Obesity Pillars 4 (2022) 100045

Contents lists available at ScienceDirect

Obesity Pillars

journal homepage: www.journals.elsevier.com/obesity-pillars

Weight-centric treatment of type 2 diabetes mellitus

Wissam Ghusn [a], Maria Daniela Hurtado [b], Andres Acosta [a,*]

[a] Precision Medicine for Obesity Program, Division of Gastroenterology and Hepatology, Department of Medicine, Mayo Clinic, Rochester, MNMayo Clinic, Rochester, MN, USA

[b] Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic, Jacksonville, FL, USA

ARTICLE INFO

Keywords:
Medications
Type 2 diabetes mellitus
T2DM
Weight gain
Weight loss

ABSTRACT

Background: Chronic non-communicable diseases (CNCD) represent a major cause of morbidity and mortality. Type 2 diabetes mellitus (T2DM) is one of the most prevalent CNCD that is associated with a significant medical and economic burden. One of the main modifiable risk factors of T2DM is obesity. Many medications used for T2DM can lead to weight gain, worsening one of the root causes of this disease.

Methods: In this clinical review, we study the effect of medications for T2DM on body weight. We used MEDLINE, Google scholar, PubMed, Scopus, and Embase databases to search for relevant studies between 1 January 1950 to 20 September 2022 in English language. Here, we review the most prescribed medications for T2DM and summarize their effect on patients' body weight. We will also present an expert opinion on a recommended weight-centric approach to treat T2DM.

Results: Multiple T2DM medications have been associated with weight gain. Insulin, sulfonylureas, thiazolidinediones and meglitinides may increase body weight. However, biguanides (e.g., metformin), glucagon-like peptide-1 agonists (e.g., semaglutide, liraglutide, tirzepatide), sodium-glucose cotransporter 2 inhibitors, and amylin analogs (e.g., pramlintide) are associated with significant weight loss. Dipeptidyl peptidase-4 inhibitors are considered weight neutral medications. Experts in the fields of endocrinology and obesity recommend utilizing a weight-centric approach when treating T2DM.

Conclusion: Considering the high prevalence and debilitating complication of T2DM, it is of utmost importance to shift from a weight gain approach (i.e., insulin, sulfonylureas) into a weight loss/neutral one (i.e., GLP-1 agonists, SGLT-2 inhibitors, metformin).

1. Introduction

Chronic non-communicable diseases (CNCD) accounted for an estimate of 40.5 million (71%) of worldwide deaths in 2016. Out of these deaths, 32.2 million (80%) can be attributed to cancers, chronic cardiovascular and respiratory diseases, and type-2 diabetes mellitus (T2DM) [1]. Considering the high morbidity and mortality rate of such diseases, significant efforts have been put to establish its modifiable risk factors. One of the most treatable contributory diseases to CNCD is obesity [2–4]. Several studies showed a higher prevalence of CNCD (e.g., T2DM, hypertension, chronic heart disease) in patients with obesity [5]. Consequently, treating obesity can aid in preventing and limiting the progression of CNCD [6].

T2DM represents one of the most significant comorbidities associated with obesity [7]. Similarly, obesity is considered a major risk factor for developing T2DM [8,9]. Their close and bidirectional relationship created the connotation "diabesity" to reflect this solid linkage [10]. Around 20% of patients with obesity have T2DM [11] and 89% of patients with diabetes have overweight or obesity [12]. These percentages are expected to increase if we fail to manage both diseases simultaneously [13,14]. In fact, patients with obesity have an odds ratio of 3.19 of developing T2DM [15]. Hence, it is of immense importance to treat each disease without aggravating the other. For example, some treatments for T2DM (i.e., medications) can lead to weight gain, worsening the pathophysiological cause behind T2DM.

Several medications carry the side effect of weight gain [16] or loss [17]. Choosing the suitable medications becomes a critical process in certain groups of patients [18]. For example, patients with overweight or obesity are more prone to stop medications causing more weight gain [19,20]. Similarly, patients whose weight is below the average might prefer medications that do not cause further weight loss. This becomes

* Corresponding author. Mayo Clinic Charlton 8-142 200 First St. S.W. Rochester, MN, 55902, USA.
E-mail addresses: Wissamghosn777@gmail.com (W. Ghusn), Hurtado.MariaDaniela@mayo.edu (M.D. Hurtado), acosta.andres@mayo.edu (A. Acosta).
URL: https://www.mayo.edu/research/labs/precision-medicine-obesity (A. Acosta).

https://doi.org/10.1016/j.obpill.2022.100045
Received 1 November 2022; Received in revised form 15 November 2022; Accepted 16 November 2022

Abbreviations

ADA	American Diabetes Association
CNCD	Chronic non-communicable diseases
DPP	Diabetes Prevention Program
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
GIP	gastric-inhibitory polypeptide;
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
RCT	Randomized Clinical Trial
SGLT-2	sodium-glucose cotransporter 2
SU	sulfonylureas
TZD	thiazolidinediones
T1DM	Diabetes Mellitus type 1
T2DM	Type 2 diabetes mellitus

more important when treating certain diseases (e.g., T2DM) as stopping the medication might pose serious long-term complications (e.g., retinopathy, nephropathy, neuropathy, and cardiovascular disease). Thus, following a weight-centric approach to manage T2DM is of extreme importance to prevent critical disease complications and reduce the burden of obesity.

