BMC Urology

RESEARCH

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Effect of GLP-1 agonists on testosterone levels: a systematic review and meta-analysis

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Abstract

Introduction Testosterone plays a central role in endocrine and metabolic functions. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), widely prescribed for type 2 diabetes and obesity, have been proposed to modulate testosterone levels. Although this association is not yet covered by clinical guidelines, emerging studies suggest favorable effects, possibly due to weight loss and improved insulin sensitivity. This systematic review and meta-analysis aim to synthesize current evidence on how GLP-1 RAs influence testosterone levels and highlight areas for future investigation.

Materials and methods A systematic search was conducted using Embase, PubMed, Scopus, Cochrane, and Google Scholar databases through December 2024. Eligible studies included RCTs, cohort studies, and retrospective analyses comparing testosterone levels before and after GLP-1 RA administration. Primary and secondary outcomes included total, free, and bioavailable testosterone, SHBG, and HbA1c. All included studies reported baseline hormone values and used validated measurement techniques. Data analysis was performed using RStudio.

Results Four studies comprising 219 patients pre-treatment and 216 post-treatment were included. GLP-1 RA use was significantly associated with increased bioavailable testosterone (MD -57.18; 95% CI -87.60 to -26.76; $p < 0.001$; $I^2 = 86\%$) and decreased HbA1c (MD 0.79; 95% CI 0.58 to 1.00; $p < 0.001$; $I^2 = 0\%$). Free testosterone (MD -1.62; $p = 0.051$) and SHBG (MD -6.62; $p = 0.120$) showed no significant changes. Sensitivity and Baujat analyses were used to explore heterogeneity.

Conclusions GLP-1 RAs appear to elevate bioavailable testosterone and improve glycemic control, while effects on free testosterone and SHBG remain inconclusive. These findings suggest possible endocrine benefits of GLP-1 therapy; however, further well-powered studies are warranted.

Keywords Functional Hypogonadism, Glucagon-like Peptide-1 Receptor Agonists, Erectile Dysfunction

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Introduction

Testosterone is a key hormone involved in regulating metabolic processes, maintaining muscle mass, and ensuring the integrity of endocrine homeostasis [1]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), medications routinely used in managing type 2 diabetes and obesity, have sparked interest due to their potential influence on circulating testosterone levels [2]. This interest is particularly relevant in the broader context of treating male hypogonadism, where testosterone replacement therapy (TRT) remains the standard intervention [3].

Although TRT is widely accepted, it is not without drawbacks—complications such as erythrocytosis, worsening of obstructive sleep apnea, and increased cardiovascular risk have been reported [1]. Consequently, alternative strategies—such as weight reduction, physical activity, or bariatric procedures—have been explored as first-line measures in appropriate patients.

Current AUA guidelines [4] do not explicitly address the effect of GLP-1 RAs on testosterone modulation. Nevertheless, emerging clinical data suggest that these agents may exert beneficial effects on testosterone levels in men, potentially mediated by improved insulin sensitivity and reductions in adiposity.

The present systematic review and meta-analysis were undertaken to comprehensively assess the impact of GLP-1 RAs on testosterone levels in men, synthesizing the latest clinical data to better understand their metabolic and endocrine roles. The objective is to consolidate existing knowledge while identifying evidence gaps that may inform future research directions.

Materials and methods

Search strategy

This systematic review and meta-analysis were performed and reported in accordance with the Cochrane Collaboration Handbook for Systematic Review of interventions and the Preferred reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [5] Statement guidelines.

We conducted a comprehensive search of MEDLINE, Embase, Scopus, and Cochrane CENTRAL, along with Google Scholar for additional internet sources, from their inception until December 2024 for randomized controlled trials of the effects of GLP-1 RAs on testosterone levels in men with functional hypogonadism. The search strategy was: ("Obese Fertile Men" OR "Functional hypogonadism" OR "Diabetes Mellitus, Type 2"[Mesh] OR "Erectile Dysfunction"[Mesh]) AND ("Glucagon-Like Peptide-1 Receptor Agonists"[Mesh] OR semaglutide OR liraglutide OR dulaglutide OR exenatide OR lixisenatide OR tirzepatide) AND ("Before treatment" OR "Testosterone"[Mesh]).

The references from all included studies, previous systematic reviews and meta-analyses were also searched manually for any additional studies. The prospective meta-analysis protocol was registered on PROSPERO under protocol CRD420251012733.

Eligibility criteria for study selection

We included studies that assessed adult men (aged ≥ 18 years) with functional hypogonadism associated with obesity or type 2 diabetes. Studies were eligible if they compared the efficacy of GLP-1 RAs, such as liraglutide or exenatide, with placebo, no treatment, or any other intervention, including testosterone replacement therapy (TRT). Eligible studies had to report at least one of the clinical outcomes of interest. Both randomized controlled trials (RCTs) and non-RCTs, such as observational or cohort studies, were considered.

Studies were excluded if they did not include a GLP-1 RAs treatment arm or an appropriate comparator, such as placebo or TRT. Studies were also excluded if they focused on participants with primary testicular disease, including Klinefelter syndrome, testicular tumors, or severe varicocele, or if they involved men with pituitary or hypothalamic organic diseases, such as prolactinomas or hypopituitarism. Additionally, studies in which participants were using opioids or other hormonal therapies that could influence testosterone levels were not considered. Case reports, systematic reviews, and bibliographic reviews were excluded to maintain a high standard of evidence.

