

REVIEW ARTICLE

Emerging Effects of Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors on Male Sexual Hormones and Behaviors: Systematic Review and Meta-Analysis

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Abstract

Background: The efficacy of glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) in weight loss and long-term cardiovascular (CV) safety is established. The role of these medications on male sexual hormones and function has not been adequately clarified.

Objective: To systematically review and meta-analyze the effects of GLP1-RA and SGLT2i on obesity-associated hypogonadism and sexual dysfunctions.

Methods: A systematic search of Medline was conducted from 1969 to August 2025, according to PRISMA and MOOSE guidelines. All observational or randomized controlled trials evaluating the effects of GLP1-RA or SGLT2i on hormonal and/or sexual parameters in overweight and obese subjects with or without diabetes mellitus (DM) were included in the analysis.

Results: Eight studies, including 375 subjects, evaluated the effects of GLP1-RAs, whereas three, accounting for 52 subjects, investigated the effects of SGLT2is. Both classes of medications showed an overall improvement of body composition and metabolic profile, resulting in positive erectile function outcomes. Only GLP1-RAs significantly increased total and calculated free testosterone along with gonadotropins. The findings of GLP1-RAs on T levels were independent from the observed weight loss, suggesting a direct, rather than an indirect, mechanism of action on the hypothalamus–pituitary–testis axis. Finally, the use of testosterone replacement therapy (TRT) showed better results as compared to GLP1-RAs when orgasm and sexual satisfaction domains were investigated.

Conclusions: Present data support the use of GLP1-RAs for improving sexual dysfunction, and its underlying CV problems, in obese patients with ED. A combination of TRT and GLP1-RAs can be considered in selected cases. Data on SGLT2is are too limited to draw final conclusions.

1 | Introduction

Noncommunicable diseases (NCDs), including cardiovascular (CV) diseases (CVD), and diabetes mellitus (DM), still represent the most important causes of death and disability-adjusted life-years, at least in Western countries [1]. Overweight and obesity secondary to physical inactivity and a diet enriched in proteins, fats, and carbohydrates can explain, at least partially, this scenario. Interestingly, although obesity-related complications, including type 2 DM (T2DM), dyslipidemia, and arterial hypertension (AH), significantly contribute to overall mortality burden, obesity *per se* plays an independent role in the stratification of CV risk [2].

Based on these data, the association between obesity and erectile dysfunction (ED) does not represent a surprise [3–5]. In particular, a recent meta-analysis, including 42,489 men, confirmed a step-wise increase in the risk of ED according to BMI even after the adjustment for confounders [4]. Low testosterone (T) represents another condition frequently observed in obese patients, which can further worsen ED-related obesity [6–8]. Metaflammation, acting either at the central or peripheral level, impairing T production, probably represents the best characterized underlying pathogenetic factor although several other mechanisms have been advocated [9–11] and revised elsewhere [12–14].

The World Health Organization (WHO) 2030 agenda for Sustainable Development Goals (SDGs target 3.4) has recognized NCDs as a key challenge for sustainable development. In order to improve overall health status, WHO has recommended its member states to control and prevent the unconditional probability of deaths from NCDs for people aged 30–70 years by modifying lifestyle and metabolic risk factors, including overweight–obesity [15].

Several studies have documented that intensive lifestyle programs, including an integrated approach with nutritional counseling and physical activity, can improve weight control and reduce the risk of progression from obesity to its associated morbidities [16]. However, the long-term success of lifestyle intervention is often limited, with only 15% of individuals reporting a sustained 10% or greater weight loss [16]. Medical or surgical interventions can represent possible alternatives.

Concerning antiobesity medications, the introduction of hormone-based preparations (incretins), including glucagon-like peptide-1 (GLP-1) receptor agonists (GLP1-RAs) or double GLP1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, has revolutionized the medical approach. In a meta-analysis, concerning 55 studies involving 16,269 participants and 12 different GLP1-RAs, it showed that at 52 weeks semaglutide 1 mg, tirzepatide 5–15 mg, and retatrutide 6.5 mg induced an 8.05%, 12.3%, and 13.23% weight reduction, respectively [17]. In addition, the same medication group has shown other specific positive effects on glycometabolic control in patients with DM and other relevant positive effects on obesity-associated comorbidities, including the risk the CV morbidity and mortality or chronic kidney ailments, easing sleep apnea symptoms, and even slowing the development of Parkinson's disease [18–20]. Sodium-glucose cotransporter 2 inhibitors (SGLT2is) represent another new class of medication showing weight reduction in

subjects with [21] and without [22] T2DM, as well as CV and nephrological long-term protection. However, at the present time, this class of medications has been approved only for T2DM-related obesity.

Emerging evidence has clearly shown that weight loss can improve obesity-related hypogonadism and ED [6]. In particular, an increase in T levels in trials was tightly associated with weight reduction from study entry [23, 24]. However, data on the specific impact of GLP1-RAs and/or SGLT2is on T levels and sexual function are still limited [25].

Based on the available evidence, the aim of this review is to summarize the results obtained in trials with GLP1-RAs and/or SGLT2is and to verify their impact on hypogonadism and sexual function in males.

2 | Methods

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The specific PRISMA and MOOSE checklists are reported as Supporting Information (Supporting Information Files 1 and 2).

The following PICO criteria have been used: **population**: overweight or obese male ≥ 18 -year-old; **intervention**: individuals treated with GLP1-RAs or SGLT2is; **comparison**: prospective or retrospective analyses from baseline or versus testosterone replacement therapy (TRT); **outcomes**: testosterone (T) level increase and sexual function modifications.

The protocol of this study (CRD420251134505) was published on the website of the University of York (Centre for Reviews and Dissemination, <https://www.crd.york.ac.uk/PROSPERO/view/CRD420251134505>).

2.1 | Information Source and Search Strategy

A comprehensive systematic review was performed using Medline search 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 August 31st, 2025 were included.

2.2 | Study Selection

All observational or randomized controlled trials (RCTs) evaluating the effects of GLP1-RAs or SGLT2is on hormonal and/or sexual parameters, in overweight and obese subjects with or without DM were included in the analysis. Case reports were excluded. Only data derived from full papers were considered. Data published as meeting abstracts were excluded from the analysis. Similarly, data derived from the use of GLP1-RAs or SGLT2is nonreporting T levels and/or sexual function parameters were excluded from the analysis.