In this review series, we have already discussed the effect of medications for depression and chronic pain on body weight [21]. We also presented a personalized approach for prescribing medication for these two prevalent diseases. In this paper, we continue to apply this approach, focusing on a weight centric management of CNCD and here we will address the treatment of T2DM.

2. Methods

In this clinical review, we used MEDLINE, Google scholar, PubMed, Scopus, and Embase databases to search for studies between 1 January 1950 to 20 September 2022 in English language. We present publications (e.g., systematic reviews and meta-analysis, randomized clinical trials [RCTs], and prospective and retrospective observational studies) that focus on the effect of T2DM medications on body weight. In addition, we present expert opinions in the fields of obesity and endocrinology on the weight-centric treatment of T2DM.

3. Results

3.1. Diabetes mellitus

Diabetes Mellitus is a chronic and heterogenous metabolic disease [22] with a rising medical and economic burden [23]. Its diagnosis can be done by measuring plasma glucose level or hemoglobin A1c (HbA1c) level. A fasting plasma glucose of 126 mg per dl or greater or HbA1c $\geq$ 6.5% confirm the diagnosis of diabetes [24]. The pathophysiology of this disease is complex and can be divided into two main categories: Diabetes Mellitus type 1 (T1DM) and T2DM. T1DM is an autoimmune disease that usually develops early in life, linked to genetic and environmental factors [25]. Autoreactive $CD4^+$ and $CD8^+$ T cells target the β cells in the pancreas that are responsible for insulin production [26]. The resulting chronic damage of the β cells results in insulin deficiency [27], causing hyperglycemia. T2DM is a chronic metabolic disorder that is mainly a result of peripheral resistance to the action of insulin [28].

T2DM can cause various debilitating complications if left untreated, leading to microvascular and macrovascular complications [29]. Microvascular complications include diabetic nephropathy, peripheral neuropathy, retinopathy, and sexual dysfunction [30]. Macrovascular complications entail myocardial infarction, stroke, and peripheral artery disease [31]. In addition to medical complications, T2DM poses a significant economic burden. A study on the rising global burden (i.e., direct and indirect costs) of T2DM concluded that there is an expected rise from 1.3 trillion dollars in 2015 to more than 2 trillion dollars in 2030 [23]. Hence, there is a demanding need to manage T2DM in addition to its risk factors (e.g., obesity). The treatment of T1DM constitutes mainly of insulin therapy [32]. In this review, we will mainly focus on the weight centric approach of T2DM.

T2DM management includes lifestyle, pharmacological and bariatric interventions. Non-pharmacological treatment focuses on weight loss achieved via caloric restriction, low carbohydrate diet, and physical exercise. Several studies confirm the positive effect of weight loss on the HbA1c levels [33,34]. In the Diabetes Prevention Program (DPP) which aimed for a minimum of 7% total body weight loss, a 58% decrease of T2DM incidence was reported compared to 31% in the metformin-treated group [35].

Pharmacological treatments include several classes of antihyperglycemic drugs with different mechanisms of action. These medications include metformin, insulin, sulfonylureas (SU), thiazolidinediones (TZDs), meglitinides (glinides), glucagon-like peptide-1 (GLP-1) agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, and pramlintide. A detailed discussion about the effect of these medications is the focus of this review.

Worth noting that bariatric procedures that result in weight loss demonstrated significant outcomes in terms of T2DM resolution. For instance, intestinal diversion with duodenal-jejunal exclusion demonstrated reduction in insulin resistance which improves the glucose homeostasis [36]. A systematic review and meta-analysis including 7883 patients, bariatric surgeries showed an improvement in T2DM status in 89.2% of patients and achieved remission in 64.7% of patients. Fasting blood glucose decreased by 59.7 mg/dl (95% CI, −74.6 to −44.9), and glycated hemoglobin by 1.8% (95% CI, −2.4 to −1.3) [37].

3.1.1. Antihyperglycemic drugs: effect on body weight

3.1.1.1. Metformin. Metformin is a biguanide drug and the first-line treatment for patients with T2DM [38]. It decreases blood glucose by decreasing liver gluconeogenesis, decreasing intestinal glucose absorption, and increasing insulin sensitivity [39]. Metformin can inhibit ghrelin signaling, reducing food intake [40]. It can also improve leptin sensitivity reflected by decreased circulating leptin levels and elevated leptin receptors levels, resulting in suppressed appetite [41]. Another mechanism involves increasing GLP-1 levels through inhibiting dipeptidyl peptidase-IV degradation of GLP-1 [42] which leads to delayed gastric emptying and reduced carbohydrates absorption [43]. The use of metformin can reduce the HbA1c by around 1.3% in 26 weeks [44]. A meta-analysis including 21 randomized controlled and high-quality case-control trials revealed a significant reduction of BMI by 1.31 kg/m^2 which was most significant in patients with obesity (95% CI -2.07 to −0.54) [45]. In a systematic review studying the effect of metformin on body weight in studies $\geq$6 months, most showed an association with weight loss while few others didn't demonstrate any significant weight change [46]. Other meta-analyses and randomized controlled trials also show the association between metformin use and weight loss [47–52].

