



Can Glucagon-Like Peptide-1 Receptor Agonists or Sodium-Glucose Cotransporter 2 Inhibitors Be Considered New Treatment Options for Male Hypogonadism and Sexual Dysfunction?

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The use of glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2is) resulted in weight loss and long-term cardiovascular (CV) and renal safety preservation. Their role in male sexual hormones and behavior is still not sufficiently investigated. This paper aims at summarizing the effects of GLP1-RA and SGLT2i on obesity-associated hypogonadism and sexual dysfunctions. Both GLP1-RA and SGLT2i resulted in an improvement of body composition and metabolic profile, supporting erectile function amelioration. Only GLP1-RA showed a weight loss dependent increase in total and calculated free testosterone with lower effects on gonadotropin levels, while for SGLT2i, the data are contradictory. Finally, the use of testosterone replacement therapy showed better results as compared to GLP1-RA when orgasm and sexual satisfaction domains were investigated. In conclusion considering the beneficial effects of GLP1-RA on long-term CV mortality and morbidity, compared to the substantially neutral effects derived from the use of testosterone replacement therapy, we support the use of this class of medications for improving sexual dysfunction and its underlying CV problems in overweight and obese patients with erectile dysfunction.

Keywords: Erectile dysfunction; Glucagon-like peptide-1 receptor agonists; Hypogonadism; Obesity; Testosterone; Weight loss

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INTRODUCTION

Overweightness and obesity are becoming a pandemic, non-transmittable health problem. A recent Global

Burden of Disease Study indicates that in 2021, more than one billion worldwide adult males and females were overweight and obese, and, as compared to 1990, the global prevalence of obesity had increased by 155%

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in males and 105% in females [1]. This study also forecasts that in 2050, more than half of the global population will be affected by the condition, *i.e.*, almost four billion persons [1].

Several obesity-related complications are well-known, including cardiovascular (CV), metabolic (*e.g.*, type 2 diabetes mellitus, T2DM), and neoplastic disorders, leading to a substantial and steep increase in disability and mortality, with an estimated four million deaths in 2021 [2]. Essentially, the frontline treatment of obesity is a recommendation to eat less, exercise more, and adopt a healthier lifestyle. Several studies have demonstrated that, in individuals at risk, intensive lifestyle interventions, along with nutritional counseling and physical activity, can reduce weight and insulin resistance, preventing the progression of obesity to other diseases, such as overt T2DM [3]. Lifestyle intervention is therefore the usual first-line approach for all patients. Although integrated obesity prevention lifestyle programs, including healthy diet and physical activity, are urgent actions, their success is limited, and weight regain is often observed, with only 15% of individuals reporting a sustained 10% or greater weight loss [3]. Hence, a medical or surgical intervention is often warranted.

Concerning medical intervention, anti-obesity medications have been stratified into three groups according to their mechanism of action: intra-gastrointestinal medication (*e.g.*, orlistat), centrally acting medications (*e.g.*, naltrexone-bupropion, phentermine alone or in combination with topiramate), and nutrient-stimulated hormone-based medications [4]. The latter group includes glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RAs), which bind to their receptor (GLP-1R) or have a double action also on glucose-dependent insulinotropic polypeptide (GIP) or glucagon (GCG) receptors (GIPR and GCGR, respectively). A dual agonist binding to GLP-1R, and GIPR (tirzepatide) is Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved and available on the market in several countries, including Italy. Triple agonists targeting all the aforementioned receptors (GLP-1R, GIPR, and GCGR, *i.e.*, retatrutide) are still in trials [5]. Nutrient-stimulated hormone-based medications (incretins), and in particular semaglutide and tirzepatide, appear, at the present time, to be the most efficacious medications available in the market for weight reduction [4]. In a meta-analysis, at 52 weeks, semaglutide

1 mg, tirzepatide 5 to 15 mg, and retatrutide 6.5 mg induced an 8.05%, 12.3%, and 13.23% weight reduction, respectively. However, substantial weight regain at the time of discontinuation of therapy remains a major drawback [6]. In another meta-analysis, it was demonstrated, by meta-regression, that GLP1-RA injectable preparations were more effective than oral ones and that the same preparations were more effective in the female and non-diabetic populations with greater body mass index (BMI) and lower glycated hemoglobin (HbA1c) at study entry [7]. In addition, GLP1-RA trials in subjects with or without T2DM showed that they have, beyond weight reduction, other relevant positive effects on obesity-associated comorbidities because they can reduce the risk of death, CV disease (CVD) or chronic kidney ailments, ease sleep apnea symptoms and even slow the development of Parkinson's disease (see [8-10] for recent reviews or meta-analyses). Among the new drugs available for treating T2DM, sodium-glucose cotransporter 2 inhibitors (SGLT2is) have also demonstrated in meta-analyses weight reduction in individuals with [11] and without [12] T2DM, as well as CV and nephrological long-term protection. However, this class of medications has only been approved for obesity treatment related to T2DM.

An often neglected complication of obesity is the reduction of the male testicular hormone testosterone (T). In a population of more than 4,000 patients seeking medical care for sexual dysfunction and therefore potentially symptomatic for T deficiency [13-15], almost 20% showed obesity (*i.e.*, BMI ≥ 30 kg/m²) [16]. Of those, 41% showed a T reduction below 10.5 nmol/L, which was associated with an elevation of luteinizing hormone (LH) in 12% of cases (primary hypogonadism) and normal or subnormal LH in the rest of the sample (88%, secondary hypogonadism) [16]. In a meta-analysis of studies describing subgroups of patients with morbid/severe obesity, the prevalence of low T ranged from 15.2 to 78.8%, with a pooled prevalence of 42.8% [17]. It is often argued that the decline of T in obesity is mostly due to a decline in its carrier protein, sex hormone binding globulin (SHBG), and therefore it represents a merely spurious phenomenon (pseudo-hypogonadism) because the biologically active fraction (free T) is almost unaffected [18]. Although such an interpretation is possible, estimation of the prevalence of obesity-related hypogonadism is only partially affected when calculated free T (cFT) (*i.e.*, corrected for SHBG)

is taken into account [17,18]. In addition, T replacement therapy (TRT) can improve the most genuine symptoms of male hypogonadism with adult onset (late onset hypogonadism, LOH), *i.e.*, sexual dysfunction, including sexual desire and spontaneous or sex-related penile erections [19,20]. This finding was also verified in trials enrolling patients with obesity, for example, in the T treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme testosterone for diabetes mellitus (T4DM) trial [21]. Nonetheless, the TRT improvement on sexual symptoms in obese patients is often marginal [20], most probably because obesity-related comorbidities (such as CVD) are not affected by restoring eugonadism.