The search was restricted to English-language articles. The identification of relevant studies was performed independently by three of the authors (Clotilde Sparano, Marilina, Romeo, and Giulia Rastrelli), and conflicts have been resolved by the consensus of other investigators. Studies not reporting data on sexual function and or on T levels have been excluded from the analysis. We have not employed search software but hand-searched the bibliographies of retrieved papers for additional references. All the authors have adequately contributed to the analysis of the paper and will review the final version of the manuscript. The main source of information has been derived from published articles.

2.3 | Outcomes

The primary outcome of this analysis was the evaluation of the effects of GLP1-RAs or SGLT2is on T levels and/or sexual function at endpoint. Secondary analyses included the effects of the same medications on body composition and glycometabolic profile. When possible, comparison with TRT was investigated. In addition, to better understand the role of GLP1-RAs on T increase, we compared the present data to those derived from a previous meta-analysis performed by our group [6] investigating the contribution of different dieting approaches.

2.4 | Quality Assessment

The quality of trials was assessed using the Risk Of Bias In Nonrandomized Studies—of Intervention (ROBINS-I) tool [26] (Supporting Information Table 1). In particular, we evaluated the following criteria: the weaknesses of the designs that have been used (such as noting their potential to ascertain causality), the execution of the studies through a careful assessment of their risk of bias, especially the potential for selection bias and confounding to which all observational studies are susceptible, and the potential for reporting biases, including selective reporting of outcomes.

2.5 | Statistical Analysis

Heterogeneity across studies was assessed using I^2 statistics, and, although the validity of tests of heterogeneity can be limited due to the small number of component studies, the random effect model was applied for analysis [27]. We used funnel plots and the Begg-adjusted rank correlation test to estimate possible publication or disclosure bias. The Duval and Tweedie's "trim and fill" was used to confirm the obtained results whenever a publication bias was detected. Forrest plots reporting the mean and/or standardized differences (SD) from baseline or in comparison to TRT on the primary and secondary endpoints were provided. When specific parameters were evaluated through different approaches and expressed in different ways, the mean difference for each study was divided by the pooled estimate of the SD in order to express the effect size for each study in a common metric, namely, the standardized mean difference (SMD). According to Cohen [28], a small treatment-effect size is considered to be about 0.2, a medium effect size to be about 0.5, and a large effect size to be about 0.8. Meta-regression analyses will be performed whenever appropriate. All analyses were performed using Comprehensive Meta-analysis Version 2, Biostat (Englewood, NJ, USA). Multivariate analyses were performed on Statistical Package for the Social Sciences (SPSS; Chicago, USA) for Windows, 25.

3 | Results

3.1 | Effect of GLP1-RAs Versus Baseline or TRT

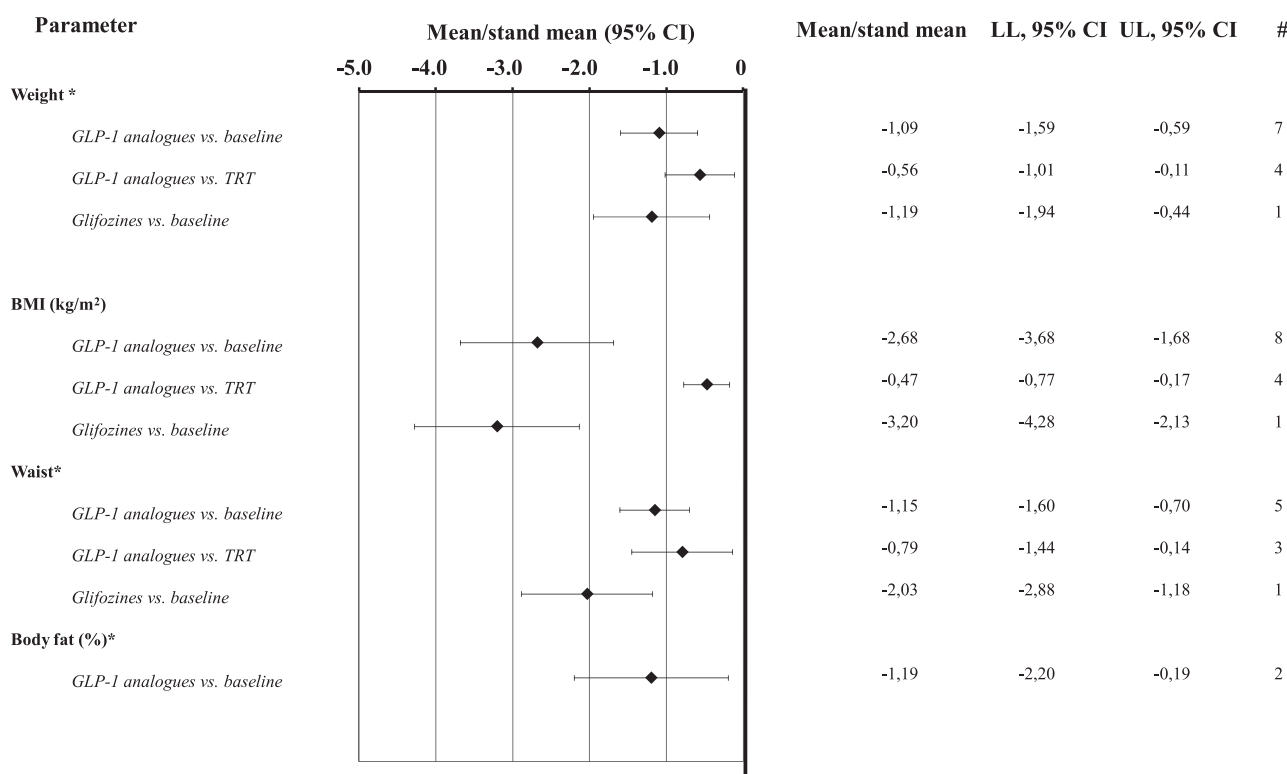
Of 103 retrieved studies, 92 were excluded for different reasons. Eight out of 11 studies evaluated the effects of GLP1-RAs on the hypothalamus–pituitary–testis (HPT) axis [29–36] (Supporting Information Figure 1). Overall, 375 subjects with a mean age of 44.7 ± 12.1 years, a mean body mass index (BMI) of 33.9 ± 5.3 kg/m², and a mean follow-up of 21.6 ± 18.1 weeks were included in the analysis (Table 1). Upon GLP1-RA treatment, a mean weight loss of 7.3 ± 3.9 kg was observed.