Outcomes

The primary outcome was the measurement of total testosterone levels before and after GLP-1 RAs administration, chosen for its strong association with the clinical manifestations of hypogonadism in men. Our objective was to investigate the potential correlation between clinical presentation and laboratory findings. Secondary outcomes included bioavailable testosterone, sex hormone-binding globulin (SHBG), and HbA1c levels, all assessed before and after GLP-1 treatment.

Screening

After deduplication, in which we used Endnote online™ 20 (Clarivate, Philadelphia, PA) [6], two independent researchers (SO and JM) screened the studies by title and abstract, and disagreements were solved by a third (JC). Following this process, full text screening was performed. No automation tools were used during the screening process.

Data extraction and quality assessment

Two authors (BP and SO) independently extracted the data based on a predefined protocol and disagreements

were solved by a third (JC). The data primarily assessed were the type of study, the language of each paper, the number of patients enrolled, mean age of patients, methenamine dosage, which antibiotic was used and each dose, the duration of follow-up, and all the outcomes previously mentioned. Risk of bias was assessed in randomized studies using version 2 of the Cochrane Risk of Bias assessment tool (RoB 2) [7]. Non-randomized studies were assessed with the Risk of Bias in Non-randomized Studies – of Interventions tool (ROBINS-I) [8]. Two independent authors completed the risk of bias assessment (SO and JM). Disagreements were resolved through a consensus after discussing reasons for discrepancy.

Statistical analysis

Continuous outcomes are presented as a mean difference (MD) with 95% confidence interval (CI). All analyses were conducted using raw MD rather than standardized mean differences (SMD), as all studies reported testosterone values in the same unit (ng/dL). Pooled estimates were calculated with the random-effects model, considering that the patients came from different populations. We considered a study to exhibit considerable heterogeneity if, following the statistical analysis, the I^2 statistic is equal to or greater than 30%.

RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL, was the software used for statistical analysis [9].

Results

Study selection and characteristics

After performing our screening, we identified 1129 articles. Following the deduplication and screening process, 4 articles [1, 10–12] were deemed relevant and included in our analysis (Fig. 1/PRISMA flow chart). For a comprehensive overview of the data of included studies, please refer to Table 1. Combining the data from these articles, we analyzed a total of 219 patients before receiving GLP-1 RAs and 216 patients after receiving the medication. The mean age of all patients was 47.2 years old. It is important to note that the GLP-1 RAs used varied across the included trials. Liraglutide was the chosen drug in three studies, while only the cohort from Graybill et al. [1] utilized Exenatide. Additionally, dosage and administration varied across studies. In Giagulli et al. (2015), liraglutide was administered subcutaneously at a daily dose of 1.2 mg. In Jensterle et al. (2016), liraglutide was titrated weekly up to 3.0 mg/day. In La Vignera et al. (2023) [12], liraglutide was similarly escalated to 3.0 mg/day. Graybill et al. (2021) employed exenatide extended-release 2 mg once weekly as the formulary option in their institution, with only one patient later switched to dulaglutide 0.75 mg weekly.

Meta-analysis

When comparing total testosterone levels, we observed a significant increase in this hormone following treatment with GLP-1 RAs (MD −129.96; 95% CI −220.44,−39.48; $p = 0.005$; $I^2 = 97\%$) (Fig. 2A). Due to the high heterogeneity, we performed a leave-one-out (LOO) analysis, which revealed no meaningful reduction in heterogeneity in any scenario (Fig. 2B). Additionally, a Baujat plot was generated, and despite the LOO results, it identified the study by Vignera et al. (2023) [12] as the primary contributor to heterogeneity (Fig. 2C).

Regarding the secondary outcomes, we also observed a significant difference in bioavailable testosterone, which was higher after treatment with GLP-1 RAs (MD −57.18; 95% CI −87.60 to −26.76; $p < 0.001$; $I^2 = 86\%$, Fig. 3A), but the same did not occur with free testosterone levels (MD −1.62; 95% CI −3.25 to 0.01; $p = 0.051$; $I^2 = 96\%$, Fig. 4A). Given the high heterogeneity observed in both outcomes, we performed a LOO analysis and generated Baujat plots (Figs. 3B and 3C for bioavailable testosterone, Figs. 4B and 4C for free testosterone).

We also observed no difference in SHBG levels following treatment with GLP-1 RAs (MD −6.62; 95% CI −14.95 to 1.72; $p = 0.120$; $I^2 = 99\%$) (Fig. 5A). Due to the substantial heterogeneity, we conducted a LOO analysis (Fig. 5B) and generated a Baujat plot (Fig. 5C). These analyses suggest that the study by Vignera (2023) [12] was primarily responsible for the observed heterogeneity. Conversely, we found a significant difference in HbA1c levels before and after the introduction of GLP-1 RAs (MD 0.79; 95% CI 0.58 to 1.00; $p < 0.001$; $I^2 = 0\%$) (Fig. 6).

Regarding the primary outcome, total testosterone levels, all studies included in this review were analyzed. For bioavailable testosterone, however, the studies by Graybill et al. (2015) [1] and Jensterle et al. (2016) [10] were not included due to lack of data on this specific outcome. As for free testosterone, the studies by La Vignera et al. (2017) [10] and Giagulli et al. (2015) [11] were excluded because they did not report on free testosterone levels. When examining SHBG levels, all studies contributed except for Jensterle et al. (2016) [10], which did not assess SHBG. Finally, for HbA1c, all studies were included in the analysis as this outcome was consistently measured across all trials.