Weight loss, as obtained by lifestyle measures or bariatric surgery, is always associated with a dose-dependent improvement in T levels [22]. In particular, an increase in T levels in trials was tightly associated with weight reduction from study entry [23,24]. A maximal increase in T levels was obtained in studies enrolling obese patients undergoing bariatric surgery, as demonstrated by all the available meta-analyses [23].

Considering that GLP1-RAs can induce a substantial decrease in weight—that is, one that is similar to that obtained by bariatric surgery [9]—and that they can reduce obesity-associated comorbidities [8-10], this review aims to summarize results obtained in trials with GLP1-RAs on obesity-associated hypogonadism and/or obesity-associated sexual dysfunctions. Comparisons with the effects obtained on these topics by another class of anti-diabetic medication (SGLT2i), able to reduce body weight [11,12], will be provided, although the number of studies available is very limited.

METHODS

A comprehensive narrative review was performed using Medline searches and including the following words: ("testosterone"[Supplementary Concept] OR "testosterone"[All Fields] OR "testosteron"[All Fields] OR "testosterone"[MeSH Terms] OR "testosterones"[All Fields] OR "testosterone s"[All Fields]) AND ("glucagon like peptide 1 receptor agonists"[Pharmacological Action] OR "glucagon like peptide 1 receptor agonists"[Supplementary Concept] OR "glucagon like peptide 1 receptor agonists"[All Fields] OR "glucagon like peptide 1 receptor agonist"[All Fields] OR "glucagon like peptide 1 receptor agonists"[MeSH Terms] OR

("glucagon like"[All Fields] AND "peptide 1"[All Fields] AND "receptor"[All Fields] AND "agonists"[All Fields]) and/or ("testosterone"[Supplementary Concept] OR "testosterone"[All Fields] OR "testosteron"[All Fields] OR "testosterone"[MeSH Terms] OR "testosterones"[All Fields] OR "testosterone s"[All Fields]) AND ("sodium glucose transport proteins"[Supplementary Concept] OR "sodium glucose transport proteins"[All Fields] OR "sodium glucose cotransporter"[All Fields] OR "sodium glucose transport proteins"[MeSH Terms] OR ("sodium glucose"[All Fields] AND "transport"[All Fields] AND "proteins"[All Fields]) OR ("sodium"[All Fields] AND "glucose"[All Fields] AND "cotransporter"[All Fields])) AND "2"[All Fields] AND ("antagonists and inhibitors"[MeSH Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors"[All Fields] OR "inhibitors"[All Fields] OR "inhibitor"[All Fields] OR "inhibitor s"[All Fields]). Publications from January 1, 1969, up to June 30, 2025, were included.

MEDICAL NEEDS

During the last decades, male hypogonadism has gone through different classifications, originally according to the suspected site of primary damage in the hypothalamus pituitary testis (HPT) axis, leading to the differentiation between primary and secondary hypogonadism, or hypergonadotropic and hypogonadotropic hypogonadism, respectively [25]. Also, a hypogonadal-like syndrome was considered due to reduced T bioactivity [25,26]. Then, it was given relevance to the timing of life at which testicular function was not as it was expected for age, distinguishing hypogonadism depending on the stage of development, *i.e.*, fetal life, pre-pubertal, post-pubertal, or age-related, also known as LOH [27]. More recently, a new classification based on the presence or absence of congenital or acquired diseases causing structural and/or irreversible impairment of the HPT axis has been introduced [28]. Functional hypogonadism, opposed to organic hypogonadism is generally caused by potentially reversible conditions, including obesity and metabolic derangements without an identified HPT axis disease [29,30]. In patients suffering from functional hypogonadism, low T is often a downstream effect of systemic metabolic dysregulation rather than an HPT failure. In this context, TRT has shown favorable effects on sexual symptoms and body

composition, whereas its role in glycometabolic control and other symptoms and signs, including mobility, cognitive function, mood, and depressive symptoms, is more conflicting [22]. For these reasons, all the major Scientific Societies, together with the regulatory agencies for drugs, emphasize managing functional hypogonadism, trying to address the primary cause. Indeed, in this context, TRT would not be a disease-modifying option, just providing symptomatic relief as a palliative treatment with modest results on some parameters [13,29-31].

1. Established treatments for male hypogonadism

During the last decades, several T formulations have been marketed, through different routes of administration (Table 1), in order to restore physiological serum levels of T [25,32]. The most commonly used formulations are the short-acting intramuscular injectable esters (*i.e.*, T enanthate, T cypionate, T propionate, and combined esters), which are usually administered every two to three weeks, with the great disadvantage of causing peaks and troughs in serum T levels. Long-acting injectable T (*i.e.*, T undecanoate) leads to more stable T serum levels [32,33]; however, its use has been rarely associated with the development of pulmonary oil micro-embolism (POME), suggesting patients monitoring after injection [25]. Other T formulations include transdermal gels, nasal, and oral preparations. The transdermal gel is easy to handle, but it requires every-day application, and T serum levels may vary in relation to gel absorption. Nasal gel is only approved in the USA; it is easy to apply and require multiple daily administrations; moreover, it can carry on nasal discomfort and high variability in absorption [34]. Older oral T formulation is no longer recommended due to its unpredictable absorption [32]. Other new oral T formulations based on a new technology supporting a better bioavailability have been developed and introduced in the US market. However, data derived from the latter formulations are often uncontrolled, of short duration, and based on limited cohorts of treated subjects [34]. The sustained-release muco-adhesive buccal-T-table and subcutaneous T pellets are still available in some countries. However, the former cannot dissolve completely in the mouth and is considered unpleasant, at least by some subjects [32]. T pellets require invasive placement [32].