3.1.1.2. Insulin. Insulin is a common medication that enhances the glucose influx from the blood into cells [53]. It results in the greatest reduction in HbA1c of up to 3.5% compared to other diabetes medications; however, it results in significant weight gain [54]. Several mechanisms have been proposed to explain the weight gain associated with insulin. First, the conservation of ingested calories due to a better regulated glycemic level below the renal threshold of excretion plays a main

role in weight gain [55,56]. Such conservation of energy intake causes an imbalance in energy metabolism resulting in weight gain. Second, being an anabolic hormone, insulin inhibits lipolysis and protein catabolism in addition to promoting lipogenesis [57]. A slight overreplacement of insulin can promote weight gain [55]. Third, an impairment in the anorectic signals of insulin to the arcuate nucleus causes an unopposed anabolic effect [55,58,59]. Another proposed mechanism is that patients increase their carbohydrate consumption to avoid insulin's most feared side effect, hypoglycemia [55].

In a systematic review and meta-analysis, Pontiroli et al. concluded that insulin use is associated with a mean body weight gain of 4.3 ± 2.74 kg (95% CI 4.32–4.38) in 14,250 patients with a mean follow up of 27.7 weeks. Increased weight was correlated with treatment intensity and type of insulin regimen used. A basal regimen resulted in lower weight gain compared to twice daily and prandial regimens. Detemir use was associated with lower weight gain than NPH and glargine [60]. In a multicenter randomized trial involving 708 patients, prandial and biphasic insulin groups were associated with a greater risk of weight gain compared to that of basal insulin after 1 year of follow up (5.7 kg, 4.7 kg, and 1.9 kg, respectively) [61]. These results were also consistent with several other randomized trials [62–65].

3.1.1.3. Sulfonylureas (SU). SU lower blood sugar by stimulating the release of insulin from the pancreas [66]. The weight gain associated with SU use is described to be most likely a result of increased caloric intake associated with effort to avoid hypoglycemia, in addition to the effect of increased insulin levels in the body [34,67]. SU has demonstrated to decrease HbA1c by 1–2% [54]. Different systematic reviews and meta-analyses demonstrated a significant body weight gain ranging between 1.99 and 2.31 kg vs. placebo or metformin [38,68–70].

3.1.1.4. Thiazolidinediones (TZDs). TZDs are a group of medications that act intracellularly to enhance insulin action and increase tissue sensitivity to insulin [71,72]. They have been shown to reduce HbA1c by 0.5–1.4% in patients with T2DM [54].Several proposed mechanisms explaining the weight gain associated with TZD use include increased appetite accompanying decreased leptin levels [73], increased subcutaneous adipose tissue with decreased visceral fat content [74–76], and fluid retention [77,78]. In a meta-analysis including 11 randomized controlled trials, weight gain was reported to be 2.7 kg within 6 months of initiating therapy (95% CI 1.8–3.7 kg) [79]. Similarly, another systematic review and meta-analysis showed an increased body weight of 2.08 kg with TZDs when compared to placebo (95% CI 0.98–3.17 kg) [68]. These results were also similar to those of other systematic reviews, meta-analyses, and randomized controlled trials [80,81].

3.1.1.5. Meglitinides (glinides). Glinides are insulin secretagogues that stimulate its release, lowering the blood glucose levels [82]. A decrease of 0.5–1.5% in HbA1c has been demonstrated in patients with T2DM [54]. Although the weight gain mechanism behind glinides is not fully understood [83], two possible explanations include decreased glycosuria and defensive snacking to avoid hypoglycemia [83]. In several systematic reviews and meta-analysis, the body weight gain associated with glinide use ranged between 1.77 kg and 2.67 kg [68,69,84]. However, a large degree of uncertainty with a large confidence interval for weight gain has been reported in one meta-analysis [84].

3.1.1.6. Glucagon-like Peptide-1 (GLP-1) agonists. GLP-1 agonists increase glucose-dependent insulin secretion, delay gastric emptying, and increase satiety [85]. GLP-1 agonists provide an improvement of 0.8–1.5% in terms of HbA1c. The delayed gastric emptying is considered a main predictor of weight loss response in patients who use GLP-1 agonists for weight loss [86,87]. Patients with faster gastric emptying respond better to GLP-1 agonists [87]. In patients with and without T2DM, several systematic reviews and meta-analyses associated the use of GLP-1 agonists with significant weight loss in a dose-dependent manner [88–92]. Importantly, GLP-1 agonists (i.e., liraglutide and semaglutide) are the only anti-diabetic medications to be FDA approved for weight loss as well [93]. Several studies demonstrated a wide variety in weight loss range between different GLP-1 agonists. For example, in a study with a GLP-1 analog, exenatide, a dose dose-dependent weight loss (−2.8+/-0.5 kg [10 mg], and −1.6+/-0.4 kg [5 mg]) was reported [94]. Weekly subcutaneous of 2.4 mg semaglutide injections resulted in 15.8% of total body weight loss percentage (TBWL%) compared to 6.4% with daily injections of liraglutide 3.0 mg in a 68-week randomized clinical trial (difference, −9.4% points [95% CI, −12.0 to −6.8]; $P < 0.001$) [95]. In addition, real-wold data of weight loss associated with semaglutide (doses up to 2.4 mg) show that patients lose a TBWL% of 5.9 at 3 months and 10.9 at 6 months. In patients with T2DM, semaglutide was associated with a weight loss of 3.9% (3.1%) (vs 6.3% in patients without diabetes) at 3 months and 7.2% (6.3%) (vs 11.8% [5.3%] in patients without diabetes) [96].