Quality assessment

Since three of the included trials were non-randomized, they were assessed using the ROBINS-I tool. The cohort study by Vignera et al. [12] demonstrated a low overall risk of bias, whereas the studies by Giagulli and Graybill [1, 11] were found to have a moderate risk of bias, primarily due to concerns related to outcome measurement and participant selection (Fig. 7A). In contrast, the randomized controlled trial conducted by Jensterle et al. [10]

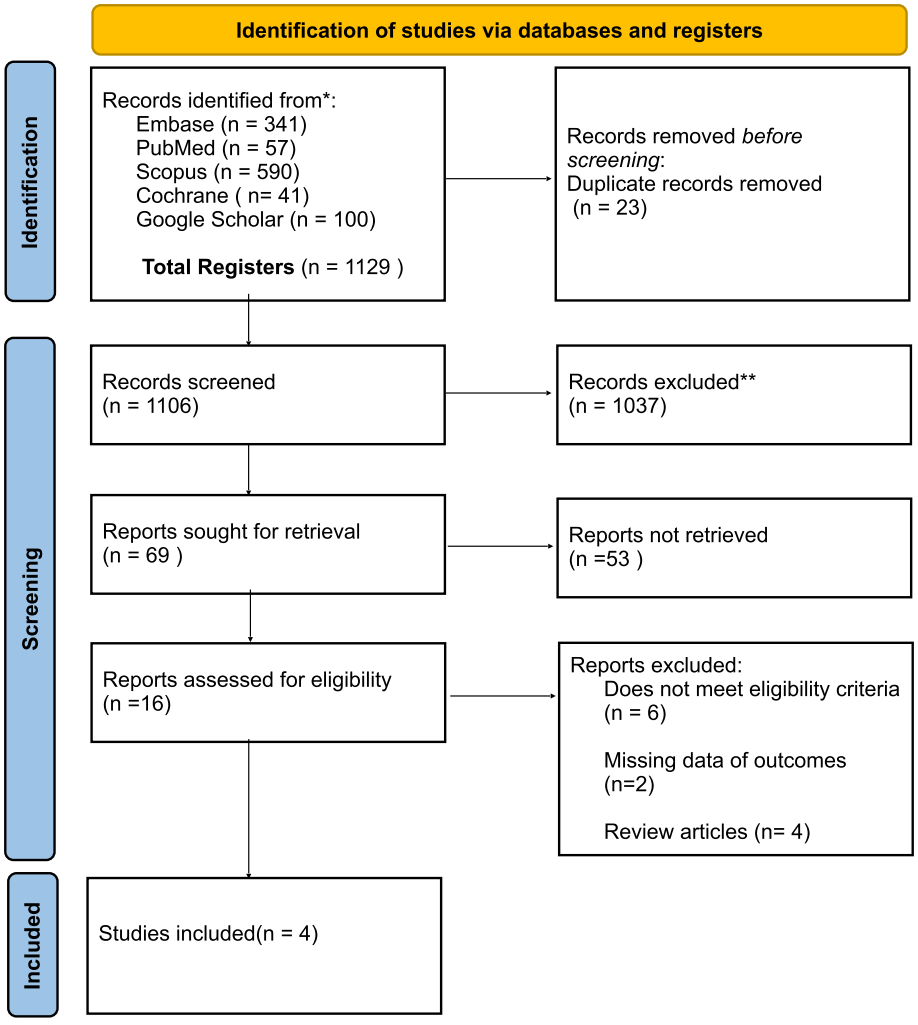


Fig. 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. Source: Page MJ, et al. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/

was evaluated using the RoB 2 tool and showed some concerns, particularly regarding potential deviations from the intended interventions (Fig. 7B).

Discussion

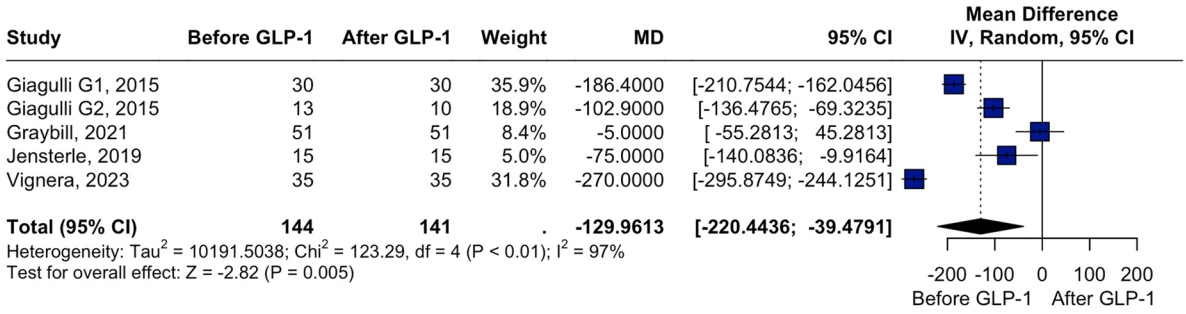
The results of this meta-analysis indicate that treatment with GLP-1 receptor agonists leads to a meaningful rise in bioavailable testosterone and a significant reduction in HbA1c levels. These findings support a possible metabolic and endocrine role for GLP-1 RAs, extending beyond their established benefits in glycemic regulation. While neither the American Urological Association (AUA) nor the European Association of Urology (EAU) explicitly address the testosterone-modulating properties of GLP-1 agonists, both emphasize the relevance of metabolic health in the management of testosterone deficiency. The AUA's 2020 guidelines underscore the need to consider comorbid conditions in hypogonadism treatment [4], and the EAU guidelines (2021) highlight the potential of pharmacologic agents to influence androgen levels indirectly [13].