Table 1. Available testosterone formulations

Compound	Trade name	Dose	Delivery method	Advantage	Disadvantage
Oral preparation					
T undecanoate	Andriol® (EU)	80–160 mg 2–3 times per day	Oral capsules	Easy application, easy to handle	Poor bioavailability Need high-fat meet
T undecanoate	Kyzatrex™ (US)	200 mg twice per day	Oral capsules	Easy application, easy to handle	Low bioavailability Need high-fat meet
T undecanoate	Jatenzo® (US)	158 to 396 mg twice per day	Oral capsules	Easy application, easy to handle	Low bioavailability Need high-fat meet
T undecanoate	Tlando® (US)	225 mg twice per day	Oral capsules	Easy application, easy to handle	Low bioavailability Need high-fat meet
Injectable preparation					
T undecanoate	Nebido®, Testomed® (EU)	Start with 1,000 mg, repeat 1,000 mg after 6 weeks and then every 10–14 weeks	Deep IM slow injection	Long-lasting	Pain at injection site Costs
T undecanoate	Aveed® (US)	Start with 750 mg, repeat 750 mg after 4 weeks and then every 10 weeks	Deep IM slow injection	Long-lasting	Pain at injection site Costs

Table 1. Continued

Compound	Trade name	Dose	Delivery method	Advantage	Disadvantage
T enanthate	Testoviron depot®	250 mg every 3–4 weeks	Deep IM slow injection	Less expensive as compared to others	Frequent IM injection Pain at injection site Peaks and valleys in T concentrations
T enanthate	Delatestryl®	200 mg, once in 2 weeks	Deep IM injection	Less expensive as compared to others	Frequent IM injection Pain at injection site Peaks and valleys in T concentrations
T cypionate	Depo-testosterone® (US)	100 mg, once in 2 weeks	Deep IM injection	Less expensive as compared to others	Frequent IM injection Pain at injection site Peaks and valleys in T concentrations
T propionate	Testovis®	50 mg every other day		Less expensive as compared to others	Frequent IM injection Pain at injection site Peaks and valleys in T concentrations
T mixed esters (propionate 30 mg, phenylpropionate 60 mg, isocaproate 60 mg, decanoate 100 mg)	Sustanon®	250 mg every 3 weeks IM	Deep IM injection	Less expensive as compared to others	Frequent IM injection Pain at injection site Peaks and valleys in T concentrations
Subcutaneous T implants	Testopel pellets®	75 mg per pellet	SC implant	Infrequent administration	Contraindicated in peanut oil allergy Surgical incision for insertion Pellet extrusion
Transdermal/Transmucosal preparation					
T nasal gel	Natesto®	Two pump actuations, one per nostril, 2–3 times daily (one pump actuation: 5.5 mg of T)	Intranasal	Easy application, easy to handle	Nasal discomfort Frequent application
T transdermal	Testogel 1%®	One sachet daily	Transdermal gel	Easy application, easy to handle	Everyday application Attention for possible gel-transfer Skin irritation
T transdermal	Tostran 2%® Tostrex 2%®	Start with six pump actuations (one pump actuation: 10 mg of T)	Transdermal gel	Easy application, easy to handle	Everyday application Attention for possible gel-transfer Skin irritation
T transdermal	Testavan®	Start with one pump actuation per day (one pump actuation: 23 mg of T)	Transdermal gel	Easy application, easy to handle	Everyday application Attention for possible gel-transfer Skin irritation
Buccal T	Striant®	30 mg twice per day	Transbuccal	Easy application, easy to handle	Oral irritation, unpleasant taste

T: testosterone, EU: Europe, US: United States, IM: intramuscular, SC: subcutaneous.

In subjects with secondary functional hypogonadism, selective estrogen receptor modulators (SERMs) have been proposed as an alternative approach, particularly in patients with obesity or metabolic diseases [35], since by inhibiting estrogen-negative feedback to the hypothalamus-pituitary, they lead to an increased release of gonadotropins that, in turn, stimulate T production [36]. A recent meta-analysis in men with obesity-related functional androgen deficiency concluded that clomiphene citrate and enclomiphene citrate could be safe and effective options [36]. However, despite several advantages, SERMs still remain off-label preparations, since more studies are needed to assess their effects on hypogonadal signs and symptoms, and their long-term safety data are still limited [37]. Accordingly, negative effects on sexual desire have been reported [24].

2. Emerging new possibilities for male hypogonadism management

Several population-based studies have clearly shown that circulating T levels progressively decline with aging [38]. Strong evidence supports that associated morbidities and metabolic derangements, in particular, are the most important pathogenetic factors, although genetic background can play an independent role [22,39]. Accordingly, meta-inflammation seems to be crucial in impairing T production, acting either at the central or peripheral level [22]. In this scenario, the need for new therapeutic options to better manage functional hypogonadism due to metabolic-associated morbidities is emerging. As reported above, a low-calorie diet and weight loss are the key elements for overweight and obese hypogonadal subjects complaining of symptoms. However, it is important to recognize that weight loss requires time and often fails in the long terms. Limited evidence has investigated the combination of TRT and lifestyle interventions. The combined approach resulted in better outcomes, including body composition (greater reduction of fat mass and waist circumference and an increase of lean mass) as well as an overall improvement of insulin resistance and better sexual function [22]. However, the evidence derived from the latter approach is still poor, including a limited number of patients. Hence, the new anti-obesity drugs such as GLP1-RAs and SGLT2is can represent a further option to correctly treat overweight and obesity related hypogonadism.