3.1.1.7. GLP-1/GIP agonists. Tirzepatide, a dual GIP and GLP-1 agonist, has been recently approved by the FDA for treatment of T2DM with a similar mechanism of action as GLP-1 agonists. In addition to the stimulation of glucose-dependent insulin secretion shared with GLP-1 agonists, GIP has glucagonotropic properties which may enhance weight loss through the anti-lipogenic and anorexic effect of glucagon [97,98]. The combination of GIP and GLP-1 has demonstrated a synergistic effect on increasing insulin response [98]. Tirzepatide has been shown to decrease HbA1c by 2.01, 2.24, and 2.3% with 5 mg, 10 mg, and 15 mg weekly doses, respectively [99]. In an RCT evaluating this medication, the TBWL % associated with tirzepatide 5 mg was 15.0%, tirzepatide 10 mg was 15.9%, and tirzepatide 15 mg was 20.9% ($p < 0.001$ for all comparisons with placebo) [100].

3.1.1.8. Dipeptidyl Peptidase-4 (DPP-4) inhibitors. DPP-4 inhibitors are a group of anti-diabetic medications that maintain glucose homeostasis by acting on incretin hormones (i.e. GLP-1 and GIP), increasing insulin, and decreasing glucagon secretions [101]. DPP-4 inhibitors are associated with a HbA1c decrease of 0.5–0.8% in patients with T2DM [54]. DPP-4 inhibitors are weight neutral drugs [102–105]. However, in a systematic review and meta-analysis comparing DDP-4 inhibitors and SU, Mishriky et al. demonstrated weight loss associated with DDP-4 inhibitors: 1.57 kg at 12 weeks, 2.11 kg at 52 weeks, and 2.13 kg at 104 weeks [106]. Hence, DDP-4 may have favorable weight loss effects, but more randomized control trials are needed to confirm this.

3.1.1.9. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors. SGLT-2 inhibitors are a class of hypoglycemic agents that suppress glucose reabsorption at the proximal tubule level to increase glucose excretion [107]. They are associated with a decrease of 0.5–0.8% in HbA1c in patients with T2DM. These drugs have been associated with weight loss due to their ability to cause calorie deficit through urine excretion of 60–100 g of glucose per day [108]. Several systematic reviews and meta-analyses associate weight lose with a dose-dependent manner [109–112]. However, the use of SGLT-2 inhibitors induces adaptive increase in energy intake (e.g., increased appetite) to counteract the loss of calories [108, 113]. Hence, this sparked the idea of using a combination of drugs with different mechanisms of action to minimize the effects of the regulatory weight maintenance pathways [114,115]. In a 26-week randomized placebo-controlled trial, the combination of canagliflozin and phentermine achieved greater weight loss than the expected additive effect of both these medications alone [116].

3.1.1.10. Pramlintide. Pramlintide is an amylin analog that reduces postprandial hyperglycemia by suppressing glucagon secretion, slowing gastric emptying, and reducing food intake [117]. Hence, it is expected to be associated with weight loss [118]. In a systematic review and meta-analysis, in patients with obesity, the mean reduction in weight was

Table 1
The effect of different medications for type-2 Diabetes Mellitus on body weight.

Disease	Medication Group	Medication	Weight Gain	Weight Neutral	Weight Loss	Reference
Diabetes	Biguanides	Metformin		X	X	[45]
	Insulin	All	X			[61]
	Sulfonylureas	All	X			[121]
	Thiazolidinediones	All	X			[122]
	Meglitinides	All	X			[123]
	GLP-1 Agonists*	Semaglutide			XX	[95]
		Tirzepatide			XX	[124]
		Others			X	[95]
	DPP-4 Inhibitors	All		X		[109,125]
	SGLT-2 Inhibitors	All			X	[109]
	Amylin Analogs	Pramlintide			X	[119]

GLP-1: Glucagon-like Peptide-1; DPP-4: Dipeptidyl Peptidase-4; SGLT-2: Sodium-Glucose Cotransporter 2.
X: <5% of total body weight change; XX: ≥5% of total body weight change.
* FDA-approved medications for weight loss (Liraglutide and Semaglutide).

reported to be 2.88 kg compared to placebo (95% CI -2.88 to −1.66; $p < 0.001$). In two randomized controlled trials following 1155 patients for 26 weeks, the placebo-corrected weight loss reported was 1.8 kg ($p < 0.001$). Nine percent of patients achieved a reduction in body weight of 5% compared to only 3% of patients in the control group [119]. In addition to weight loss, pramlintide has demonstrated a decrease in Hba1c of 0.5–1% [54].

3.1.2. Expert opinion: weight-centric approach

The management of T2DM in patients with obesity, should be weight centric. In fact, the first line non-pharmacological treatment of T2DM includes weight loss, proving the importance of treating excess adiposity in managing T2DM [120]. The recent European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) consensus recommended weight loss and engagement in an intensive lifestyle management in patients with T2DM. Hence, the treatment of T2DM should be tailored to decrease body weight which can enhance the decrease in plasma glucose levels and improve overall diabetes outcomes and complications. For this reason, there should be a shift from using weight gain promoting medications (e.g., insulin, SU) into weight loss/neutral medications (GLP-1 agonists, SGLT-2 inhibitors, metformin, DPP-4 inhibitors).