Despite the observed increases in total and bioavailable testosterone, free testosterone levels did not show a statistically significant change. Total testosterone represents the sum of free testosterone plus the fraction bound to albumin and SHBG, with the majority being protein-bound and biologically inactive. Bioavailable testosterone, in contrast, includes both free testosterone and the portion loosely bound to albumin, which can readily dissociate and exert physiological effects. This distinction is clinically important, as bioavailable testosterone more accurately reflects the androgenic activity available to

Table 1 Testosterone levels after using GLP-1 agonists

Author, Year	Type os study	Numer of patients—I/C	Age (mean)	GLP-1 receptor agonist	Length of use	Total Testosterone B/A	Bioavailable T (BioT) B/A	Free-testosterona B/A	SHBG B/A	HbA1c	Drug regimen (dose and route)
Giagulli G1, 2015 [11]	Retrospective observational trial	30/30	53.4 ± 4.4	Liraglutide	12 months	G1: 278.4 ± 23.7/464.8 ± 63.8	G1: 120.5 ± 14.5/204.7 ± 35.1	5.2 ± 0.6/8.7 ± 1.5	G1: 36.3 ± 3.5/37.3 + 3.2	G1: 8.8 ± 0.6/7.8 ± 0.6	G1: Liraglutide 1.2 mg/day subcutaneous added during the second year of follow-up
Giagulli G2, 2015 [11]	Retrospective observational trial	13/10	50.6 ± 4.3	Liraglutide	12 months	G2: 309.4 ± 29.7/412.3 ± 47.5	G2: 135.9 ± 15.8/181.8 ± 27.1	5.8 ± 0.7/7.7 ± 1.2	G2: 36.6 ± 2.7/37.6 ± 2.4	G2: 8.6 ± 0.4/7.9 ± 0.4	G2: Liraglutide 1.2 mg/day subcutaneous added during the second year of follow-up
Jensterle, 2019 [10]	Randomized controlled trial	15/15	46.5 ± 10.9	Liraglutide	16 weeks	219.2 ± 43.3/294.2 ± 121.1	124.9 ± 29.7/158.9 ± 61.1	4.90 ± 1.15/6.34 ± 2.31	26.3 ± 13.6/29.3 ± 14.1	5.9 ± 0.8/5.3 ± 0.4	Liraglutide titrated from 0.6 mg/day to 3.0 mg/day subcutaneous; treatment duration 16 weeks
Graybill, 2021 [1]	Retrospective observational trial	51/51	57.6 ± 8.8	Exanatide	6 months	334 ± 126/339 ± 133	NR	6,4 ± 1,7/6,0 ± 1,8	36 ± 15/41 ± 22	8.1 ± 1.5/7.4 ± 1.4	Exenatide extended-release 2 mg subcutaneous once weekly (institutional formulary); one patient switched to dulaglutide 0.75 mg subcutaneous once weekly
Vignera, 2023 [12]	Prospective study, non randomized	35/35	26 ± 6	Liraglutide	9 weeks	140 ± 60/410 ± 50	NR	NR	14.0 ± 3.0/36 ± 4	NR	Liraglutide titrated from 0.6 mg/day to 3.0 mg/day subcutaneous; treatment duration 4 months

A.



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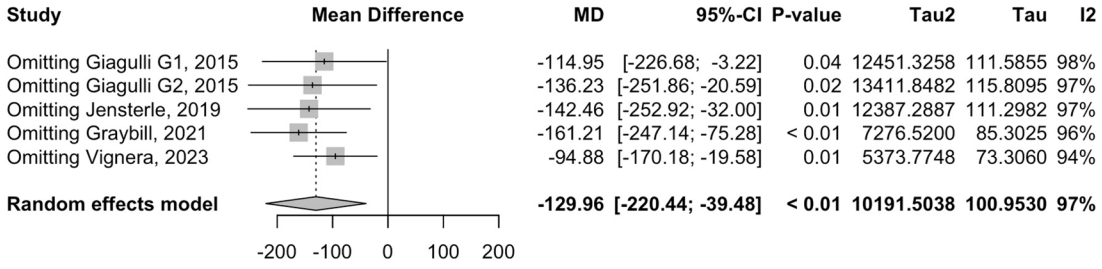