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

3.1.1 | Body Composition and Metabolic Controls

Among the included studies, I^2 was 81.97, $p < 0.0001$. Funnel plot and Begg-adjusted rank correlation test suggested no major publication bias (Kendall's τ : 0.03; $p = 0.92$). GLP1-RAs resulted in a significant improvement in body composition, including body weight, BMI, waist circumference, and body fat (Figure 1 Panel A and Supporting Information Figure 2 Panels A–D).

A



B

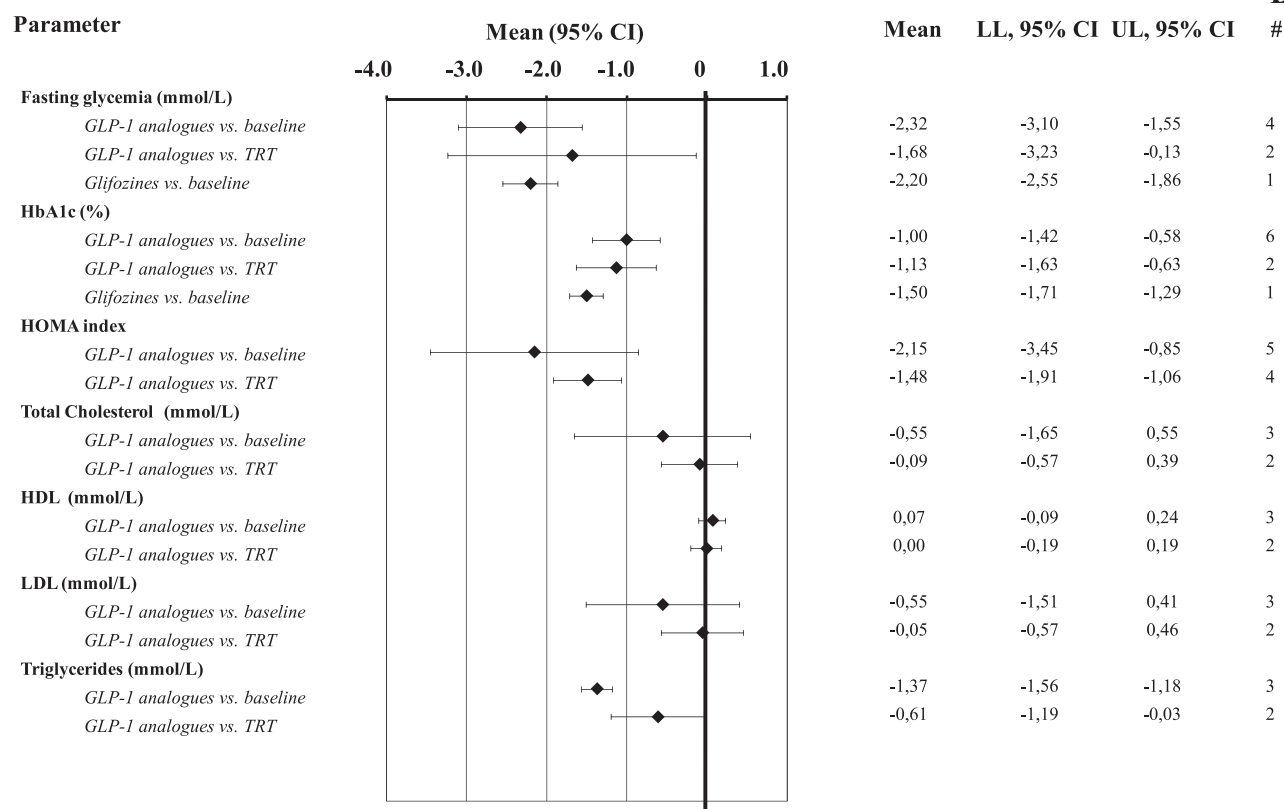


FIGURE 1 | Weighted standardized (Stand)/mean differences (with 95% CI) of the effect of glucagon-like peptide-1 receptor agonists (GLP-1-RAs) or sodium-glucose cotransporter 2 inhibitors (SGLT2is) versus baseline or testosterone replacement therapy (TRT) on body composition (A) and glycometabolic controls (B) as derived from studies included in the analysis. BMI, body mass index; HDL, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein cholesterol; LL, low levels; UL, upper levels. * Reported as standardized mean for graphical purposes.

TABLE 1 | Moderators and outcome variables in individual studies included in the meta-analysis.

Study [Refs.]	Location	Type of study	FU (weeks)	Age (years)	BMI (kg/m ²)	DM (%)	Type of drug	TRT arm	TT (nmol/L)	IIEF
Shao et al., 2018 [29]	Harbin, China.	CBA	12	43.0	30.5	100	Exenatide and metformin	–	12.9	–
Jensterle et al., 2019 [30]	Ljubljana, Slovenia	RCT	16	43.9	43.2	40	Liraglutide	+	7.6	–
Giagulli et al., 2020 [31]	Bari, Italy	CBA	52	51.1	33.5	100	Dulaglutide and metformin	–	9.4	IIEF5
Giagulli et al., 2020 [31] ^a	Bari, Italy	CBA	52	48.9	34.0	100	Liraglutide and metformin	–	8.9	IIEF5
Graybill et al., 2021 [32]	Houston, TX, US	BA	24	57.6	34.9	100	Exenatide and metformin	–	11.5	–
La Vignera et al., 2023 [33]	Catania, Italy	CBA	12	26.0	36.0	0	Liraglutide	+	4.8	IIEF5
Lengsfeld et al., 2024 [34]	Basel, Switzerland	RCT	4	24.5	23.0	0	Dulaglutide	–	20.3	MGH-SFQ,
Gregorič et al., 2025 [35]	Ljubljana, Slovenia	RCT	14	50.0	35.9	100	Semaglutide	+	6.1	IIEF-15
La Vignera et al., 2025 [36]	Catania, Italy	CBA	8	57.0	34.0	0	Tirzepatide	+	6.4	IEEF-5

All data are reported as mean $\pm$ standard deviation.

Abbreviations: BA, controlled cohort before-and-after comparisons in the same group of patients; BMI, body mass index; CBA, controlled before-and-after study between two or more groups of participants receiving different interventions; DM, diabetes mellitus; FU, follow-up (weeks); IIEF, International Index of Erectile Function; MGH-SFQ, Massachusetts General Hospital-Sexual Functioning Questionnaire; RCT, randomized controlled trials; TRT, testosterone replacement therapy; TT, total testosterone.

^aSame study, different groups.

Similarly, GLP1-RAs were associated with an improvement of glycometabolic control and insulin resistance (Figure 1 Panel B and Supporting Information Figure 2 Panels E–G), whereas more conflicting data were observed when the lipid profile was investigated (Figure 1 Panel B and Supporting Information Figure 2 Panels H–M). 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 (Figure 1 Panels A and B, and Supporting Information Figure 3 Panels A–L).