1) Available GLP1-RAs and SGLT2is preparations

GLP1-RAs can be distinguished as short-acting or long-acting, substantially depending on their resistance to the enzymatic dipeptidyl peptidase-4 (DPP4) degradation, which is responsible for their half-life. Among the GLP1-RAs currently approved and marketed (Table 2), semaglutide 2.4 mg weekly has shown a mean weight reduction of up to 15%, becoming a benchmark in obesity pharmacotherapy [40], also thanks to its favorable pharmacokinetics allowing one injection per week, as opposed to liraglutide 3.0 mg which requires daily injection and leads to a more modest weight loss of about 5% [41]. More recently, tirzepatide has entered the market, becoming the first-in-class dual GIP/GLP1-RA. Firstly, only considered for diabetes treatment, in the SURPASS studies, tirzepatide demonstrated higher efficacy in reducing both HbA1c and body weight *vs.* placebo [42]. Then, the SURMOUNT studies assessed its efficacy as a cornerstone of obesity treatment. A recent meta-analysis of 14 randomized controlled trials (RCTs), involving 14,713 patients reported that tirzepatide at all doses led to a higher proportion of patients achieving a weight loss target of at least 5%, 10%, and 15% *vs.* placebo and *vs.* insulin [43]. Also, in a head-to-head phase 3 comparison of tirzepatide *vs.* semaglutide, the former lead to a statistically and clinically superior weight loss, with a significantly higher proportion of patients reaching the 10%, 15%, 20%, and 25% weight loss targets [44].

In the pipeline, three promising GLP1-RA-based compounds have reached Phase 3 trials demonstrating outstanding results. Retatrutide, an injectable triple agonist (GLP/GIP/GCGR), showed a highly significant weight reduction, up to -24%, in Phase 2 [5]. CagriSema, a fixed-dose combination of a long-acting amylin analogue, cagrilintide 2.4 mg and semaglutide 2.4 mg, has been studied for diabetes or obesity in the REDEFINE trials, demonstrating in a Phase 3a trial an estimated body weight change of -13.7% *vs.* -3.4% in the placebo group [45]. In parallel, an orally administered compound has shown promising results in Phase 2: the non-peptide GLP1-RA orfoglipron led to up -14.7% of weight loss [46], comparable to that of injectable semaglutide [40]. Hence, taking together available data suggest that at the present time tirzepatide and retatrutide seem to be the most effective in terms of HbA1c reduction and dose-dependent weight loss. Also, for all the GLP1-RAs, CV benefits are well established, demonstrating a reduction in major adverse CV events (MACE), CV

Table 2. Competitive environment table on GLP1-RA preparations

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Exenatide (Bydureon Bcise [®] , Bydureon SC [®] , Byetta [®])	AstraZeneca (originally Amylin/BMS)	Exendin-4 analog	T2DM	Marketed (global)	Through GLP-1 receptor agonism: Pancreatic effects (β-cells and hormonal secretion) Enhance insulins secretion
Liraglutide (Saxenda [®] , Victoza [®])	Novo Nordisk	Modified human GLP-1 analog (acylated)	T2DM, obesity, CV risk reduction	Marketed (global)	Inhibit glucagon release Stimulate proliferation of pancreatic β-cells and inhibit their apoptosis
Dulaglutide (Trulicity [®])	Eli Lilly	GLP-1 analog fused to Fc IgG4	T2DM	Marketed (global)	Increase somatostatin secretion
Semaglutide (Ozempic [®] , Rybelsus [®] , Wegovy [®])	Novo Nordisk	Modified human GLP-1 analog (acylated)	T2DM, obesity, CV risk reduction	Marketed (global)	Central nervous system and appetite regulation Act on hypothalamic appetite-regulating center
Lixisenatide (Lyxumia [®])	Sanofi-Adventis	Exendin-4 analog	T2DM	Marketed (global)	Enhance satiety signals and suppress appetite Gastrointestinal and hepatic effects
					Inhibit hepatic gluconeogenesis
					Reduce hepatic steatosis and fibrosis
					Slow gastric emptying
					Delays small intestinal peristalsis
					Stimulate pancreatic enzyme secretion
					Adipose tissue and energy metabolism
					Increase brown adipose tissue metabolism
					Reduce lipid accumulation in white adipose tissue
					Promote body weight loss
Orforglipron	Eli Lilly	Small molecule (oral)	T2DM, obesity	Phase 3	Oral non-peptide GLP1-RA
Insulin degludec+Liraglutide (Xultophy [®])	Novo Nordisk	Fixed-ratio combo of insulin and GLP-1 analog	T2DM	Marketed (global)	Basal insulin for fasting glucose control+GLP1-RA for postprandial glucose and weight control
Insulin glargine+Lixisenatide (Soliqua [®])	Sanofia	Fixed-ratio combo of insulin and GLP-1 analog	T2DM	Marketed (global)	Basal insulin for fasting glucose control+GLP1-RA for postprandial glucose and weight control
Tirzepatide (Zepbound [®] , Mounjaro [®])	Eli Lilly	Dual GIP and GLP-1 receptor agonist	T2DM, obesity	Marketed (global)	Activates both GIP and GLP-1 receptors to improve glycemic control and induce weight loss
CagriSema (Cagrilintide+Semaglutide)	Novo Nordisk	Fixed-dose combo of amylin analog and GLP-1 analog	Obesity, T2DM	Phase 3	GLP1-RA+plus amylin receptor agonist; synergistic weight loss and glucose control
Retatrutide	Eli Lilly	Triple agonist (GIP/GLP-1/glucagon)	Obesity, T2DM	Phase 3	Activates GIP, GLP-1, and glucagon receptors to improve glycemic control and induce weight loss

GLP1-RA: glucagon-like peptide-1 receptor agonist, GLP-1: glucagon-like peptide-1, GIP: glucose-dependent insulinotropic polypeptide, T2DM: type 2 diabetes mellitus, CV: cardiovascular.

mortality, and all-cause mortality risk, although with some differences depending on the drug [47]. The most common side effects, shared across all the above-mentioned drugs, remain gastrointestinal, typically mild to moderate, dose-dependent, and transient [4,48].

On the other side, even if with milder results as compared to incretin-based therapies, SGLT2is have also shown positive effects on weight reduction. A network meta-analysis of 29 RTCs, including 11,999 patients, suggested a more pronounced beneficial effect on weight loss with SGLT2i monotherapy as compared to both metformin and DPP4 inhibitors (DPP4is) [49]. Among the SGLT2is currently marketed (Table 3), canagliflozin 300 mg showed the greatest weight loss effect [49]. Moreover, similar to what was observed for GLP1-RAs, they have demonstrated multi-organ protective benefits, with particular focus on cardio-renal endpoints. In a meta-analysis on three trials, including 34,322 patients, SGLT2is reduced the risk of myocardial infarction, stroke, or CV death only in patients with established atherosclerotic CVD; in contrast, the protective effects against heart failure and renal disease progression were consistent irrespective of baseline CVD

or heart failure status [50]. Even if at the moment the major indication for SGLT2i is for diabetes treatment, they have shown a broader therapeutic action which goes beyond glycemic control, being repurposed as “drugs for cardiorenal protection” [50,51]. Despite these major clinical advantages, some adverse events should be considered, especially regarding polyuria and urogenital infections [50,51].