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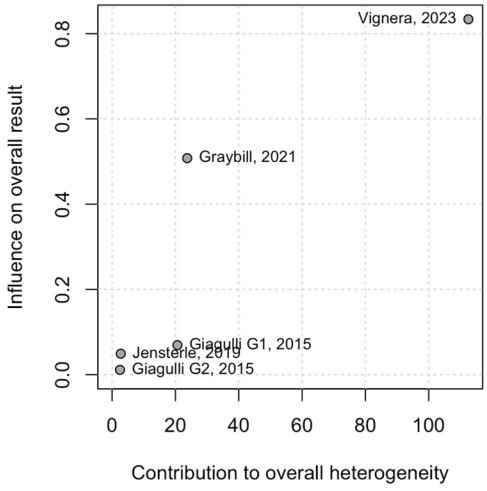
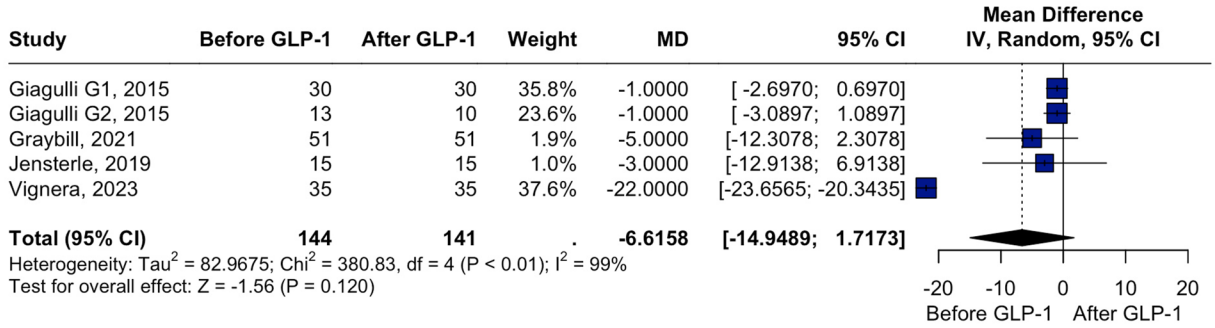


Fig. 2 Forest plot (**A**), leave one out (**B**), Baujat plot (**C**), for Total Testosterone

target tissues. The rise in bioavailable testosterone suggests an improvement in the fraction of the hormone that is biologically active and capable of exerting physiological effects. This aligns with previous evidence linking insulin resistance and obesity with impaired testosterone production [14], implying that the metabolic improvements induced by GLP-1 therapy may restore androgen levels. In contrast, the absence of significant variation in free testosterone may reflect the complexity of hormonal regulation, as free testosterone is subject to several factors including albumin and SHBG binding dynamics.

SHBG concentrations also remained largely unaffected by GLP-1 RA treatment. Given that SHBG is closely associated with insulin sensitivity and body composition [15], it is plausible that more prolonged exposure to these medications or greater weight loss might be necessary to elicit measurable changes. The observed reduction in HbA1c confirms the expected glycemic benefit of GLP-1 agonists, consistent with previous large-scale trials [16].

A.



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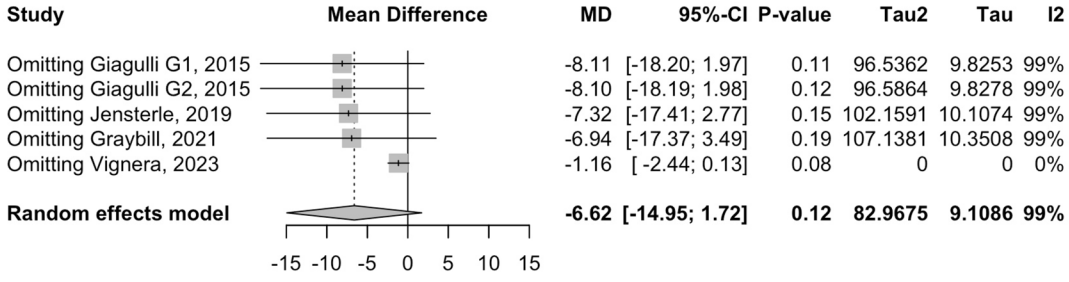


C.

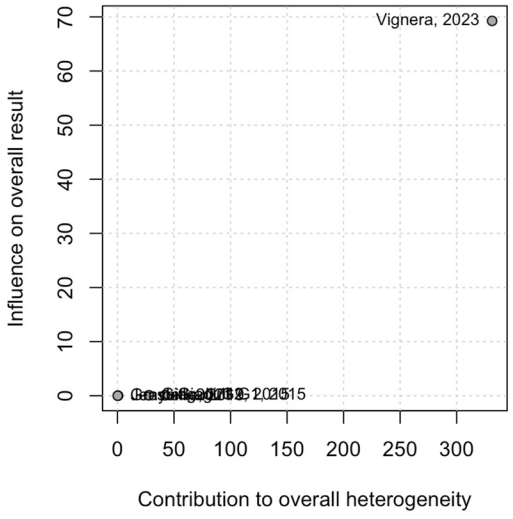
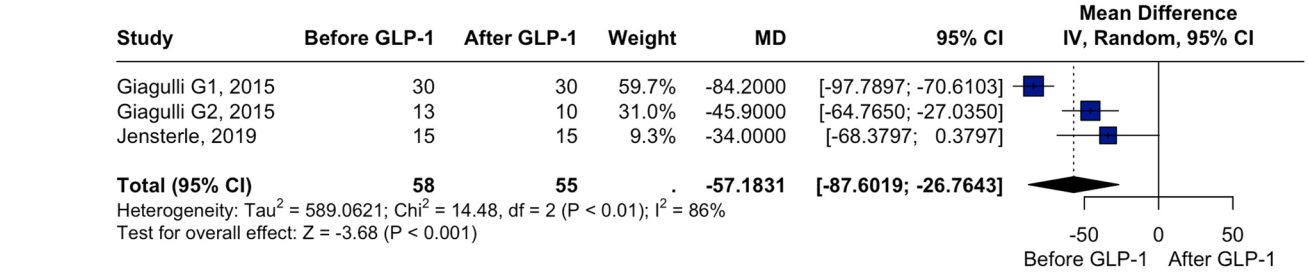