3.1.2 | Hormonal Parameters

GLP1-RAs showed a significant increase in total T, calculated free T (cFT), and sex hormone binding globulin (SHBG) levels (Figures 2 and 3 Panel A, and Supporting Information Figure 4 Panels A,B). Similarly, an increase in luteinizing hormone (LH) and follicular stimulating hormone (FSH) levels was also detected (Figure 2 and Supporting Information Figure 4 Panels C,D). However, the positive results on either LH or FSH were not confirmed when the use of tirzepatide was excluded from the analysis (LH = 0.50[–0.13;1.12] mU/L and FSH = 0.83[–0.32;1.98] mU/L; both $p > 0.05$).

When total T was considered, no differences were observed when studies including only diabetic subjects were compared to the rest of the sample or when studies including metformin were compared to those applying only GLP1-RAs (not shown). Similar

results were observed when the only study using tirzepatide was excluded from the analysis (T rise 2.85[0.42;5.27] nmol/L; $p < 0.022$). Meta-regression analysis showed that the effects of GLP1-RAs on T levels were more evident in younger patients and in those with higher BMI at baseline and increased as a function of weight loss over the trial period (Figure 3 Panels B–D). The impact of weight loss on T increase upon GLP1-RA therapy was confirmed in a multivariate analysis, weighting each study for the number of subjects enrolled and after adjusting for baseline BMI, age, and trial duration ($\beta = 1.082$; $p < 0.0001$).

Interestingly, to better understand the role of GLP1-RAs on T increase, we compared the present data to those derived from a previous meta-analysis performed by our group [6] investigating the contribution of different dieting approaches. By performing a logistic multivariate analysis, weighting each study for the number of subjects enrolled, and after adjusting for age, baseline BMI, and trial duration, the observed increase in T levels at the endpoint was independent of the amount of weight loss obtained ($B = 2.92 \pm 0.27$ nmol/L, $p < 0.001$ for T increase after GLP1-RAs at endpoint).

3.1.3 | Sexual Function

Among studies investigating the effects of GLP1-RAs, five trials reported data on sexual function (Table 1). When compared to the baseline, GLP1-RAs resulted in a significant improvement in the erectile function and sexual desire domain (Figure 4 and

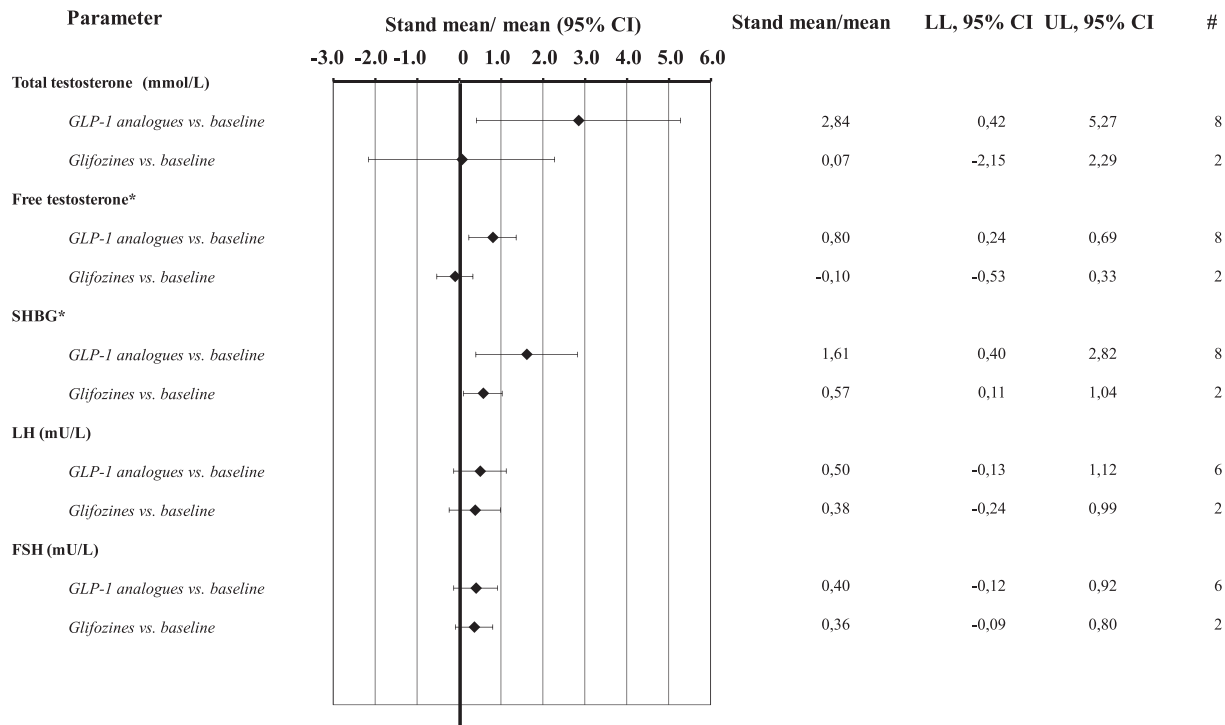


FIGURE 2 | Weighted standardized (Stand)/mean differences (with 95% CI) of the effect of glucagon-like peptide-1 receptor agonists (GLP-1-RAs) or sodium-glucose cotransporter 2 inhibitors (SGLT2is) versus baseline on hormonal parameters as derived from studies included in the analysis. FSH, follicular stimulating hormone; LH, luteinizing hormone; LL, low levels; SHBG, sex hormone binding globulin; UL, upper levels. * Reported as standardized mean for graphical purposes.

Supporting Information Figure 5 Panels A,B). Conversely, no difference in orgasm and sexual satisfaction before and after GLP1-RAs administration was observed (Figure 4 and Supporting Information Figure 5 Panels C,D). Finally, an overall improvement in the aging male scale (AMS) was also observed (Figure 4 and Supporting Information Figure 5 Panel E). When the use of GLP1-RAs was compared to TRT, the use of T resulted in better scores in orgasm and sexual satisfaction domains, whereas no difference in erectile function and sexual desire, as well as on AMS, was observed (Figure 4 and Supporting Information Figure 5 Panels F,G).

3.2 | Effect of SGLT2i Versus Baseline

Three out of eleven studies investigated the role of gliflozins on several parameters, including T and sexual function [31, 37, 38] (Supporting Information Figure 1). 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 2) 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.

