49, - 1.66)	- 1.38 (- 2.02, - 0.73)	- 0.10 (- 0.16, - 0.04)
DPP-4 INHIBITORS Kim et al 2013[132]	57	17 191	+ 0.52 (0.37, 0.67)	- 0.72 (- 0.77, - 0.67)	- 1.08 (- 1.18, - 0.98)	NA	NA	NA
Monami et al 2013[133]	70	41 959	NA	- 0.40 (- 0.5, - 0.3)	NA	- 0.1 (- 1.2, + 1.8)	NA	- 0.28 (- 0.46, - 0.10)
SGLT-2 INHIBITORS	13	4063	- 1.17 (*)	- 0.52	- 1.02	- 4.08	- 1.16	NA

Musso et al 2012[134]			(- 1.41, - 0.92)	(- 0.46, - 0.57)	(- 1.15, - 0.88)	(- 4.91, - 3.24)	(- 1.67, - 0.66)	

(*) Change expressed as percentage of initial body mass index

GLP-1 RA : glucagon-like peptide-1 receptor agonist. DPP-4 : dipeptidyl peptidase-4 inhibitor. SGLT-2 : sodium glucose cotransporter-2. BW : body weight. HbA1c : glycated haemoglobin. FPG : fasting plasma glucose. SBP : systolic blood pressure. DBP : diastolic blood pressure. NA : not available.

Table 5 : Mean effects of GLP-1 receptor agonists on weight loss, reduction in total fat mass and visceral adipose tissue, appetite/energy intake and energy expenditure, vs background therapy **[A:OK?]**. Mean results reported in completers. All controlled trials of potential interest, whatever the number of randomised subjects and the duration of treatment, were considered in this summary table. * References available in appendix.

References*	Back-ground therapy	GLP-1 RA	Duration Weeks	N	Δ HbA1c %	Δ Body weight kg	Δ Total fat kg	Δ Visceral fat %	Δ appetite/ energy intake	Δ energy expenditure %
Bunck et al 2010[135]	Metformin	Exe 2x10µg	52	69	NA	-3.9	-2.4	-13	NA	NA
Bradley et al 2012[136]	No diabetes	Exe 2x10 µg	14	45	NA	-2.0	-1.3	NA	NA	No change
Jendle et al 2009[137]	Metformin	Lira 1.2 mg Lira 1.8 mg	26	31 37	-0.9 -1.0	-2.0 -3.2	-1.6 -2.4	-17 -16	NA NA	NA NA
Jendle et al 2009[137]	Diet	Lira 1.2 mg Lira 1.8 mg	52	23 20	-0.5 -0.9	-2.4 -2.3	-2.0 -1.0	NA	NA NA	NA NA
Inoue et al 2011[138]	OAD/insulin	Lira 0.9 mg	26	29	-1.1	-8.2	NA	NA	Reduced	NA
Suzuki et al 2013[139]	OAD/insulin	Lira 0.9 mg	26	46	-0.3	-2.0	NA	-6	NA	NA
Horowitz et al 2012[140]	Diet/OAD	Lira 1.8 mg	4	38	NA	-1.3	NA	NA	Reduced	+7.6%
Flint et al 2013[141]	Diet/OAD	Lira 0.6-1.8 mg	3	18	NA	-0.55	NA	NA	Reduced	NA

OAD : oral antidiabetic drug. GLP-1 RA : GLP-1 receptor agonist. Exe : exenatide. Lira : liraglutide. HbA1c : glycated haemoglobin. Δ : change versus baseline. NA : not available.

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Other references

(A: please provide the remaining references in a separate file, to be supplied as Appendix. Please also note that these references may not be checked/edited by us.)

[OK : Sarah : However, how I have to quote the references in the tables (???)

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