It is evident that GLP1-RAs and SGLT2is are reshaping the therapeutic approach to metabolic diseases, with exceptionally strong prospects accompanied by a continuous and irrepressible evolution. However, drugs accessibility, supply constraints, real-world tolerability, and long-term safety in patients with hypogonadism still remain an open challenge.

2) Potential development issues of GLP1-RAs and SGLT2is

In the following section the possible role of GLP1-RAs and SGLT2is in patients with metabolic related hypogonadism and/or sexual dysfunctions will be systematically analyzed.

Table 3. Competitive environment table on SGLT2i preparations

Compound	Company	Structure	Indication	Stage of development	Mechanism of action
Dapagliflozin (Forxiga [®])	Bristol Myers Squibb Pharma Eeig	C-aryl glucoside	T2DM, HF, CKD	Marketed (global)	Through SGLT2 inhibition: inhibition of renal glucose reabsorption
Empagliflozin (Jardiance [®])	Boehringer Ingelheim	C-aryl glucoside	T2DM, HF, CKD	Marketed (global)	
Canagliflozin (Invokana [®])	Janssen Cilag International	C-aryl glucoside	T2DM, CKD	Marketed (global)	
Ertugliflozin (Steglatro [®])	Merck Sharp & Dohme Ltd	C-aryl glucoside	T2DM	Marketed (US/EU)	
Ipragliflozin (Suglat [®])	Astellas Pharma	C-aryl glucoside	T2DM, T1DM	Marketed (Japan, South Korea)	
Bexagliflozin (Brenzavvy [®])	TheracosBio	C-aryl glucoside	T2DM	Marketed (US)	SGLT2i+enhanced insulin sensitivity
Dapagliflozin+Metformin (Xigduo [®])	AstraZeneca	C-aryl glucoside +Biguanide	T2DM	Marketed (global)	
Empagliflozin+Metformin (Synjardy [®])	Boehringer Ingelheim/Eli Lilly	C-aryl glucoside +Biguanide	T2DM	Marketed (global)	
Canagliflozin+Metformin (Vokanamet [®])	Janssen	C-aryl glucoside +Biguanide	T2DM	Marketed (global)	
Ertugliflozin+Metformin (Segluromet [®])	Merck/Pfizer	C-aryl glucoside +Biguanide	T2DM	Marketed (global)	
Ertugliflozin+Sitagliptin (Steglujan [®])	Merck/Pfizer	C-aryl glucoside +DPP4i	T2DM	Marketed (global)	
Empagliflozin+Linagliptin (Glyxambi [®])	Boehringer Ingelheim/Eli Lilly	C-aryl glucoside +DPP4i	T2DM	Marketed (global)	
Dapagliflozin+Saxagliptin (Qtern [®])	AstraZeneca	C-aryl glucoside +DPP4i	T2DM	Marketed (global)	

SGLT2i: sodium-glucose cotransporter 2 inhibitor, DPP4i: dipeptidyl peptidase-4 inhibitor, T2DM: type 2 diabetes mellitus, HF: heart failure, CKD: chronic kidney disease, T1DM: type 1 diabetes mellitus, US: United States, EU: Europe.

(1) Effect of GLP1-RA vs. baseline or TRT

Eight studies evaluated the effects of GLP-1-RAs on the HPT axis [52-59]. Overall, 367 subjects with a mean age of 42.7 ± 10.6 years, a mean BMI of 33.5 ± 5.1 kg/m², and a mean follow-up of 29.0 ± 20.4 weeks were included in the analysis (Table 4). Upon GLP1-RA treatment, a mean weight loss of 5.5 ± 5.2 kg was observed.

Liraglutide and exenatide were used in three and two studies, respectively, whereas one author compared the effects of liraglutide with dulaglutide. Finally, one study investigated the use of dulaglutide or semaglutide only, respectively. Four studies included only subjects with T2DM, one a mixed population of diabetic and non-diabetic patients, and three studies only non-diabetic individuals (Table 4). Metformin was used in combination with GLP-1-RAs in three studies, whereas physical exercise was used in one trial (Table 4). Finally, a TRT arm in comparison with the use of GLP1-RAs was included in three studies (Table 4).

(2) Body composition and metabolic controls

GLP1-RAs resulted in an improvement in body composition, including body weight, BMI, waist circumference and body fat in the vast majority of the studies (Table 5). Similarly, GLP1-RAs were associated with an improvement of glycometabolic control and insulin resistance (Table 5), whereas more conflicting data were observed when the lipid profile was investigated (Table 5). When the use of GLP1-RAs was compared to TRT, the former medical approach showed better results when either body composition or glycometabolic parameters were investigated, particularly when one study was considered [57].

(3) Hormonal parameters

GLP-1-RAs showed an increase in total T, cFT, and SHBG levels (Table 5). Conversely, no difference in LH and follicular stimulating hormone (FSH) levels was detected (Table 5) except when 2 studies were considered [53,57]. In addition, several studies also documented an SHBG circulating level increment (Table 5).

(4) Sexual function

Among studies investigating the effects of GLP1-RAs, five trials reported data on sexual function (Table 4, 5). When compared to the baseline, GLP1-RAs resulted in a significant improvement in the erectile function and sexual desire domain (Table 5). Conversely, no

difference in orgasm and sexual satisfaction before and after GLP1-RAs administration was observed (Table 5). Finally, an overall improvement in the aging male scale (AMS) was also observed at least in one trial (AMS; Table 5) [59]. When the use of GLP1-RAs was compared to TRT, the use of T resulted in better scores in orgasm and sexual satisfaction domains (Table 5). Only one study showed better erectile function when GLP1-RA were compared to TRT whereas no difference was reported in another study (Table 5). Similarly, no difference in sexual desire as well as in AMS was reported (Table 5).