Fig. 3 Forest plot (**A**), leave one out (**B**), Baujat plot (**C**), for SHBG

An important source of variability arises from the pharmacological properties of the drugs evaluated. While three studies employed liraglutide, only one study (Graybill et al., 2021) investigated exenatide. Exenatide is a shorter-acting GLP-1 receptor agonist with lower affinity and reduced half-life compared to liraglutide, which may partly explain its neutral effect on testosterone levels [17]. Moreover, the study itself did not provide a clear rationale for the choice of exenatide, though formulary restrictions and cost considerations are plausible explanations. These pharmacological differences highlight the challenge of pooling these agents together.

A.



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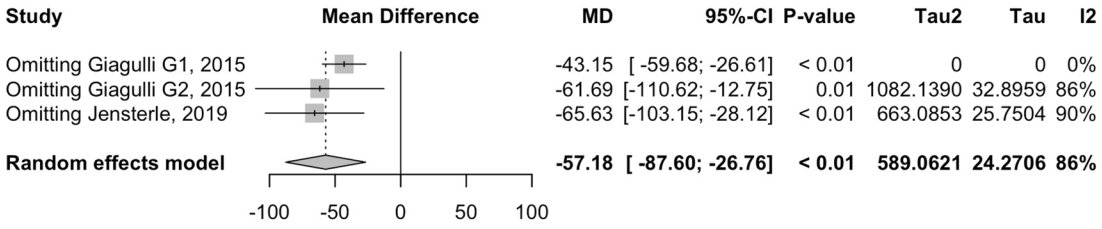

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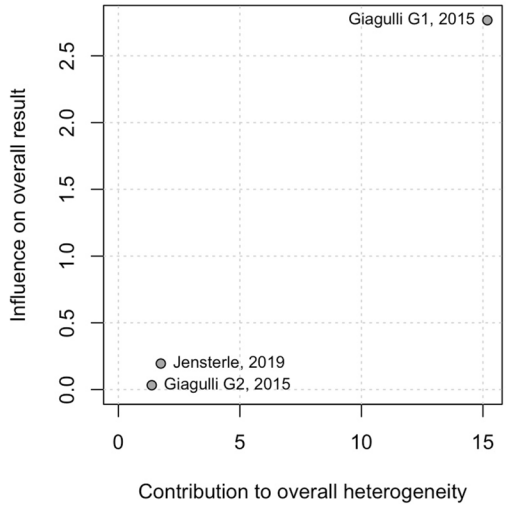
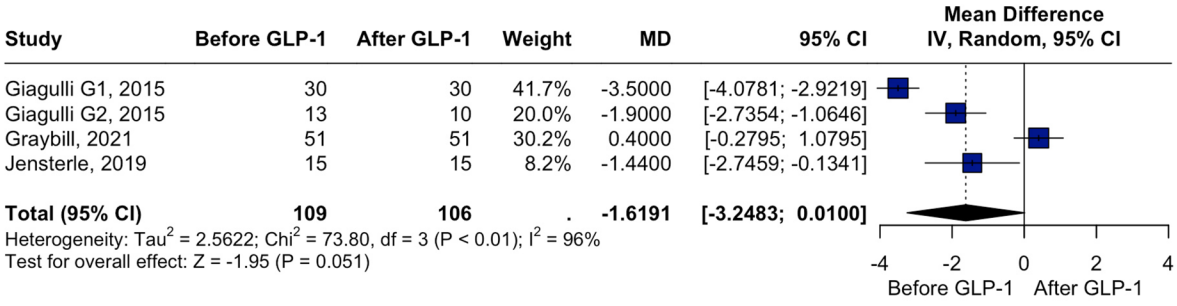


Fig. 4 Forest plot (**A**), leave one out (**B**), Baujat plot (**C**), for Bioavailable Testosterone (BioT)

These findings are aligned with prior research, including the randomized study by Kahal et al. [18], which evaluated 29 obese men with type 2 diabetes randomized to liraglutide or placebo for 16 weeks. That trial reported modest increases in total testosterone in the GLP-1 group, alongside significant improvements in weight and insulin sensitivity. However, changes in free testosterone and SHBG were less pronounced. Differences in baseline characteristics such as age, BMI, and treatment duration among studies may explain discrepancies in outcomes, particularly regarding SHBG and free testosterone.

Recent evidence published after our initial search cutoff also supports the endocrine benefits of GLP-1 receptor agonists. Chen et al. [19] conducted a RCT evaluating the combined use of semaglutide and metformin in overweight and obese women with polycystic ovary syndrome. The authors reported significant reductions in total testosterone and free androgen index, accompanied by increases in SHBG and improved reproductive

A.