3.3 | Body Composition and Metabolic Controls

Gliflozins resulted in a significant improvement in body composition, including body weight, BMI, and waist circumference reduction (Figure 1 Panel A). Similarly, they induced a significant improvement of fasting glycaemia and HbA1c (Figure 1 Panel B).

No data related to the effect of gliflozins on lipid profile and on markers of insulin resistance were available among the studies analyzed.

3.4 | Hormonal Parameters

No significant modification in total T, cFT, LH, and FSH levels after the use of gliflozins was observed (Figure 2 and Supporting Information Figure 6 Panels A–D). Conversely, a significant reduction of SHBG levels after gliflozins administration was detected (Figure 2 and Supporting Information Figure 6 Panel E).

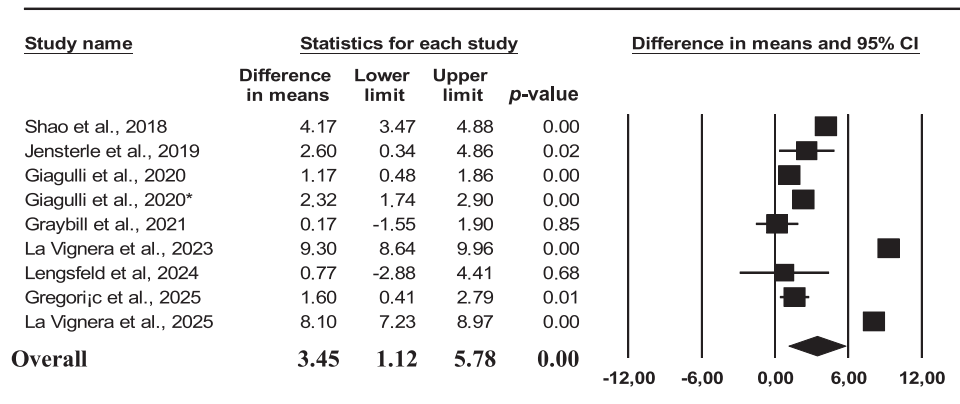
3.5 | Sexual Function

Only two studies, including 26 subjects, evaluate the effect of dapagliflozin on erectile function. The use of dapagliflozin resulted in a significant improvement in the erectile function domain (Figure 4 and Supporting Information Figure 6 Panel F). No data on other sexual function domains were available.

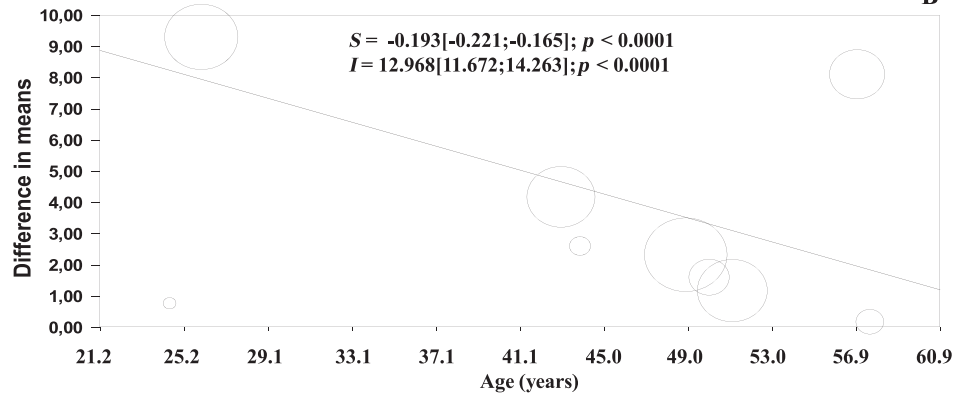
4 | Discussion

The study confirms that the use of either GLP1-RAs or SGLT2is induces body composition and glycometabolic improvement, whereas their impact on lipid metabolism is less evident. In addition, we reported, for the first time, that GLP1-RAs, but not SGLT2is, resulted in a significant increase in total T and cFT. Both classes of medications were associated with an overall

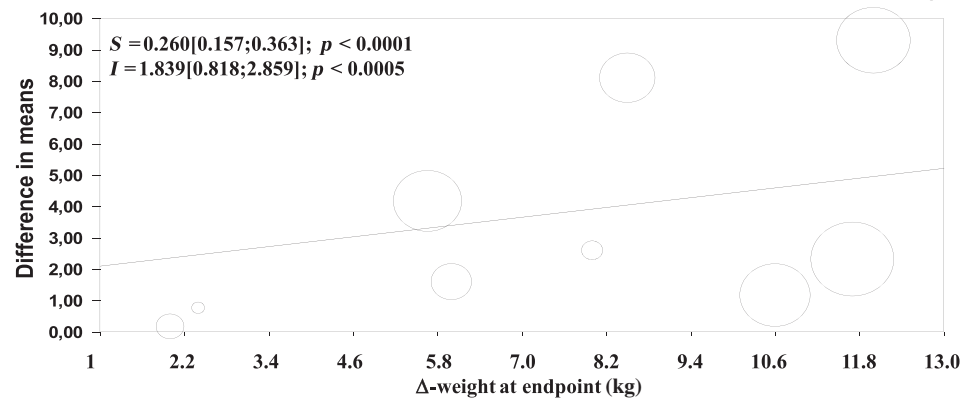
A



B



C



D

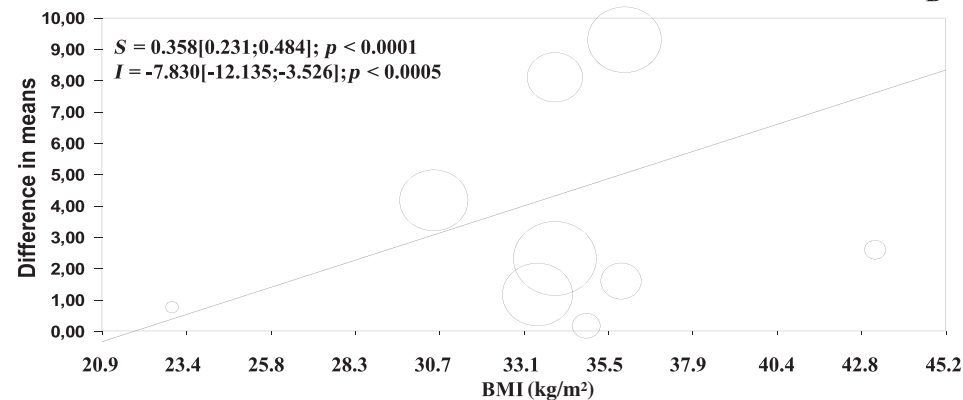


FIGURE 3 | Weighted mean differences (with 95% CI) of the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RA) versus baseline on total testosterone levels (A). Impact of age (B), Δ -weight loss from baseline (C) and baseline body mass index (BMI; D) on total testosterone increased levels after GLP1-RA as derived from studies included in the analysis. * Same study different group.