3) Effect of SLT2i vs. baseline

Three studies investigated the role of gliofzines on several parameters, including T and sexual function [54,60,61]. Overall, 52 subjects with a mean age of 47.2 ± 14.1 years, a mean BMI of 31.7 ± 2.5 kg/m², and a mean follow-up of 22.7 ± 25.7 weeks (Table 4) were analyzed. Two studies were based on the administration of dapagliflozin (10 mg), and one investigated the use of empagliflozin (10 mg) alone or add-on metformin.

(1) Body composition and metabolic controls

Gliofzines resulted in an improvement in body composition, including body weight, BMI, and waist circumference reduction (Table 5). Similarly, they induced an improvement of fasting glycaemia and HbA1c (Table 5). However, for all the aforementioned parameters, only one study was available [54]. No data related to the effect of gliofzines on lipid profile and on markers of insulin resistance were available among the studies analyzed.

(2) Hormonal parameters

No significant modification in total T, cFT, LH, and FSH levels after the use of gliofzines was observed (Table 5). Conversely, a significant increase in SHBG levels after gliofzines administration was detected in one study [54] but not confirmed in another [61] (Table 5).

(3) Sexual function

Only 2 studies, including 26 subjects evaluate the effect of dapagliflozin on erectile function. The use of dapagliflozin resulted in an improvement in the erectile function domain (Table 5). No data on other sexual function domains were available.

Table 4. Moderators and outcome variables in individual studies included in the analysis

Study	Location	Type of study	FU (wk)	Age (y)	BMI (kg/m ²)	DM (%)	Type of drug	TRT arm	TT (nmol/L)	IIEF
GLP1-RA										
Shao et al, 2018 [52]	Harbin, China	CBA	12	43.0	30.5	100	Exenatide and metformin	-	12.9	-
Jensterle et al, 2019 [53]	Ljubljana, Slovenia	RCT	16	43.9	43.2	40	Liraglutide	+	7.6	-
Giagulli et al, 2020 [54]	Bari, Italy	CBA	52	51.1	33.5	100	Dulaglutide and metformin	-	9.4	IIEF5
Giagulli et al, 2020 [54] ^a	Bari, Italy	CBA	52	48.9	34.0	100	Liraglutide and metformin	-	8.9	IIEF5
Graybill et al, 2021 [55]	Houston, TX, US	BA	24	57.6	34.9	100	Exenatide and metformin	-	11.5	-
Andersen et al, 2022 [56]	Copenhagen, Denmark	RCT	52	41.0	32.0	0	Liraglutide and physical exercise	-	-	-
Andersen et al, 2022 [56] ^a	Copenhagen, Denmark	RCT	52	41.0	32.0	0	Liraglutide	-	-	-
La Vignera et al, 2023 [57]	Catania, Italy	CBA	12	26.0	36.0	0	Liraglutide	+	4.8	IIEF5
Lengsfeld et al, 2024 [58]	Basel, Switzerland	RCT	4	24.5	23.0	0	Dulaglutide	-	20.3	MGH-SFQ
Gregorič et al, 2025 [59]	Ljubljana, Slovenia	RCT	14	50.0	35.9	100	Semaglutide	+	61	IIEF-15
SGLT2i										
Giagulli et al, 2020 [54] ^a	Bari, Italy	CBA	52	50.6	34.3	100	Dapagliflozin and metformin	-	9.4	IIEF-5
Cannarella et al, 2024 [60]	Catania, Italy	CBA	52	59.8	31.5	100	Dapagliflozin	-	-	IIEF-5
Kosinski et al, 2024 [61]	Lausanne, Switzerland	RCT	4	31.7	29.3	0	Empagliflozin	-	19.4	-

All data are reported as mean.

FU: follow-up, BMI: body mass index, DM: diabetes mellitus, TRT: testosterone replacement therapy, TT: total testosterone, IIEF: International Index of Erectile Function, GLP1-RA: glucagon-like peptide-1 receptor agonist, SGLT2i: sodium-glucose cotransporter 2 inhibitor, CBA: controlled before-and-after study between two or more groups of participants receiving different interventions, RCT: randomized controlled trial, BA: controlled cohort before-and-after comparisons in the same group of patients, MGH-SFQ: Massachusetts General Hospital-Sexual Functioning Questionnaire.

^aSame study, different groups.

Table 5. Outcome variables in individual studies included in analysis

GLP1-RA	Shao et al, 2018 [52]	Jensterle et al, 2019 [53]	Giagulli et al, 2020 [54] ^a	Giagulli et al, 2020 [54] ^b	Graybill et al, 2021 [55]	Andersen et al, 2022 [56] ^c	Andersen et al, 2022 [56] ^d	La Vignera et al, 2023 [57]	Lengsfeld et al, 2024 [58]	Gregorič et al, 2025 [59]
Metabolic parameters vs. baseline										
Body weight	→	→	→	→	→	↔	→	→	↔	→
BMI	→	→	→	→	→	↔	→	→	↔	→
Waist	→	→	→	→	→	↔	→	→	↔	→
Fat mass	→	→	→	→	→	↔	→	→	↔	→
FG	→	→	→	→	→	↔	→	→	↔	→
HbA1c	→	→	→	→	→	↔	→	→	↔	→
HOMA	→	→	→	→	→	↔	→	→	↔	→
TC	→	→	→	→	→	↔	→	→	↔	→
HDL	→	→	→	→	→	↔	→	→	↔	→
LDL	→	→	→	→	→	↔	→	→	↔	→
TG	→	→	→	→	→	↔	→	→	↔	→
Metabolic parameters vs. TRT										
Body weight	-	↔	↔	↔	↔	-	↔	↔	↔	↔
BMI	-	↔	↔	↔	↔	-	↔	↔	↔	↔
Waist	-	↔	↔	↔	↔	-	↔	↔	↔	↔
FG	-	↔	↔	↔	↔	-	↔	↔	↔	↔
HbA1c	-	↔	↔	↔	↔	-	↔	↔	↔	↔
HOMA	-	↔	↔	↔	↔	-	↔	↔	↔	↔
TC	-	↔	↔	↔	↔	-	↔	↔	↔	↔
HDL	-	↔	↔	↔	↔	-	↔	↔	↔	↔
LDL	-	↔	↔	↔	↔	-	↔	↔	↔	↔
TG	-	↔	↔	↔	↔	-	↔	↔	↔	↔
Hormonal parameters vs. baseline										
TT	↑	↑	↑	↑	↔	-	↑	↑	↔	↑
cFT	↑	↔	↑	↑	↔	-	↑	↑	↔	↑
SHBG	↑	↔	↑	↑	↔	-	↑	↑	↔	↑
LH	↔	↑	↔	↔	↔	-	↔	↔	↔	↔
FSH	-	↑	↔	↔	-	-	↔	↔	↔	↔