4. Weight-centric management

Overweight and obesity are major risk factors for the development of T2DM, hence the term “diabesity”. The relation between excess weight and T2DM is evidenced by the increased prevalence of overweight and obesity among patients with T2DM compared to the patients without. In clinical practice, it is important to emphasize that the cornerstone of T2DM treatment is weight loss. A moderate amount of weight loss, through lifestyle style, pharmacologic, and/or surgical interventions, can potentially lead to T2DM remission. Factors that predict T2DM remission include amount of total body weight loss (greater than 10%), duration of T2DM, and pancreatic function reserve. Even if T2DM does not remit, weight loss can lead to decreased number and/or decreased doses of medications used for hyperglycemia control.

Paradoxically, many medications historically used to treat hyperglycemia in patients with T2DM, have been known to promote weight gain (e.g., sulfonylureas, insulin, and thiazolidinediones). With the advent of newer therapies, we are now in an era in which most T2DM medications are either weight neutral (e.g., metformin and DPP-4 inhibitors) or promote weight loss (e.g., GLP-1 agonists with or without gastric-inhibitory polypeptide [GIP] receptor agonists, SGLT-2 inhibitors). As a matter of fact, GLP-1 receptor agonists liraglutide and semaglutide are now approved for T2DM and obesity treatment, with the later showing impressive results. Medications that promote concomitant hyperglycemia control and weight loss not only decrease cardiovascular disease and mortality risk but may be associated with an improvement in microvascular diabetic complications as well.

In patients with difficult to control T2DM while on multiple diabetes medications, including insulin, and those who fail lifestyle and/or pharmacologic interventions, bariatric surgery should be highly considered. Bariatric surgery is the most effective and efficient intervention for sustained weight loss and is an alternative therapeutic modality for patients with diabesity as it is associated with high rates of T2DM remission of 30–95%. The mechanisms behind T2DM remission after bariatric surgery are not fully understood but include post-operative aggressive caloric restriction, massive weight loss, and changes in gastrointestinal peptides, bile acids, and microbiome, among others.

Although the pathophysiologic relationship between obesity and T1DM remains to be fully characterized, obesity has been identified as a risk factor for T1DM as well. Furthermore, therapeutic options for patients with T1DM are limited to insulin, which is a weight-promoting medication. Patients with T1DM and obesity require sometimes large doses of insulin given the added component of insulin resistance to that one of insulin deficiency. Treating patients with T1DM and obesity poses a challenge that requires a multidisciplinary approach to avoid life-threatening complications like hypoglycemia. Despite this, weight management can be effectively and safely achieved in patients with T1DM through lifestyle, pharmacological, and/or surgical interventions.

In summary, given the epidemiologic trends and relationship between diabetes and obesity, providers caring for patients with diabetes, should aim at developing a comprehensive weight loss program that includes lifestyle modification, pharmacotherapy, and/or bariatric surgery. Health care providers must understand the mechanism of action, side effect profile in the case of medications, complications in the case of surgical approaches, and contraindications for current antiobesity interventions to safely implement them (Table 1).

5. Conclusion

In conclusion, weight loss is crucial in treating T2DM. Taking this into consideration, some medications used to treat T2DM can contribute to weight gain, worsening the pathophysiological cause of T2DM. Hence, physicians must follow a weight-centric approach while treating T2DM and shift towards a weight-conscious approach. By using weight loss/neutral antihyperglycemic medications, the goal of controlling T2DM and reducing excess adiposity becomes more achievable.

Ethical review

The submission represents original work. The submission does not involve any human test subjects or volunteers.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

Acknowledgment

The concept of the submission was by Wissam Ghusn and Andres Acosta. Andres Acosta participated as an Investigator in this review. Wissam Ghusn wrote the first draft. Wissam Ghusn, Maria Daniela Hurtado and Andres Acosta all reviewed, edited, and approved the final submission and publication.