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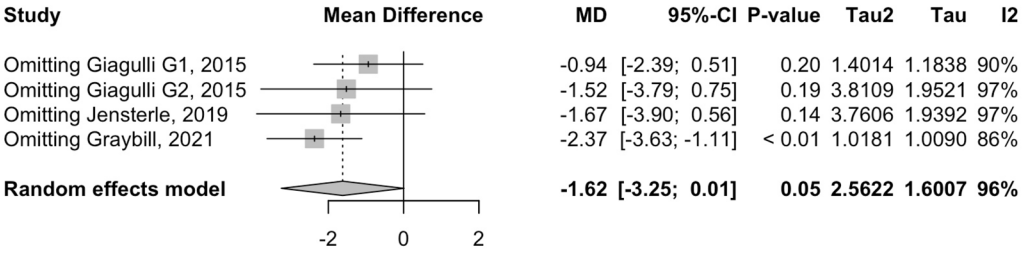

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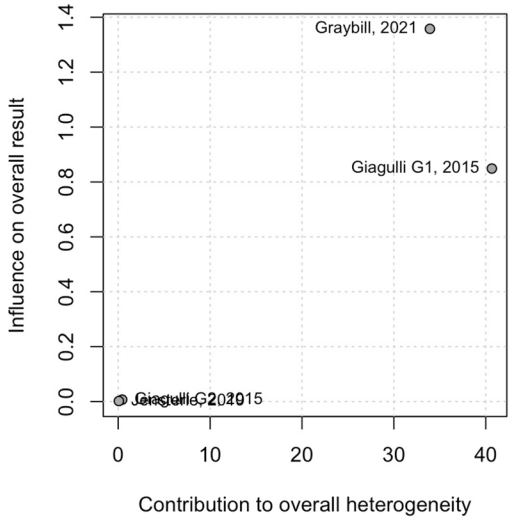


Fig. 5 Forest plot (**A**), leave one out (**B**), Baujat plot (**C**), for Free Testosterone

outcomes. These findings further reinforce the androgen-modulating potential of GLP-1-based therapies across different populations. However, this study was not included in our quantitative synthesis because our eligibility criteria were restricted to *male*participants with functional hypogonadism, while Chen et al. focused exclusively on *female* participants with PCOS. Nevertheless, its results complement our conclusions by expanding the evidence base for GLP-1 receptor agonists as regulators of gonadal function and metabolic homeostasis.

This review also highlights several limitations. First, only four studies comprising 435 participants were included, which restricts the ability to perform subgroup analyses or meta-regression and diminishes the robustness of the conclusions. Second, there was substantial heterogeneity across outcomes (I^2 values exceeding 90%

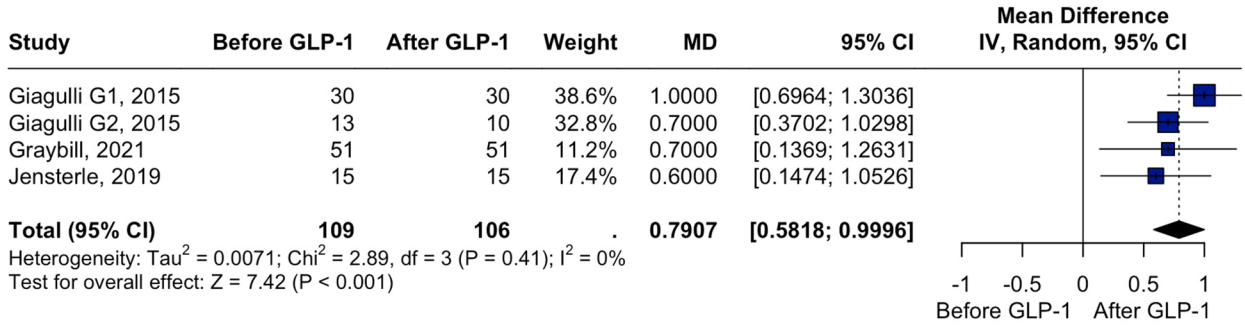
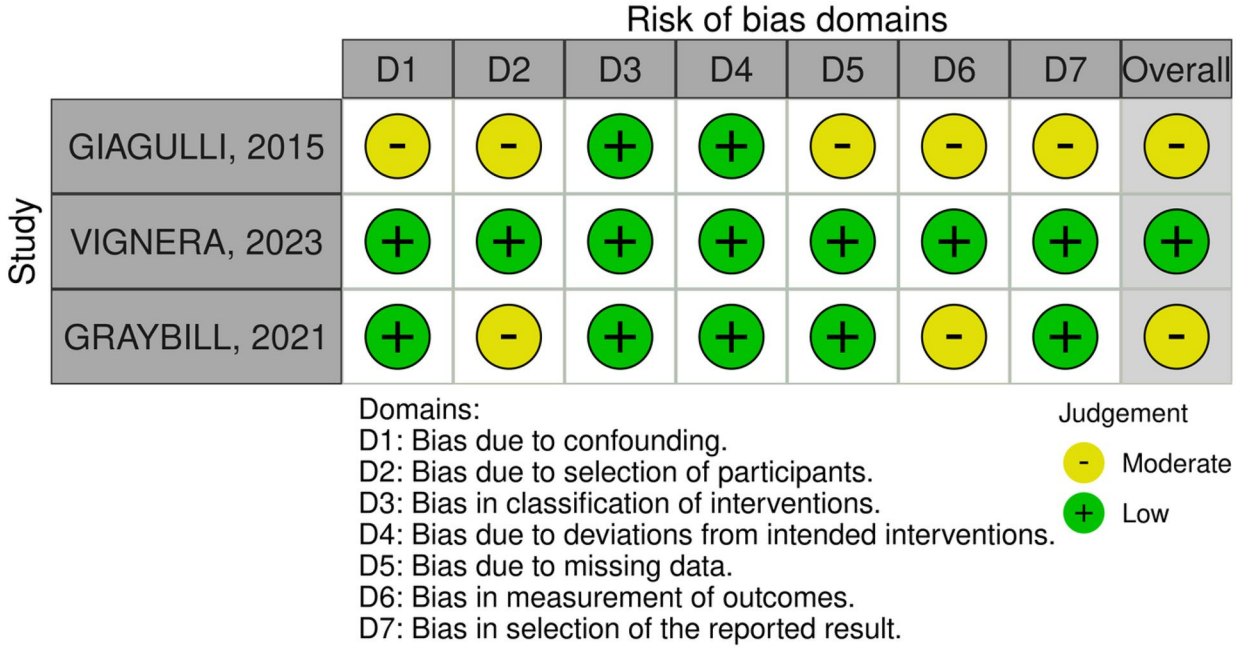