Table 5. Continued

GLP1-RA	Study									
	Shao et al, 2018 [52]	Jensterle et al, 2019 [53]	Giaquelli et al, 2020 [54] ^a	Giaquelli et al, 2020 [54] ^b	Graybill et al, 2021 [55]	Andersen et al, 2022 [56] ^c	Andersen et al, 2022 [56] ^d	La Vignera et al, 2023 [57]	Lengsfeld et al, 2024 [58]	Gregorič et al, 2025 [59]
Sexual parameters vs. baseline										
Erectile function ^e	-	-	↑	↑	-	-	-	-	↔	↔
Sexual desire ^e	-	-	-	-	-	-	-	-	↔	↑
Orgasm ^e	-	-	-	-	-	-	-	-	↔	↔
Sexual satisfaction ^e	-	-	-	-	-	-	-	-	↔	↔
AMS	-	↔	-	-	-	-	-	-	-	→
Sexual parameters vs. TRT										
Erectile function	-	-	-	-	-	-	↑	-	-	↔
Desire	-	-	-	-	-	-	-	-	-	↔
Orgasm	-	-	-	-	-	-	-	-	-	→
Sexual satisfaction ^e	-	-	-	-	-	-	-	-	-	→
AMS	-	↔	-	-	-	-	-	-	-	↔
SGLT2i										
Metabolic parameters vs. baseline										
Body weight			↓							
BMI			↓							
Waist			↓							
FG			↓							
HbA1c			↓							
Hormonal and sexual parameters vs. baseline										
TT			↔	↔					↔	
cFT			↔	↔					↔	
LH			↔	↔					↔	
FSH			↔	↔					↔	
SHBG			↑	↑					↔	
Erectile function			↑	↑					-	

GLP1-RA: glucagon-like peptide-1 receptor agonist, SGLT2i: sodium-glucose cotransporter 2 inhibitor, BMI: body mass index, FG: fasting glucose, HbA1c: glycated hemoglobin, TC: total cholesterol, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, TG: triglycerides, TT: total testosterone, cFT: calculated free testosterone, SHBG: sex hormone binding globulin, LH: luteinizing hormone, FSH: follicular stimulating hormone, AMS: Aging male scale.

^aDulaglutide; ^bliraglutide; ^cliraglutide and physical exercise; ^dliraglutide same study, different groups.

^eDerived from International Index of Erectile Function.

DISCUSSION

Available data confirm that the use of either GLP1-RAs or SGLT2is can result in body weight reduction as well as in body composition improvement. Similarly, both medications can induce an improvement in glycometabolic profile, whereas their effects on lipid metabolism are less evident. When the impact of these medications on the HPT axis was investigated, GLP1-RAs showed an increase in total T and cFT with more limited effects in gonadotropin levels. The latter results seem to be only partially dependent on the observed weight loss, suggesting a direct, rather than only indirect, mechanism of action based on body composition modifications. Accordingly, similar results were not observed for SGLT2is despite comparable effects on body weight. On the other hand, both GLP1-RAs and SGLT2is resulted in an improvement of erectile function that can be explained, at least partially, by the concomitant improvement of the metabolic profile. Similar results were recently reported by our group when only T2DM patients were considered [62]. Finally, when the use of GLP1-RAs was compared to TRT, as expected, the former showed better results on glycometabolic parameters, whereas TRT resulted in better scores on orgasm and sexual satisfaction domains.

A large body of evidence has documented that in almost one in two obese subjects there is an LH-uncompensated T deficiency [16,17,63], which could be associated with sexual dysfunctions, the most genuine symptoms of LOH [13,64,65]. In addition, obesity, and in particular visceral obesity, has been considered the most predictive parameter of forthcoming secondary hypogonadism in a longitudinal study on middle-aged and older European males [66]. In a meta-analysis, weight loss obtained with lifestyle measures (diet or physical exercise) or bariatric surgery was able to restore T levels and improve erectile function [22]. This was also observed in our preclinical studies using a rabbit model of metabolic syndrome (MetS) [67,68]. In MetS rabbits, we described a visceral obesity-induced hypothalamic metaflammation with a disruption of the complex network of neurotransmitters controlling gonadotropin-releasing hormone (GnRH) release (including Kiss-1 and its receptor) and an overt and symptomatic (erectile dysfunction) secondary hypogonadism. By training MetS rabbits to perform endurance exercises, hypothalamic metaflammation was restored,

and the function of the HPT axis and erectile function were normalized [67]. Hence, lifestyle measures (dieting and physical exercise) could be effective in counteracting obesity-induced secondary hypogonadism. However, they often ultimately fail for various reasons, as reviewed elsewhere [69]. In that case, medical or surgical treatment could be considered.

Considering that the use of GLP1-RAs is the most efficacious medical treatment for obesity [4], it is obvious to hypothesize that this class of medications could induce a rise in T levels in obese, hypogonadal subjects [22]. Present results confirm that GLP1-RAs consistently increase total T over the baseline values in obese subjects with a consistent rise in cFT. Similar results were observed in another recent meta-analysis [70]. Interestingly, an even higher T rise (up to 8 nmol/L) was more recently reported in a RCT including 83 obese hypogonadal subjects randomized to tirzepatide, T gel, or lifestyle modifications for 2 months [71]. The mechanism of action of GLP1-RAs in inducing a T rise is still a matter of debate.

It has been proposed that GLP1-RAs could upregulate the HPT axis by increasing Kiss-1 neuron activity within the hypothalamus and, in particular, in the arcuate nucleus (ARC), where GLP-1 fiber projections from the nucleus tractus solitarius (NTS) and GLP-1R are abundant [72,73]. In particular, it was observed that GLP-1 increased mRNA expression of KISS-1 in the rat clonal hypothalamic cell line rHypoE-8, in GT1-7 GnRH-producing neurons, and in primary cultures of fetal rat brain [73]. In addition, electrophysiological recordings revealed that liraglutide increased action potential firing and caused a direct membrane depolarization of ARC Kiss-1 cells in brain slices of male and female mice [74]. These studies are in line with a previous observation that, in GT1-7 cells, GLP-1 caused a dose-dependent increase in GnRH secretion and that intracerebroventricular injection of GLP-1 produced an increase in LH levels [75]. Accordingly, GLP-1 microinjections within the median eminence of ovariectomized sheep (supplemented with estrogen and progesterone) were able to elicit a dose-dependent surge in LH [76]. A subsequent study by the same group documented that in sheep, the intravenous infusion of a GLP1-RA (exendin-4) during the follicular phase of the estrous cycle increased plasma LH concentrations and its pulse amplitude [77]. An increase in LH and T was also documented in obese mice upon chronic (12 weeks) liraglu-

tion administration [78]. In that study, the reversion of obesity-associated hypogonadism by liraglutide was associated with an overall improvement in body weight and glucose metabolism [78].

Human studies considering sex hormone measurements and sexual function evaluation upon GLP1-RA treatment are few and often uncontrolled (Table 4). However, in these studies, results with GLP1-RAs on metabolic and anthropometric parameters (Table 5) were in line with those derived from meta-analyses of larger, placebo-controlled RCTs [6,7]. In the aforementioned studies, a statistically significant, GLP1-RA-induced LH increase was observed only in one trial, but not in the other seven (Table 5). In contrast, the present data demonstrate a significant effect on T levels (Table 5). In addition, two separate studies, one from Germany [79] and the other from the UK [80], failed to demonstrate any effect of GLP-1 infusion (0.4 and 0.8 pmol/kg/min, respectively) on LH secretion or pulsatility [79,80], despite a decrease in food intake [80]. One study [79] even found a decrease in the number of T pulses upon GLP-1 infusion during euglycemic clamp, which was not confirmed in the UK study [80]. Hence, GLP1-RAs might have some additional effect on the HPT axis, besides the hypothalamic one. In an experimental study on rat undergoing a protocol of ischemia-reperfusion, it was found that semaglutide administration counteracted the negative effect of the testicular damage on several genes involved in androgen formation within the penis, thereby restoring T, without affecting circulating LH and FSH [81]. The effect of semaglutide was counteracted by a GLP1-R antagonist (exendin 9-39) [81]. Hence, it is conceivable that GLP-1 might have direct beneficial effects within the testis by decreasing oxidative stress markers and favoring androgen formation [78,81].

In addition, the T increase observed upon GLP1-RA administration is associated with a decrease in hypogonadal symptom scoring (though AMS) and with an improvement in erection and sexual desire (Table 5). Interestingly, the effect of GLP1-RAs on erection and desire is similar to that obtained with TRT in the few studies that investigated this point (Table 5). Considering that the improvement of penile erection could also be mediated by the general improvement in metabolic parameters [82-84], besides T increase, this is not the case for the reduced sexual desire that is recognized as the most genuine symptom of LOH, *i.e.*, not affected

by eventual comorbidities [22,85]. This finding suggests that the increased T level upon GLP1-RAs has biological effects: amelioration of sexual dysfunctions, in particular, reduced sexual desire. On the other hand, the improvement of body image after weight loss can reinforce a patient's self-esteem, supporting an improvement of sexual desire [86-88].

GLP1-RAs are not the only new diabetes medications that are associated with weight loss. SGLT2is in both diabetic [11] and non-diabetic [12] populations are able to induce weight loss, although to a lower extent than with the most recent GLP1-RAs [89]. Only two studies were available investigating the effect of SGLT2is on the male HPT axis [54,61]. In a small (26 subjects without diabetes), short-term (one month), randomized, double-blind, placebo-controlled study, it was found that empagliflozin administration had no effect on gonadotropin or T levels [61]. In that study, empagliflozin had no effect on weight, and only a subset (11 subjects) of enrolled subjects was obese. In another retrospective, uncontrolled trial on subjects with diabetes, a modest increase in T levels was detected after a SGLT2i addition to metformin [54]. An improvement in erection was also observed [54]. By analyzing these very preliminary results, SGLT2is do not apparently affect the HPT axis, although they were associated with weight loss [54,61]. Nonetheless, erections were improved, most probably because of the improved glucose metabolism [54,61] and overall CV health [11,12]. However, it should be clarified that the limited data related to SGLT2is prevent drawing any final conclusions.

CONCLUSIONS

According to position statements and guidelines of several endocrine societies [29,30,64,65], including the Italian one [13,14], losing weight is the cornerstone treatment for obesity-associated hypogonadism. Our opinion is that, if lifestyle measures fail, the use of GLP1-RAs could be an efficient treatment for the condition, including the T deficiency. The present study, suggests that they were not inferior to standard TRT, as far as sexuality is concerned. Similar, results have been reported in a recent meta-analysis [90]. In addition, GLP1-RAs showed superiority to TRT in improving anthropometric parameters and glucose metabolism. Considering the beneficial effects of GLP1-RAs on the CV system [8-10], as opposed to the neutral effects

of TRT [24,91,92], we believe that this class of medications could resolve the underlying CV problems that often cause erectile dysfunction. Hence, in sexual dysfunction related to obesity-associated hypogonadism, the use of GLP1-RAs could treat the condition, while TRT appears only as a symptomatic opportunity. The only pitfall of GLP1-RAs, when compared to TRT, is that their cost is almost 6-fold higher than a standard treatment with T.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: GC, MM. Data curation: MR, GC. Formal analysis: GC, MR, GR. Funding acquisition: CS, MM. Investigation: GC, MR, OS, GR. Methodology: GC, MR, GR. Project administration: GC, MM. Resources: CS, MM. Software: GC, MR. Supervision: GC, MM, LV. Validation: GC, MM. Visualization: GC, MM. Writing – original draft: GC, MR. Writing – review & editing: GC, CS, MR, OS, CB, GR, LV, MM.

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