References

[1] NCD Countdown 2030: worldwide trends in non-communicable disease mortality and progress towards Sustainable Development Goal target 3.4. Lancet 2018; 392(10152):1072–88.
[2] Nyberg ST, et al. Obesity and loss of disease-free years owing to major non-communicable diseases: a multicohort study. Lancet Public Health 2018;3(10): e490–7.
[3] Bell JA, et al. Incidence of metabolic risk factors among healthy obese adults: 20-year follow-up. J Am Coll Cardiol 2015;66(7):871–3.
[4] Poirier P, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American heart association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. Circulation 2006; 113(6):898–918.
[5] Zatońska K, et al. Obesity and chosen non-communicable diseases in PURE Poland cohort study. Int J Environ Res Publ Health 2021;18(5):2701.
[6] Di Daniele N. The role of preventive nutrition in chronic non-communicable diseases. Nutrients 2019;11(5):1074.
[7] Mata-Cases M, et al. Prevalence and coprevalence of chronic comorbid conditions in patients with type 2 diabetes in Catalonia: a population-based cross-sectional study. BMJ Open 2019;9(10):e031281.
[8] Pi-Sunyer X. The medical risks of obesity. PGM (Postgrad Med) 2009;121(6): 21–33.
[9] Mokdad AH, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors. JAMA 2003;289(1):76–9. 2001.
[10] Leitner DR, et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies - EASO can lead the way. Obesity facts 2017;10(5): 483–92.
[11] Mandal A. Study of prevalence of type 2 diabetes mellitus and hypertension in overweight and obese people. J Fam Med Prim Care 2014;3(1):25–8.
[12] Report, N.D.S.. Estimates of diabetes and its burden in the United States. 2020.
[13] Lo E, et al. Projection scenarios of body mass index (2013-2030) for public health planning in quebec. BMC Publ Health 2014;14:996.
[14] Shi L, van Meijgaard J, Fielding J. Forecasting diabetes prevalence in California: a microsimulation. Prev Chronic Dis 2011;8(4):A80.
[15] Ganz ML, et al. The association of body mass index with the risk of type 2 diabetes: a case-control study nested in an electronic health records system in the United States. Diabetol Metab Syndrome 2014;6(1):50.
[16] Leslie WS, Hankey CR, Lean ME. Weight gain as an adverse effect of some commonly prescribed drugs: a systematic review. QJM 2007;100(7):395–404.
[17] Verhaegen AA, Van Gaal LF. Drugs that affect body weight, body fat distribution, and metabolism. Endotext [Internet]; 2019.
[18] Loke YK, Golder SP, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Therapeutic advances in drug safety 2011;2(2):59–68.
[19] Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. MedGenMed : Medsc Gen Med 2007;9(3). 58-58.
[20] Riche DM, Cleary JD, King ST. Medication-induced adverse effects: important concepts for the hand therapist. J Hand Ther 2010;23(2):230–7.
[21] Ghusn W, et al. Weight-centric treatment of depression and chronic pain. Obesity Pillars 2022;3:100025.
[22] Banday MZ, Sameer AS, Nissar S. Pathophysiology of diabetes: an overview. Avicenna J Med 2020;10(4):174–88.
[23] Bommer C, et al. Global economic burden of diabetes in adults: projections from 2015 to 2030. Diabetes Care 2018;41(5):963–70.
[24] Pippitt K, Li M, Gurgle HE. Diabetes mellitus: screening and diagnosis. Am Fam Physician 2016;93(2):103–9.
[25] Blanter M, et al. Genetic and environmental interaction in type 1 diabetes: a relationship between genetic risk alleles and molecular traits of enterovirus infection? Curr Diabetes Rep 2019;19(9). 82-82.
[26] Giwa AM, et al. Current understandings of the pathogenesis of type 1 diabetes: genetics to environment. World J Diabetes 2020;11(1):13–25.
[27] Wilcox G. Insulin and insulin resistance. The Clinical biochemist. Review 2005; 26(2):19–39.
[28] Goyal R, Jialal I. Diabetes mellitus type 2. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC; 2022.
[29] Papatheodorou K, et al. Complications of diabetes 2017. J Diabetes Res 2018; 2018. 3086167-3086167.
[30] Faselis C, et al. Microvascular complications of type 2 diabetes mellitus. Curr Vasc Pharmacol 2020;18(2):117–24.
[31] Huang D, et al. Macrovascular complications in patients with diabetes and prediabetes. BioMed Res Int 2017;2017:7839101.
[32] Pathak V, et al. Therapies for type 1 diabetes: current scenario and future perspectives. Clin Med Insights Endocrinol Diabetes 2019;12: 1179551419844521.
[33] Wing RR, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011;34(7):1481–6.