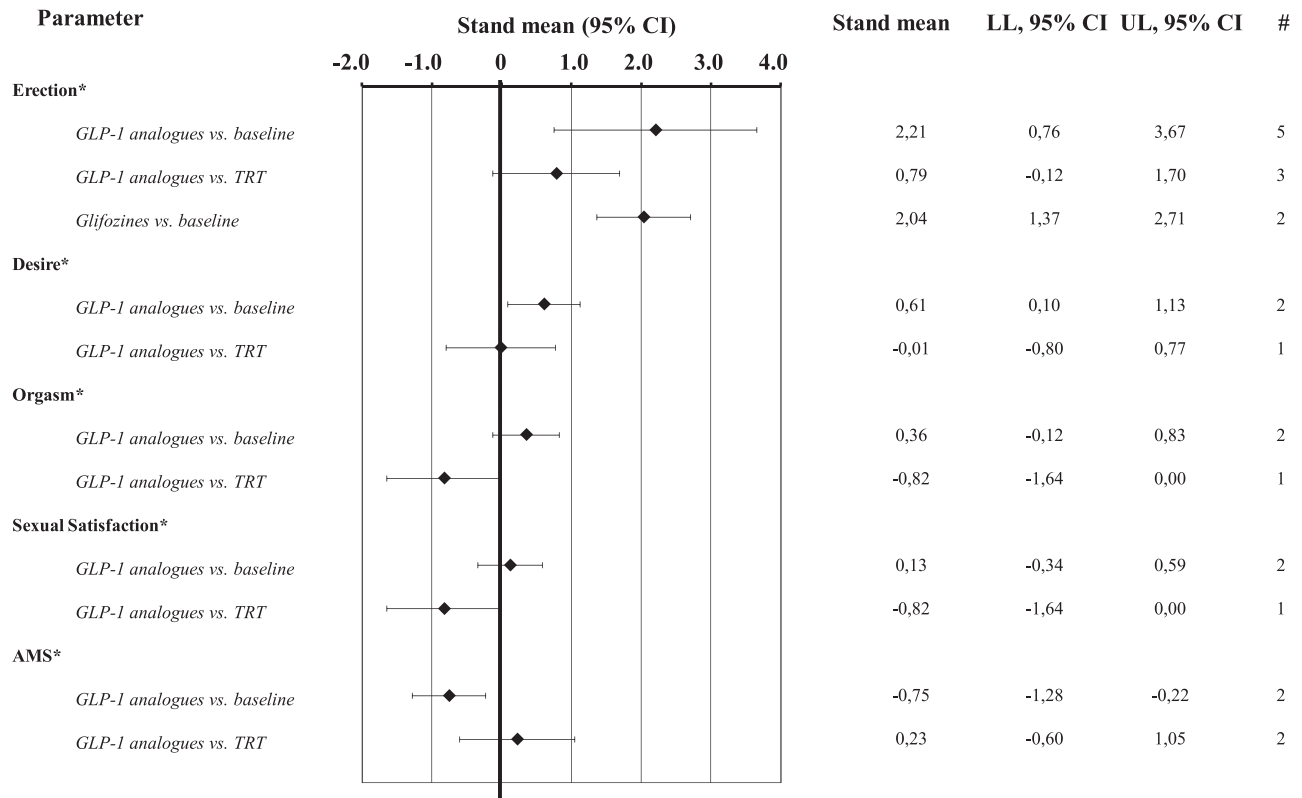


FIGURE 4 | Weighted standardized mean differences (with 95% CI) of the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) or sodium-glucose cotransporter 2 inhibitors (SGLT2is) versus baseline or versus testosterone replacement therapy (TRT) on sexual function parameters as derived from studies included in the analysis. LL, low levels; UL, upper levels. * Reported as standardized mean for graphical purpose.

TABLE 2 | Moderators and outcome variables in individual studies included in the meta-analysis.

Study [Refs.]	Location	Type of study	FU (weeks)	Age (years)	BMI (kg/m ²)	DM (%)	Type of drug	TT (nmol/L)	IIEF
Giagulli et al., 2020 [31]	Bari, Italy	CBA	52	50.6	34.3	100	Dapagliflozin and metformin	9.1	IIEF5
Cannarella et al., 2023 [37]	Catania, Italy	CBA	12	59.8	34.0	100	Dapagliflozin and metformin	8.9	IIEF5
Kosinski et al., 2024 [38]	Lausanne, Switzerland.	RCT	4	31.7	29.3	0	Empagliflozin	19.4	–

All data are reported as mean ± standard deviation.
Abbreviations: BMI, body mass index; CBA, controlled before-and-after study between two or more groups of participants receiving different interventions; DM, diabetes mellitus; FU, follow-up (weeks); IIEF, International Index of Erectile Function; RCT, randomized controlled trials; TT, total testosterone.

improvement in erectile function. Finally, when the use of GLP1-RAs was compared to TRT, the former showed better results on glycometabolic and body composition parameters, whereas TRT resulted in better scores on orgasm and sexual satisfaction domains.

As reported above, the association between obesity, metabolic derangements, and HPT axis impairment is well known [12, 39–41]. Several pathogenetic mechanisms have been advocated to describe the latter association. Emerging evidence supports a crucial role played by an endocrine-immune-metabolic cross-talk. Insulin resistance, which is a key element of obesity, induces the

macrophage polarization to the M1 stage, promoting the secretion of several proinflammatory cytokines such as IL-1, IL-6, and TNF-α resulting in a condition of systemic low-grade inflammation [41, 42]. The latter state is crucial for several obesity-related long-term complications, including the development of T2DM, CVD, and some types of cancers [43, 44]. Similarly, low-grade-inflammation can disrupt the HPT axis and directly impair T production at the testis level. In line with these data, we previously reported that, in an animal model of metabolic syndrome (MetS), visceral obesity-induced hypothalamic metaflammation led to 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 (ED) secondary hypogonadism [9, 10, 45]. In the same animal model, we also observed that the combination of testicular microenvironment modifications along with nutrient overload promoted proinflammatory response, leading to Sertoli and Leydig cell disruption, supporting T and sperm production impairment [9, 10, 46].