Fig. 6 Forest plot, for HbA1c

A.



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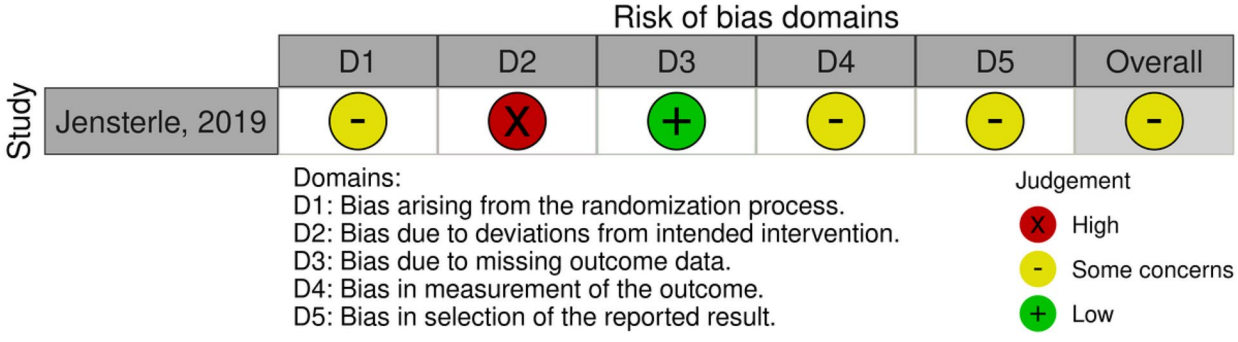

Fig. 7 Risk of Bias **A**, **B**

in several analyses). This heterogeneity likely reflects differences in patient populations (age, BMI, baseline testosterone), drug type (liraglutide vs. exenatide), dosage regimens, and treatment duration. Although leave-one-out and Baujat analyses were performed, they did not meaningfully reduce heterogeneity, indicating that the variability is intrinsic to the studies themselves. Third, although publication bias is always a concern in meta-analyses, formal assessment through funnel plots or Egger's test is not statistically reliable with fewer than ten studies, and therefore was not performed. Nevertheless, the possibility of selective reporting cannot be excluded. Finally, the lack of standardization in testosterone measurement methods across trials, particularly regarding free testosterone (often calculated rather than directly measured), represents an additional limitation that may affect comparability.

In summary, this analysis raises important considerations regarding the interplay between metabolic and reproductive health. While current evidence suggests a promising role for GLP-1 agonists in modulating testosterone, further investigation is warranted to establish definitive conclusions and inform clinical guidelines.

Conclusion

This meta-analysis synthesized current evidence on the effects of GLP-1 receptor agonists on testosterone and metabolic outcomes in men. While no significant changes were observed in free testosterone or SHBG levels, treatment with GLP-1 RAs was associated with a significant rise in bioavailable testosterone and a notable reduction in HbA1c, indicating potential dual metabolic and endocrine benefits. The presence of high heterogeneity in some outcomes underscores the importance of sensitivity analyses—such as leave-one-out and Baujat plots—to explore and account for study-level variability.

These findings contribute to the growing body of literature suggesting that GLP-1–based therapies may have applications beyond glycemic control, particularly in the context of hypogonadism related to obesity and insulin resistance. Nevertheless, given the limitations of current evidence, robust randomized controlled trials with larger cohorts and longer follow-up are necessary to confirm these outcomes and further elucidate the therapeutic implications of GLP-1 RAs in hormonal regulation.

Acknowledgements
Nothing to declare.

Clinical trial number
Not applicable.

Authors' contributions
Substantive scientific and intellectual contributions to the study: Conception and design: José A. S. da Cruz and Breno C. Porto; Acquisition of data: Breno C. Porto and Juan Victor Nabhan Martinez; Analysis and interpretation of data: Soraya Hussein Orra and Juan Victor Nabhan Martinez; Technical procedures: Juan Victor Nabhan Martinez and Breno C. Porto; Statistics analysis: Breno C. Porto, Carlo C. Passerotto and José A. S. da Cruz; Manuscript preparation: Breno C. Porto, Rodrigo A. S. Sardenberg and José A. S. da Cruz; Manuscript writing: Soraya Hussein Orra and Breno C. Porto; Critical revision: Breno C. Porto, Rodrigo A. S. Sardenberg and José A. S. da Cruz.

Funding
Not applicable.

Data availability
Available upon request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors have reviewed and approved the manuscript for publication.

Competing interests
The authors declare no competing interests.

Received: 29 April 2025 / Accepted: 19 November 2025
Published online: 25 November 2025

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