[34] Group UPDS. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352(9131):837–53.
[35] The Diabetes Prevention Program (DPP). Description of lifestyle intervention. Diabetes Care 2002;25(12):2165–71.
[36] Rubino F, et al. Metabolic surgery to treat type 2 diabetes: clinical outcomes and mechanisms of action. Annu Rev Med 2010;61:393–411.
[37] Yu J, et al. The long-term effects of bariatric surgery for type 2 diabetes: systematic review and meta-analysis of randomized and non-randomized evidence. Obes Surg 2015;25(1):143–58.
[38] Apovian CM, Okemah J, O'Neil PM. Body weight considerations in the management of type 2 diabetes. Adv Ther 2019;36(1):44–58.
[39] Corcoran C, Jacobs TF. Metformin. In: StatPearls. Treasure Island (FL: StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC; 2022.
[40] Stevanovic D, et al. Intracerebroventricular administration of metformin inhibits ghrelin-induced Hypothalamic AMP-kinase signalling and food intake. Neuroendocrinology 2012;96(1):24–31.
[41] Aubert G, et al. The anorexigenic effects of metformin involve increases in hypothalamic leptin receptor expression. Metabolism 2011;60(3):327–34.
[42] Lindsay JR, et al. Inhibition of dipeptidyl peptidase IV activity by oral metformin in Type 2 diabetes. Diabet Med 2005;22(5):654–7.
[43] Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes 2014;21(5).
[44] Rosenstock J, et al. Initial combination therapy with canagliflozin plus metformin versus each component as monotherapy for drug-naïve type 2 diabetes. Diabetes Care 2016;39(3):353–62.
[45] Pu R, et al. Effects of metformin in obesity treatment in different populations: a meta-analysis. Therapeutic advances in endocrinology and metabolism 2020;11. 2042018820926000-2042018820926000.
[46] Lentferink YE, Knibbe CAJ, van der Vorst MMJ. Efficacy of metformin treatment with respect to weight reduction in children and adults with obesity: a systematic review. Drugs 2018;78(18):1887–901.
[47] Hui F, et al. Role of metformin in overweight and obese people without diabetes: a systematic review and network meta-analysis. Eur J Clin Pharmacol 2019;75(4): 437–50.
[48] Solymár M, et al. Metformin induces significant reduction of body weight, total cholesterol and LDL levels in the elderly - a meta-analysis. PLoS One 2018;13(11). e0207947-e0207947.
[49] Ning HH, et al. The effects of metformin on simple obesity: a meta-analysis. Endocrine 2018;62(3):528–34.
[50] Solymár M, et al. Metformin induces significant reduction of body weight, total cholesterol and LDL levels in the elderly - a meta-analysis. PLoS One 2018;13(11): e0207947.
[51] Hiluy JC, et al. Effectiveness of pharmacologic interventions in the management of weight gain in patients with severe mental illness: a systematic review and meta-analysis. Prim Care Companion CNS Disord 2019;21(6).
[52] Desilets AR, Dhakal-Karki S, Dunican KC. Role of metformin for weight management in patients without type 2 diabetes. Ann Pharmacother 2008;42(6):817–26.
[53] Thota S. Insulin. StatPearls [Internet] 2021:1. In this issue, https://www.ncbi.nlm.nih.gov/books/NBK560688/. [Accessed 23 October 2022].
[54] Nathan DM, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American diabetes association and the European association for the study of diabetes. Diabetes Care 2009;32(1):193–203.
[55] Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes – causes, effects and coping strategies. Diabetes Obes Metabol 2007;9(6):799–812.
[56] Carlson MG, Campbell PJ. Intensive insulin therapy and weight gain in IDDM. Diabetes 1993;42(12):1700–7.
[57] Otto-Buczkowska E, Jarosz-Chobot P. [Lipid metabolism. I. Role of insulin in lipid metabolism]. Pol Merkur Lek 2001;10(57):180–4.
[58] Schwartz MW, Porte Jr D. Diabetes, obesity, and the brain. Science 2005; 307(5708):375–9.
[59] Schwartz MW, Niswender KD. Adiposity signaling and biological defense against weight gain: absence of protection or central hormone resistance? J Clin Endocrinol Metab 2004;89(12):5889–97.
[60] Pontiroli AE, Miele L, Morabito A. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metabol 2011;13(11):1008–19.
[61] Holman RR, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. N Engl J Med 2007;357(17):1716–30.
[62] Raskin P, et al. Initiating Insulin Therapy in Type 2 Diabetes : a comparison of biphasic and basal insulin analogs. Diabetes Care 2005;28(2):260–5.
[63] Kvapil M, et al. Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes. Diabetes Obes Metabol 2006;8(1):39–48.