According to current guidelines, life-style modifications and weight loss should be considered the first step for preventing obesity-related complications, including T2DM [47] and CVD [48]. A similar approach has been recognized by the available T-related guidelines [49–52]. Accordingly, available meta-analyses clearly documented that lifestyle measures (diet or physical exercise) and/or bariatric surgery are associated with a significant T level rise, tightly dependent on the amount of weight loss obtained [6, 23, 53]. Similar data can be derived from preclinical models. In our aforementioned study, by training MetS rabbits to perform endurance exercises, hypothalamic metaflammation was restored, and the function of the HPT axis was normalized, along with erectile function [9, 10]. Despite this evidence, it should be recognized that the long-term success rate of dieting programs is quite low, with around 50% of individuals regaining weight within 2 years of completing healthy programs [54]. The reasons for that failure are complex and include either medical (e.g., genetic background and type of diet), or psycho-social factors [54]. In latter cases, a combined therapy including a medical and/or surgical approach could be considered.

GLP1-RAs are the most efficacious medical treatment for obesity [55]. More recently, the introduction of tirzepatide, a dual agonist engaging both GIP and GLP-1 receptors, has shown more convincing results [56]. Interestingly, present data showed that GLP1-RAs consistently revert obesity-related secondary hypogonadism by increasing (up to 5.3 nmol/L) total T over the baseline values with a consistent rise in both cFT and gonadotropin levels. Similar results were observed in other meta-analyses or systematic reviews, including a lower number of studies [25, 57, 58].

The mechanisms of action of GLP1-RAs in inducing T rise are not completely clarified. Preclinical models have suggested that GLP1-RAs might directly stimulate the HPT axis by increasing Kiss-1 neuron activity within the hypothalamus [59, 60]. Similarly, GLP-1 central microinjections (within the median eminence of ovariectomized sheep) or intravenous infusion in a sheep model, during a follicular phase, resulted in a dose-dependent surge in LH [61, 62]. Similar results have been reported in an obese mice model after 12 weeks of liraglutide administration [63].

Data derived from humans are more conflicting. By combining all available studies, our results support an overall improvement of both LH and FSH after GLP1-RA administration. However, the latter finding was not confirmed when the only study using a dual GIP/GLP1-RA was excluded from the analysis. Two separate studies failed to demonstrate any effect of GLP-1 infusion on LH secretion or pulsatility in humans. However, in both cases, healthy normal weight subjects were considered [64, 65]. Hence, it can be speculated that the positive effect of GLP1-RA administration on T may be evident only after chronic administration in obese subjects, mainly due to weight reduction. In line with this hypothesis, meta-regression analyses indicated that the GLP1-RA-induced T rise was greater in younger subjects

with higher BMI at study entry and greater weight loss upon therapy. In addition, at multivariate regression analysis, weight loss upon GLP1-RA therapy was the most important determinant of the T rise. However, at logistic multivariate analysis, weighting each study for the number of subjects enrolled and after adjusting for age, baseline BMI, and trial duration, the observed increase upon GLP1-RA on T levels at the endpoint resulted in partial independence from the amount of weight loss obtained. Hence, our data seem to support a possible direct role of GLP1-RAs on the HPT axis. Data derived from testis damage in a rat model based on a protocol of ischemia–reperfusion showed that semaglutide administration was able to ameliorate the testicular damage on several genes involved in androgen formation within the testis, without any effects on gonadotropins [66]. Similarly, in a rat model, liraglutide was able to counteract DM induced signaling alterations either at the central (Kiss-1 and GnRH) or testis (several steroidogenesis-related genes) level [67]. On the other hand, conflicting results have been reported for the specific role of GIP on gonadotropins. In fact, in the rat model, intraventricular injection of GIP produced a significant FSH decrease without any effects on LH. However, when dispersed anterior pituitary cells from the same rat model were cultured with GIP, the peptide was found to induce both FSH and LH release [68]. Hence, although it is clear that GLP-RAs can play a specific indirect role by reducing inflammatory chronic reaction associated with obesity, whether or not they exert a direct role on HPT hormonal balance needs to be confirmed in further dedicated studies.

When the role of GLP1-RAs on hypogonadism-related symptoms was investigated, a significant improvement of AMS scoring was observed, supporting not only a T rise but also a specific clinical effective improvement of the so-called “functional hypogonadism.” Interestingly, when the specific sexual symptoms were analyzed, GLP1-RAs resulted in a significant improvement of erectile function and sexual desire, which have been considered the most specific symptoms related to functional hypogonadism [69, 70]. Data derived from mice have shown that the central administration of Exendin-4 (EX4), a potent GLP1-RA, correlated with a decrease in sexual interaction behavior [71]. We provide here the first specific evidence that in obese men the use of GLP1-RAs resulted in an improvement, and not in impairment, of sexual function and desire. The amelioration of ED can also be related to the GLP1-RA metabolic profile optimization. On the other hand a large body of evidence has clearly documented that weight loss and life-style modifications can result in ED improvement [72–74]. Hence, a possible direct effect of GLP1-RA on ED amelioration cannot be excluded. However, the latter should be proven by specific studies. A significant weight regain has been reported after discontinuation of antiobesity medications and after GLP1-RAs withdrawal in particular [75]. Data on sexual function outcomes in the latter conditions are lacking. The specific role of TRT in improving ED is limited [76, 77]. Conversely, the direct impact of TRT in improving sexual desire is more evident [76, 78]. Hence, although GLP1-RA T rise can justify the observed improvement of sexual desire, weight loss can reinforce patients’ self-esteem, explaining, at least partially, the observed rise of sexual desire [79–81].

Although a limited number of studies provided a head-to-head comparison, the use of GLP1-RAs resulted in a better body composition and glycometabolic outcomes when compared to TRT.

In addition, no difference in erectile function and sexual desire scoring was observed, although TRT resulted in better orgasm and overall satisfaction outcomes. Hence, current data suggest that although GLP1-RAs alone can guarantee an improvement of sexual function, the overall quality of sexual response seems to be enhanced by the use of TRT. The correct interpretation of the latter finding is not easy. The central effects of T, and in particular, its role in regulating orgasm response can explain, at least partially, these observations [82, 83].