[64] Malone JK, et al. Combined therapy with insulin lispro mix 75/25 plus metformin or insulin glargine plus metformin: a 16-week, randomized, open-label, crossover study in patients with type 2 diabetes beginning insulin therapy. Clin Therapeut 2004;26(12):2034–44.
[65] Malone JK, et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type 2 diabetes. Diabet Med 2005;22(4):374–81.
[66] Sulfonylureas, in LiverTox. Clinical and research information on drug-induced liver injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
[67] Schwartz S, Herman M. Revisiting weight reduction and management in the diabetic patient: novel therapies provide new strategies. Postgrad Med 2015; 127(5):480–93.
[68] Phung OJ, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303(14):1410–8.
[69] McIntosh B, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2011;5(1):e35.
[70] Hirst J, et al. Estimating the effect of sulfonylurea on HbA1c in diabetes: a systematic review and meta-analysis. Diabetologia 2013;56(5):973–84.
[71] Eggleton JS, Jialal I. Thiazolidinediones. Natl Libr Med 2019:1. In this issue.
[72] Yamanouchi T. Concomitant therapy with pioglitazone and insulin for the treatment of type 2 diabetes. Vasc Health Risk Manag 2010;6:189–97.
[73] Shimizu H, et al. Troglitazone reduces plasma leptin concentration but increases hunger in NIDDM patients. Diabetes Care 1998;21(9):1470–4.
[74] Kelly IE, et al. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. Diabetes Care 1999;22(2):288–93.
[75] Nakamura T, et al. Thiazolidinedione derivative improves fat distribution and multiple risk factors in subjects with visceral fat accumulation—double-blind placebo-controlled trial. Diabetes Res Clin Pract 2001;54(3):181–90.
[76] Akazawa S, et al. Efficacy of troglitazone on body fat distribution in type 2 diabetes. Diabetes Care 2000;23(8):1067–71.
[77] Muto S, et al. Troglitazone stimulates basolateral rheogenic Na+/HCO–3 cotransport activity in rabbit proximal straight tubules. Nephron Exp Nephrol 2001;9(3):191–7.
[78] Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med 2003;115(8, Supplement 1):42–8.
[79] Chiquette E, Ramirez G, DeFronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med 2004;164(19): 2097–104.
[80] Wang W, et al. Efficacy and safety of thiazolidinediones in diabetes patients with renal impairment: a systematic review and meta-analysis. Sci Rep 2017;7(1):1717.
[81] Filipova E, et al. Effects of pioglitazone therapy on blood parameters, weight and BMI: a meta-analysis. Diabetol Metab Syndrome 2017;9(1):90.
[82] Milner Z, Akhondi H. Repaglinide. StatPearls 2020:1. https://pubmed.ncbi.nlm.nih.gov/32644731/.
[83] Provilus A, Abdallah M, McFarlane SI. Weight gain associated with antidiabetic medications. Clin Pract 2011;8(2):113.
[84] McIntosh B, et al. Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis. Open Med : a peer-reviewed, independent, open-access journal 2012;6(2):e62–74.
[85] Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an updated review of head-to-head clinical studies. Therapeutic advances in endocrinology and metabolism 2021;12. 2042018821997320-2042018821997320.
[86] Halawi H, et al. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. Lancet Gastroenterol Hepatol 2017;2(12):890–9.
[87] Acosta A, et al. Selection of antiobesity medications based on phenotypes enhances weight loss: a pragmatic trial in an obesity clinic. Obesity 2021;29(4): 662–71.
[88] Potts JE, et al. The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. PLoS One 2015;10(6):e0126769.
[89] Vilsbøll T, et al. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. BMJ 2012; 344:d7771.
[90] Uneda K, et al. Systematic review and meta-analysis for prevention of cardiovascular complications using GLP-1 receptor agonists and SGLT-2 inhibitors in obese diabetic patients. Sci Rep 2021;11(1):10166.
[91] Ryan PM, et al. Safety and efficacy of glucagon-like peptide-1 receptor agonists in children and adolescents with obesity: a meta-analysis. J Pediatr 2021;236: 137–147.e13.
[92] Zhang F, et al. Weight loss effect of glucagon-like peptide-1 mimetics on obese/overweight adults without diabetes: a systematic review and meta-analysis of randomized controlled trials. J Diabetes 2015;7(3):329–39.
[93] Latif W, Lambrinos KJ, Rodriguez R. Compare and contrast the glucagon-like peptide-1 receptor agonists (GLP1RAs). 2021. StatPearls [Internet].
[94] DeFronzo RA, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. Diabetes Care 2005;28(5):1092–100.
[95] Rubino DM, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. JAMA 2022;327(2):138–50.
[96] Ghusn W, et al. Weight loss outcomes associated with semaglutide treatment for patients with overweight or obesity. JAMA Netw Open 2022;5(9). e2231982-e2231982.
[97] Christensen M, et al. Glucose-dependent insulinotropic polypeptide: a bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. Diabetes 2011;60(12):3103–9.
[98] Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS clinical trials. Diabetes Ther 2021; 12(1):143–57.
[99] Newsome PN, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2020;384(12):1113–24.
[100] Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022;387:205–16.
[101] Kasina SVSK, Baradhi KM. Dipeptidyl Peptidase IV (DPP IV) Inhibitors. 2021. StatPearls [Internet].
[102] Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract 2014; 68(5):557–67.
[103] Gerich J. DPP-4 inhibitors: what may be the clinical differentiators? Diabetes Res Clin Pract 2010;90(2):131–40.
[104] Ling J, et al. The efficacy and safety of dipeptidyl peptidase-4 inhibitors for type 2 diabetes: a Bayesian network meta-analysis of 58 randomized controlled trials. Acta Diabetol 2019;56(3):249–72.
[105] Karagiannis T, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. BMJ 2012;344:e1369.
[106] Mishriky BM, Cummings DM, Tanenberg RJ. The efficacy and safety of DPP4 inhibitors compared to sulfonylureas as add-on therapy to metformin in patients with Type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract 2015;109(2):378–88.
[107] Saisho Y. SGLT2 inhibitors: the star in the treatment of type 2 diabetes? Diseases 2020;8(2).
[108] Pereira MJ, Eriksson JW. Emerging role of SGLT-2 inhibitors for the treatment of obesity. Drugs 2019;79(3):219–30.
[109] Zaccardi F, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. Diabetes Obes Metabol 2016;18(8):783–94.
[110] Maruthur NM, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164(11):740–51.
[111] Mearns ES, et al. Comparative efficacy and safety of antidiabetic drug regimens added to metformin monotherapy in patients with type 2 diabetes: a network meta-analysis. PLoS One 2015;10(4):e0125879.
[112] Cai X, et al. The association between the dosage of SGLT2 inhibitor and weight reduction in type 2 diabetes patients: a meta-analysis. Obesity 2018;26(1):70–80.
[113] Ferrannini G, et al. Energy balance after sodium-glucose cotransporter 2 inhibition. Diabetes Care 2015;38(9):1730–5.
[114] Frías JP, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2016;4(12):1004–16.
[115] Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med 1995;332(10):621–8.
[116] Hollander P, et al. Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. Diabetes Care 2017;40(5):632–9.
[117] Want LL, Ratner RE. Pramlintide: a new tool in diabetes management. Curr Diabetes Rep 2006;6(5):344–9.
[118] Dunican KC, Adams NM, Desilets AR. The role of pramlintide for weight loss. Ann Pharmacother 2010;44(3):538–45.
[119] Hollander P, et al. Effect of pramlintide on weight in overweight and obese insulin-treated type 2 diabetes patients. Obes Res 2004;12(4):661–8.
[120] Pfeiffer AFH, Klein HH. The treatment of type 2 diabetes. Deutsches Arzteblatt international 2014;111(5):69–82.
[121] Apovian CM, Okemah J, O'Neil PM. Body weight considerations in the management of type 2 diabetes. Adv Ther 2019;36(1):44–58.
[122] Phung OJ, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA 2010;303(14):1410–8.
[123] McIntosh B, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2011;5(1):e35–48.
[124] Pirro V, et al. Effects of tirzepatide, a dual GIP and GLP-1 RA, on lipid and metabolite profiles in subjects with type 2 diabetes. J Clin Endocrinol Metab 2022; 107(2):363–78.
[125] Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract 2014; 68(5):557–67.