Limited data are available concerning the role of SGLT2is on HPT and sexual function. Similar to what was observed for GLP1-RAs, the meta-analytic approach showed that gliflozins resulted in weight loss and in improving body composition and glycemic profile. In addition, an improvement of erectile function was also observed, but any modification of the HPT axis was not detected. Considering the strong relationship between ED and CVD [84], the observed erectile function amelioration can be related to the specific role of SGLT2i on glucose metabolism [31, 38] and overall CV health [21, 22]. In addition, even if gliflozins have been associated with weight loss in either diabetic [21] or nondiabetic [22] populations, their effect is more limited when compared to what is observed for GLP1-RAs [85]. The small weight loss observed with the use of SGLT2is can support the observed lack of T modifications in the present meta-analysis. However, it should be clarified that the limited data related to SGLT2is prevents drawing any final conclusions.

Several limitations should be recognized. First, most data were derived from uncontrolled studies, and only a few RCTs are available. All the available data should be interpreted with caution and no specific causal relationship can be clearly stated. Hence, it should be recognized that the specific direct role of GLP-1 RAs on T levels independently of weight loss is based on cross-study comparisons and should be framed as exploratory and hypothesis. Meta-analyses have been considered as a particularly useful tool to address questions for which multiple data sources are conflicting, or when there is a variety of reports with low statistical power since pooling data can improve statistical power providing more convincing results. Our analyses included one study using dual GIP/GLP1-RAs which can represent a possible source of bias. The observed increase in gonadotropin levels was not confirmed when the tirzepatide study was excluded, suggesting an agent-specific rather than class-wide effect. However, the data on T were confirmed in a sensitivity analysis by excluding the latter study. Sexual function improvements were largely derived from uncontrolled and subjective measures which may have overestimated the true treatment effects. Previous meta-analyses have investigated only the use of GLP1-RAs on the HPT axis and sexual function in a more limited number of studies [57, 58]. However, no comparisons between SGLT2is and GLP1-RAs or between GLP1-RAs and TRT were provided in the previous studies. In addition, Salvio et al. [57] included one study [86] where liraglutide was added on to TRT resulting, in our opinion, in major bias even if this study was excluded from the analysis of effects on gonadotropins. The reported incidence of side effects was limited, preventing specific analyses. Restriction to Medline and English-language studies might have increased selection bias. Data on T assay measurement and free-T calculation methods were limited and could have represented a source of heterogeneity and selection bias.

In conclusion, life-style modifications and weight reduction should be the cornerstone treatment for obesity-associated hypogonadism [50, 52, 84, 87–89]. Present data support the evidence that the use of GLP1-RAs in combination with specific diet programs can provide better outcomes, particularly in symptomatic subjects complaining of sexual dysfunction. In addition, it should be important to recognize that a decrease in lean mass accounts for approximately 20%–30% of total weight loss after GLP1-RAs administration [90]. Hence, considering the positive role of TRT on body composition and lean mass [76, 91, 92], the combination of TRT and GLP1-RAs can be considered at least at the beginning of patient management in order to guarantee better cardiometabolic [18–20], and sexual outcomes [76, 82]. More specific studies particularly related to gliflozins are advisable to better clarify the latter possibility.

Author Contributions

Acquisition (Clotilde Sparano, Marilina, Romeo, Giulia Rastrelli), analysis or interpretation of the data (Giovanni Corona, Giulia Rastrelli, Marilina, Romeo, Mario Maggi), drafted the paper (Giovanni Corona, Marilina, Romeo, Giulia Rastrelli, Mario Maggi), or revised it critically (Giovanni Corona, Clotilde Sparano, Marilina, Romeo, Giulia Rastrelli, Linda Vignozzi, Mario Maggi).

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information Figure 1: Flow chart of the included studies.

GLP-1-RAs, glucagon-like-peptide-1 receptor agonists; SGLT-2 is, sodium-glucose cotransporter 2 inhibitors. **Supporting Information Figure 2:** Weighted standardized mean or mean differences (with 95% CI) of the effect of Glucagon-like peptide-1 receptor agonists (GLP-1 RA) versus baseline on body weight (kg; A), body mass index (BMI, kg/m²; B), waist circumference (cm; C), fat mass (%; D), fasting glucose (mmol/L; E), HbA1c (%; F), homeostasis model assessment index (HOMA; G), total cholesterol (mmol/L; H), high-density lipoprotein cholesterol (HDL, mmol/L; I), low-density lipoprotein cholesterol (LDL, mmol/L; L), and triglycerides level (mmol/L; M) as derived from studies included in the analysis. * Same study different groups. **Supporting Information**

Figure 3: Weighted standardized mean or mean differences (with 95% CI) of the effect of Glucagon-like peptide-1 receptor agonists (GLP-1 RA) versus testosterone replacement therapy (TRT) on body weight (kg; A), body mass index (BMI, kg/m²; B), waist circumference (cm; C), fasting glucose (mmol/L; D), HbA1c (%; E), homeostasis model assessment index (HOMA; F), total cholesterol (mmol/L; G), high-density lipoprotein cholesterol (HDL, mmol/L; H), low-density lipoprotein cholesterol (LDL, mmol/L; I), and triglycerides level (mmol/L; L) as derived from studies included in the analysis. **Supporting Information Figure 4:** Weighted mean differences (with 95% CI) of the effect of Glucagon-like

peptide-1 receptor agonists (GLP-1 RA) versus baseline on calculated free testosterone (pmol/L; A), sex hormone binding globulin (SHBG, nmol/L; B), luteinizing hormone (LH, mU/L; C), follicular stimulating hormone (FSH, mU/L; D) as derived from studies included in the analysis. * Same study different groups. **Supporting Information Figure 5:** Weighted standardized/mean differences (with 95% CI) of the effect of Glucagon-like peptide-1 receptor agonists (GLP1 RA) versus baseline on overall erectile function (A), sexual desire (B), orgasm (C), sexual satisfaction (D) and aging male scale (AMS; E). Weighted standardized/mean differences (with 95% CI) of the effect of GLP1 RA versus testosterone replacement therapy (TRT) on overall erectile function (F), and AMS (G). * Same study different groups. **Supporting Information Figure 6:** Weighted mean differences (with 95% CI) of the effect of glifozines versus baseline on total testosterone (nmol/L, A) calculated free testosterone (pmol/L; B), luteinizing hormone (LH, mU/L; C), follicular stimulating hormone (FSH, mU/L; D) sex hormone binding globulin (SHBG, nmol/L; E), and erectile function (IIEF-5 score; F) as derived from studies included in the analysis. **Supporting Information Table 1:** Risk of bias according to the ROBINS-I tool **Supplementary File 1:** PRISMA 2009 Checklist. **Supplementary File 2:** MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist.