Received: 18 February 2022 | Revised: 3 October 2022 | Accepted: 6 October 2022

DOI: 10.1111/andr.13318

ANDROLOGY

WILEY

REVIEW ARTICLE

Effects of treatment for diabetes mellitus on testosterone concentrations: A systematic review

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Abstract

Background: Low testosterone levels are frequently present in men with obesity and insulin resistance. Currently available treatment options (testosterone replacement therapy or lifestyle changes) hold possible risks or are insufficient. Since low testosterone levels are closely related to obesity and type 2 diabetes, treatment modalities for these conditions could result into improvement of testosterone levels.

Objectives: To summarize the available evidence on the effects of traditional and recent treatment modalities for diabetes mellitus on testosterone levels and androgen-deficiency-related signs and symptoms.

Materials and methods: PubMed was searched from the year 2000 till present using MESH terms: "hypogonadism," "testosterone," "testosterone deficiency," "functional hypogonadism," and the different classes of medications. Studies with observational and experimental designs on humans that evaluated the effect of antidiabetic medications on gonadotropins and testosterone were eligible for inclusion.

Results: Current available data show no or only limited improvement on testosterone levels with the classic antidiabetic drugs. Studies with GLP1-receptor analogues show beneficial effects on both body weight and testosterone levels in men with low testosterone levels and obesity with or without type 2 diabetes. However, data are limited to small and heterogeneous study groups and only few studies report data about impact on androgen-deficiency-related signs and symptoms.

Discussion and conclusion: With the recent advances in the knowledge of the pathophysiological pathways in obesity, there is an enormous progress in the development of medications for obesity and type 2 diabetes. Newer incretin-based agents have a great potential for the treatment of functional hypogonadism due to obesity since they show promising weight reducing results. However, before the use of GLP1-receptor analogues can be suggested to treat functional hypogonadism, further studies are needed.

KEYWORDS
antidiabetic agents, antihyperglycemic agents, functional hypogonadism, GLP1 receptor analogues, hypogonadism, obesity

1 | INTRODUCTION

Functional hypogonadism (also referred to as late-onset hypogonadism) is defined as the presence of low normal or low serum testosterone levels in the presence of clinical symptoms or signs of hypogonadism with the absence of intrinsic structural hypothalamic-pituitary-testicular (HPT) axis pathology. The HPT axis is intact while the rise in gonadotropin levels is absent due to a functional HPT axis suppression. This entity is mostly observed in men with obesity and associated illnesses (e.g., metabolic syndrome, type 2 diabetes) or with the use of specific medications (e.g., opioids or glucocorticoids).[1,2] The prevalence estimates ranges from 2.1% to 12.3%, depending on the definition, and there is an 8- to 13-fold increased prevalence in men with obesity or comorbidities.[1,3] Furthermore, weight gain in the general population clearly leads to a decrease of total and free testosterone and hereby increase of sexual symptoms.[4–6] How men with functional hypogonadism should be treated remains a topic of debate. Treatment with testosterone replacement suffers from a lack of convincing data on efficacy and holds possible risks.[2] For example, the risk of erythrocytosis is present but appears to be dependent on the formulation of testosterone used.[7] The risk of cardiovascular disease, venous thromboembolism or prostate-related problems seems no higher with the use of testosterone replacement therapy in the treatment of hypogonadal men, but well-conducted studies and definite evidence are currently still lacking.[7] Furthermore, treatment with testosterone impairs fertility due to interference with spermatogenesis. Moreover, low testosterone secondary to obesity is potentially reversible.[8,9] A recent guideline by the European Academy of Andrology states that lifestyle changes, including physical activity and weight reduction, in overweight and obese men, is therefore recommended.[2] This recommendation is supported by a meta-analysis, evaluating 24 studies, were weight loss, achieved by low calorie diet or bariatric surgery, indeed resulted in a significant increase in plasma total testosterone, calculated free testosterone, sex hormone binding globulin (SHBG) and gonadotropins. The elevation of plasma testosterone was more pronounced in subjects with a higher body mass index (BMI) at entry. Furthermore, a larger decline in BMI was associated with a higher testosterone increase. This is reflected in the effects of the different methods for achieving weight loss: lifestyle interventions lead to a mean weight loss of 9.8 ± 4.5% and a modest increase in plasma testosterone (mean difference 82.8 ng/dl) while bariatric surgery resulted in a higher mean weight loss (32 ± 5.4%) and plasma testosterone rise (mean difference 251.8 ng/dl).[8] Nevertheless, both lifestyle interventions and bariatric surgery have their limitations. The achievement and maintenance of body weight loss with lifestyle interventions is often challenged by lack of compliance, failure on the long term and high dropout rates.[10] On the other hand, bariatric surgery results more frequently in a rapid body weight reduction[10] but poses a risk of acute and long-term complications (e.g., surgical complications, osteoporosis, vitamin deficiencies,…). Furthermore, the weight loss induced by standard antiobesity medication is moderate, for example, Orlistat, which showed a mean weight loss of 3.1kg (CI: −3.8 to −2.4 kg).[11] Recently, the US Food and Drug Administration did approve high-dose semaglutide (2.4 mg once weekly SC), a glucagon-like-peptide-1 receptor analogue (GLP1-RA) for treatment of obesity, with a mean weight loss ranging from 9.6% to 17.4%.[12–15] Due to the link between metabolic disorders (obesity, metabolic syndrome), type 2 diabetes mellitus and functional hypogonadism, treatment with these and new promising antidiabetic agents could hypothetically provide benefits for men in the treatment of functional hypogonadism. Nevertheless, data on the effects of antihyperglycemic agents on hypogonadism are scarce.

The aim of this systematic review is to summarize the available evidence on the effects of treatments for diabetes mellitus on testosterone levels and androgen-deficiency-related signs and symptoms.

2 | MATERIALS AND METHODS

We performed a literature search, based on the PRISMA guidelines, using PubMed and one of the following search terms: "hypogonadism," "testosterone," "testosterone deficiency," "functional hypogonadism," and the different classes of medications.[16] A filter was used to limit the results to male subjects and studies published from 2000 till present. Studies with observational and experimental designs on humans that evaluated the effect of antidiabetic medications on gonadotropins and testosterone were eligible for inclusion. Studies that only reported on a single administration of medication or that reported only on women or only on men with hypergonadotropic hypogonadism were excluded. Figure 1 shows the process of inclusion. One study was excluded due to serious design errors and errors in reporting of study results. To provide uniformity in the description of the results, we chose to represent total testosterone and free testosterone in ng/dl. When results were presented in nmol/l, a conversion factor of 28.842 was used to calculate the concentration in ng/dl.

3 | RESULTS

3.1 | Medications associated with weight gain or neutral effects on weight

3.1.1 | Sulfonylureas

Sulfonylureas (SU) have been routinely prescribed to people with type 2 diabetes mellitus. They stimulate release of insulin from the pancreatic β-cells by binding to SU receptors tightly linked to ATP-sensitive K-channels.[17] Furthermore, they reduce hepatic insulin clearance and glucagon secretion from pancreatic α-cells.[18] Unfortunately, weight gain may occur in people treated with SU. Consequently, a negative effect on functional hypogonadism could be expected. Nevertheless, it has been reported that gliclazide (SU) promotes testosterone synthesis by increasing the precursor of testosterone biosynthesis duo to inhibition of pro-11β-hydroxysteroid dehydrogenase type 1. This effect was not seen with glipizide or tolbutamide.[19]

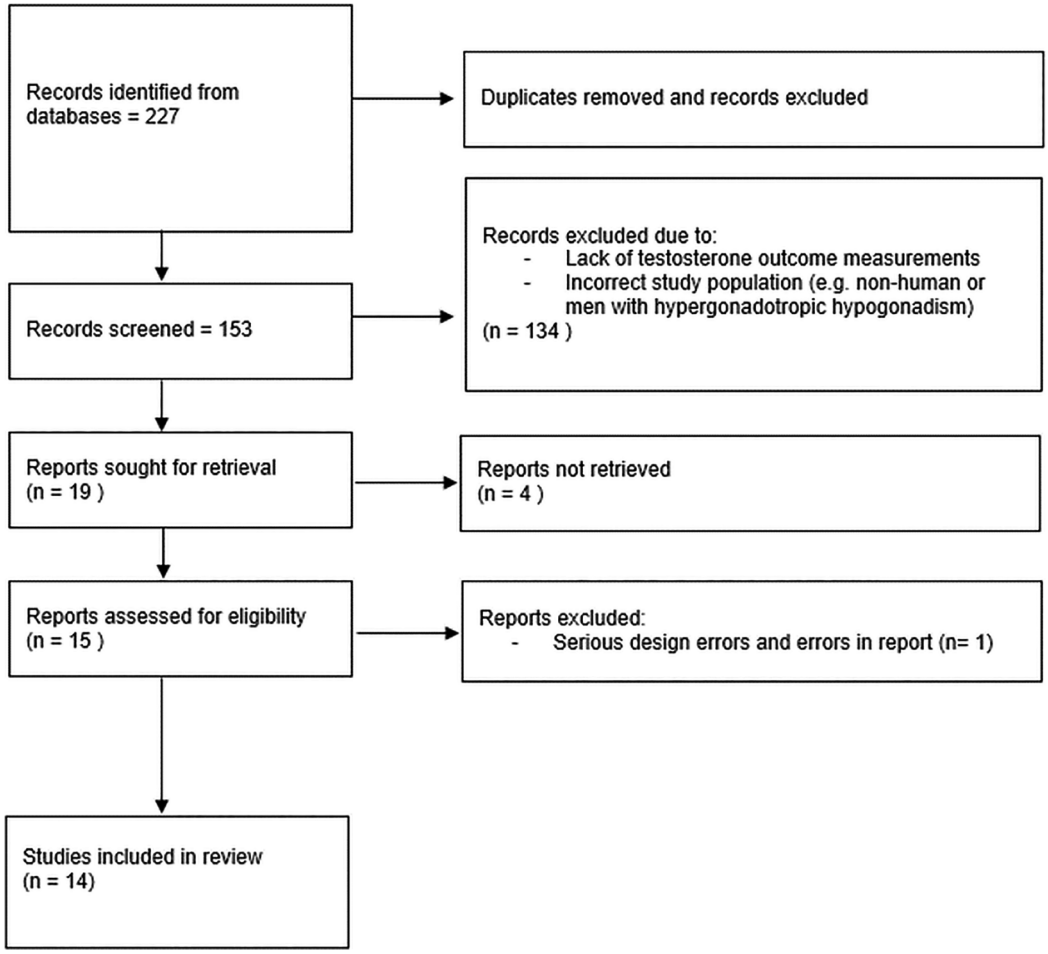

FIGURE 1 Flow chart of included studies

A pilot study in 15 middle-aged men with type 2 diabetes mellitus treated with glimepride during 16 weeks showed a significant increase in total testosterone (68.6 ± 39.8 vs. 103.5 ± 35.8 ng/dl) with no effect on SHBG. There was a significant decrease in HbA1c and no difference in weight after the 16 weeks of treatment.[20] Noteworthy, the levels of testosterone were very low at the start of the trial, and five of the 15 participants also received treatment with metformin. There was no information on power calculations available. In a prospective study in 86 men with type 2 diabetes and obesity, treatment with glimepiride and metformin showed an increase in total testosterone levels after 12 weeks of treatment (380.0 ± 84.7 vs. 414.7 ± 80.2 ng/dl), with a larger increase in serum testosterone in men who lost ≥ 5% of bodyweight.[21] Both studies did not evaluate the presence of hypogonadal signs or symptoms. The preliminary results may seem favorable on testosterone levels, but unfortunately no other well-designed studies on the use of SU in (functional) hypogonadism are available. Nevertheless, with the advent of new therapeutic options in type 2 diabetes mellitus and obesity with a positive effect on weight loss and beneficial effects on cardiovascular and/or renal outcomes (e.g., SGLT-2 inhibitors and GLP1-RA), the use of SU will decrease. Therefore, we believe there is no role for SU in the treatment of low testosterone levels in men with functional hypogonadism.

3.1.2 | Pioglitazone

Pioglitazone acts as an insulin sensitizer in the muscles and reduces the production of glucose in the liver.[22] It was hypothesized that a beneficial effect of pioglitazone on hypogonadism could be expected duo to reduction of visceral fat. Nevertheless, in a study performed on 50 men with low testosterone levels and type 2 diabetes, treatment with pioglitazone for 6 months resulted in an increase in mean SHBG (25.1–31.2 nmol/l in pioglitazone group vs. 25.5–25.2 nmol/L in placebo group), decrease in mean total testosterone (464.4–429.7 ng/dl in pioglitazone group vs. and 493.2–490.3ng/dl in placebo group) and a decrease in mean free testosterone (10.38–8.65 ng/dl in the pioglitzone group vs. 10.96–10.96 ng/dl in the placebo group). Since there was also an increase noted in plasma androstenedione, this could indicate a direct effect of pioglitazone on testosterone synthesis, more specifically the inhibitory effect on 17β-hydroxysteroid dehydrogenase III with a decrease in the conversion of androstenedione tot testosterone.[23] Concordantly, another study found that pioglitazone lowered the androgen production in human adrenal cells by the inhibition of P450c17 and 3β-hydroxysteroid dehydrogenase II, which are key enzymes of androgen biosynthesis, and by reducing the expression of CYP17 and HSD3B2 genes, which encode for essential enzymes for

androgen biosynthesis.[24] In contrast, a randomized placebo controlled double-blinded trial, in 30 eugonadal men (42% had BMI > 28.7 kg/m^2 and 26% had diabetes), pioglitazone treatment for 19 weeks had no effect on total serum testosterone (438 ± 23 ng/dl pretreatment vs. 426 ± 25 ng/dl posttreatment).[25] To the best of our knowledge, no trials are published on men with functional hypogonadism. With the current available data, we advise against the use of pioglitazone in men with functional hypogonadism.

3.2 | Medications associated with weight loss

3.2.1 | Metformin

Metformin is a first-line therapy for diabetes mellitus type 2 and is often used in other conditions associated with insulin resistance due to its inhibiting effect on hepatic gluconeogenesis, its effect on intestinal glucose uptake and its GLP-1 augmenting action.[26] Nevertheless, the molecular mechanisms remain still mostly unclear.[27,28] Due to its positive effects on insulin resistance and modest weight lowering potential, it has been proposed that metformin could have a beneficial effect on functional hypogonadism. Only a few studies have investigated the effect of metformin on testosterone concentrations. Observational, case studies and case-control studies show conflicting results with some studies reporting a negative effect of metformin on total testosterone[29–31], while others report a beneficial[32] or even no effect.[31] Similarly, both negative and beneficial effects are reported by observational and case (-controlled) studies on free or bioavailable testosterone.[29,31,32] In a randomized double-blind study, 24 obese men with impaired glucose tolerance or type 2 diabetes mellitus and low serum total testosterone (≤ 300 ng/dl) were treated with metformin and clomiphene citrate/placebo for 12 weeks. During the treatment with metformin alone, a significant increase in free testosterone (6.59 ± 2.94 vs. 8.01 ± 2.64 ng/dl) was noted in subjects with type 2 diabetes mellitus but no change in SHBG or total testosterone. There were no changes in total or free testosterone in the subjects with impaired glucose tolerance (12/24). Unfortunately, no information on signs or symptoms of hypogonadism were available.[33] Similarly, in a randomized trial by Kim et al., 886 men with impaired glucose tolerance and overweight or obesity, no effect on total testosterone, SHBG of bioavailable testosterone was seen after 1 year of treatment, compared to placebo.[34] The study performed by Giaguilli et al. is the only study, to our knowledge, to include participants with a diagnosis of functional hypogonadism (testosterone < 300 ng/dl and mild to moderate erectile dysfunction (assessed with the International Index of Erectile Function [IIEF]-5 score). Twenty-five obese men with uncontrolled diabetes were prescribed metformin 2–3 g a day. After 12 months of therapy an improvement was noted in total testosterone (275 ± 10 vs. 283 ± 9 ng/dl), free testosterone (5.1 ± 0.2 vs. 5.3 ± 0.2 ng/dl), and IIEF-5 score (15.7 ± 1.7 vs. 18.0 ± 1.0). Nevertheless, only one of the 25 participants achieved a testosterone >300 ng/dl after 12 months of therapy, and nine participants (36%) had an improvement of erectile dysfunction.[35]

In summary, the current available data on the effect of metformin on testosterone levels are limited to observational studies or studies performed on small groups with a short treatment duration. Furthermore, the vast majority of studies are in subjects with normal testosterone levels and suffering from insulin resistance or type 2 diabetes mellitus. The results of these studies are conflicting (Table 1.) Only one study assessed the effect of metformin on functional hypogonadism and showed no clinically significant improvement of testosterone levels but an improvement on erectile dysfunction in about one third of participants.[35] Overall, there are insufficient data to suggest the use of metformin to increase testosterone levels in men with functional hypogonadism.

3.2.2 | SGLT2 inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2 inhibitors) improve the glycemic control in people with diabetes due to the stimulation of glucosuria. This glucosuria can provide a negative energy balance and result in weight loss in people with diabetes (2–3 kg over the first 6 months of treatment), depending on the HbA1c at baseline. In the longer term, due to changes in glucagon, glycogen, and gluconeogenesis, a depletion of liver glycogen is achieved with the loss of fat mass, especially by reduction of steatosis, visceral, and subcutaneous adipose tissue.[36] This mechanism might, theoretically, provide a benefit for men with functional hypogonadism due to obesity, metabolic syndrome and/or type 2 diabetes mellitus. Only one study assessed the effect of SGLT2 inhibitor on functional hypogonadism in obese men with uncontrolled type 2 diabetes. In this study, by Giuagulli et al., 16 participants were treated with dapagliflozin 10mg once daily, as add-on to metformin, during 12 months. An improvement in total testosterone (265 ± 11 vs. 296 ± 27 ng/dl), free testosterone (5.0 ± 0.3 vs. 5.2 ± 0.4 ng/dl), and IIEF-5 score (15.8 ± 1.5 vs. 18.8 ± 1.4) was seen. 44% (7/16) of participants reached testosterone levels >300 ng/dl, and 44% (7/16) participants had an improvement of erectile dysfunction.[35] Of note, a significant reduction of mean body weight was achieved (from 100.1 ± 6.3 to 93.6 ± 4.5kg) after 12 months. Although these results appear promising, additional prospective studies in larger study populations are needed.

3.2.3 | Incretin mimetics

Glucagon-like-peptide-1 receptor analogues (GLP1-RA) and dipeptidyl peptidase-4 (DPP4) inhibitors act as glucose lowering drugs by stimulating the GLP1-R or by reducing the breakdown of GLP1, respectively. This stimulates insulin secretion, reduces glucagon secretion, slows down gastric emptying and induces satiety leading to a better glycemic control and reduced weight.[37,38] Since the use of DPP4 inhibitors only leads to a limited prolonged activity of GLP1 activity, they have moderate reduction in HbA1c (0.5 – 0.8%) and are weight neutral. Furthermore, up till now, no data are available on the impact of DPP4 inhibitors on testosterone levels in men and pharmacologically there

TABLE 1 Effects of antidiabetic agents on gonadotropins and testosterone levels in men

		LH	FSH	TT	SHBG	Free or bioavailable T	Change in weight or BMI	Remarks
Glimepride	Wong et al. (2015)	=	=	+	=	/	=	• Noncontrolled prospective study • 15 men with T2D • Low TT levels at baseline • Five participants also metformin
	Shao et al. (2018)	=	/	+	+	+	-	• Noncontrolled prospective study • 86 men with uncontrolled T2D and obesity • Normal TT levels at baseline
Glitazones (pioglitazone)	Sridhar et al. (2013)	=	=	-	+	-	=	• Randomized double blinded clinical trial • 50 men with T2D and normal TT
	Gholamine et al. (2008)	/	/	=	/	/	/	• Randomized, placebo-controlled, double blinded trial • 38 men (42% BMI > 28.7 kg/m^2 and 26% DM) • Normal TT levels at baseline
Metformin	Martin Martins et al. (2021)	/	/	-	/	/	/	• Observational • Participants with T1D and T2D • 37/173 men with secondary hypogonadism
	Ozata et al. (2001) With T2D Without T2D	= =	= =	- =	= +	= -	- -	• Case-control study • 20 men with obesity • Low normal TT at baseline
	Cai et al. (2021)	/	/	-	/	- (bioavalaible T) = (free T)	/	• Controlled study • 80 men with T2D and treated with premix insulins • 19/80 participants had low levels of TT at baseline
	Morgante et al. (2011)	+	=	+	-	+	=	• Noncontrolled prospective study • 45 men with metabolic • Syndrome • TT levels ranged from low to normal at baseline
	Kim et al. (2016)	/	/	=	=	=	-	• Randomized, nonblinded, clinical trial • 886 men with IGT and overweight or obesity • 44% low TT levels at baseline
	Pelusi et al. (2017) With IGT With T2D M	= =	= +	= =	= =	= +	= =	• Cross-over randomized, double-blind study • 24 men with low or low normal TT at baseline
	Giagulli et al. (2020)	+	+	+	+	+	-	• Retrospective observational study • 25 men with uncontrolled T2D, obesity and hypogonadism • Improvement of erectile dysfunction assessed with the IIEF-5
SGLT2 inhibitors	Giagulli et al. (2020)	=	+	+	+	+	-	• Retrospective observational study • 30 men with uncontrolled T2D, obesity and hypogonadism • Improvement of erectile dysfunction assessed with IIEF-5

(Continues)

TABLE 1 (Continued)

		LH	FSH	TT	SHBG	Free or bioavailable T	Change in weight or BMI	Remarks
GLP1-RA	Shao et al. (2018)	=	/	+	+	+	-	• Noncontrolled prospective observational study • 90 men with uncontrolled T2D and obesity
	Graybill et al. (2021) TT < 320 ng/dl	/ /	/ /	= +	+ /	= +	- /	• Prospective, observational cohort study • 51 men with T2D
	Giagulli et al. (2015)	/	/	+	+	=	-	• Retrospective, observational study • 43 middle-aged men with uncontrolled T2D, obesity and hypogonadism • Improvement of erectile dysfunction assessed with IIEF-5
	Jensterle et al. (2019)	+	+	+	=	=	-	• Randomized, open label, prospective trial • 30 men with obesity and hypogonadism • Five men with hypogonadism due to pituitary adenoma or head trauma • Improvement of the number of morning erections and ejaculations and a self-reported measurement of libido • No improvement Aging Male Syndrome Scale
	Giagulli et al. (2020)	=	=	+	+	+	-	• Retrospective observational study • 16 men with uncontrolled T2D, obesity and hypogonadism • Improvement of erectile dysfunction assessed with IIEF-5

Abbreviations: DM, diabetes mellitus; IIEF-5, International Index of Erectile Function; IGT, impaired glucose tolerance; TT, total testosterone; T1D, type 1 diabetes; T2D, type 2 diabetes.
/, no information available; -, significantly decreased; +, significtantly increased; =, no significant changes.

is no reason to hypothesize a beneficial effect. In contrast, treatment with a GLP1-RA can lead to a reduction of body weight up to 15% in people with overweight or obesity with or without type 2 diabetes.[12,39] This clinically important weight reduction and the finding that GLP1 receptors have been identified in testicular Leydig cells make GLP1-RA interesting agents for the treatment of functional hypogonadism.[40] Two observational studies in men with T2D, obesity and normal testosterone values at baseline showed conflicting results on total, free or bioavailable testosterone (Table 1).[21,41] To the best of our knowledge, only three studies investigated the effect of GLP1-RA in functional hypogonadism. In the study by Giagulli et al., 30 middle-aged men with uncontrolled type 2 diabetes (HbA1c > 8.0%/64 mmol/mol), obesity (BMI >30 kg/m^2) and hypogonadism (total testosterone levels <300 ng/dl, calculated free testosterone <6.5 ng/dl and erectile dysfunction defined by a score <14 on the International Index of Erectile Function Questionnaire (IEFF)) were treated with liraglutide (1,2 mg/day) for 12 months. There was a significant increase in testosterone levels (466,1 ± 63,6 ng/dl vs. 481.7 ±57.3 ng/dl) and a significant decrease in body weight (99.0 ± 7.6 kg vs. 93.7 ± 6.3 kg) when treatment with liraglutide was added. Concerning erectile dysfunction, the IIEF score increased significantly (14.6 ± 1.7 vs. 19.9 ± 2.0), leading to an almost complete resolution of erectile dysfunction.[42] Noteworthy, patients were also treated with exogenous testosterone, making the effects on serum testosterone difficult to interpret. Furthermore, 5 participants had no diagnosis of functional hypogonadism but were diagnosed with organic hypogonadotropic hypogonadism (due to a pituitary adenoma or head trauma). In the study performed by Jensterle et al. treatment with liraglutide was compared with transdermal testosterone gel in 30 middle-aged men with obesity and functional hypogonadism (defined as serum testosterone ≤ 317.62 ng/dl, the presence of ≥2 symptoms of sexual dysfunction and (inappropriate) low LH). The study lasted 16 weeks and was open label. Total testosterone significantly increased in both treatment arms with no difference between the two groups (207.7–377.8 ng/dl vs. 219.2–294. 2ng/dl, in testosterone gel and liraglutide group respectively). Subjects treated with liraglutide had an average weight loss of 6.0 ± 3.2% compared to 0.8 ± 3.3% in the testosterone treatment group. The number of morning erections and ejaculations improved significantly in both treatment arms without significant between-treatment differences. The presence of symptoms of androgen-deficiency, assessed through the Aging Male Syndrome questionnaire, significantly improved in the testosterone treated group but not in the liraglutide treated group. However, the difference between the treatments was not significant. The authors state that, if treatment with lifestyle measures is not sufficient, treatment with liraglutide should be advised over testosterone replacement therapy, due to the overall health improvement.[43] Accordingly, in another study, by Giagulli et al., obese men with uncontrolled type 2 diabetes and functional hypogonadism (testosterone < 300 ng/dl and mild to moderate erectile dysfunction assessed with the IIEF-5) were treated with dulaglutide 1.5 mg once weekly (14 participants) or with liraglutide 1.2 mg once daily (16 participants). A significant increase in total testosterone (mean difference 51 ± 10 ng/dl and 66 ± 9 ng/dl for dulaglutide and liraglutide respectively), free testosterone (mean difference 0.7 ± 0.2 ng/dl and 1.2 ± 0.2 ng/dl for dulaglutide and liraglutide respectively), and IIEF-5 scores (mean difference 3.6 ± 0.4 and 4.0 ± 0.4 for dulaglutide and liraglutide respectively) was noted after 12 months of therapy.[35]

Overall, there is a consistent rise in total testosterone levels after treatment with GLP1-RA in men with obesity and/or T2D. Concerning the effect of GLP1-RA on symptoms of hypogonadism, data remain limited. Up to now, only three studies with GLP1-R analogues reported on androgen-deficiency-related signs and symptoms. These studies showed an improvement of libido and erectile function after treatment with GLP1-RA.[35,42,43]

4 | DISCUSSION AND PERSPECTIVE

Since low testosterone levels are closely related to obesity and its comorbidities, such as insulin resistance and type 2 diabetes, treatment modalities for obesity and type 2 diabetes could result into improvement of testosterone levels. Current available data show no or only limited improvement on low testosterone levels with the classic antidiabetic drugs, and studies on the effect on androgen-deficiency-related symptoms are not available. Thus far, there have been very few data of SGLT2i on testosterone levels in men with type 2 diabetes with hypogonadism. On the other hand, studies with GLP1-R analogues show beneficial effects on both body weight and testosterone levels in men with low testosterone levels and obesity with or without type 2 diabetes. Overall, it is expected that the weight-lowering effect is the main contributor for improvement of low testosterone levels in the treatment with antidiabetic drugs. Nevertheless, the current available data suggest that the rise in testosterone levels due to treatment with GLP1-RA is higher than what could be expected for the amount of weight loss.[21,43] This might be explained by acting on the testicular GLP1-R and/or by the decrease of the antioxidants in the testes, but this hypothesis needs further exploration.[40,44] Similarly, one might hypothesize that apart from weight loss, the improvement in glycemic control leads to an improvement of testosterone levels in men treated with antidiabetic medications. Observational data in men with suboptimal T2D (mean HbA1c 7.6%) showed that total testosterone was inversely correlated with HbA1c, meaning that improvement of HbA1c led to an improvement of total testosterone.[45] However, recent data suggest that weight loss caused by antidiabetic medications is the main contributor for improvement of total testosterone and not improvement in glycemic control.[35] Up to know, evidence in functional hypogonadism is limited to small, heterogeneous study groups and trials on a larger number of participants will be necessary. However, acquiring an appropriate study group is difficult due to the nonstandardized definition of functional hypogonadism and the low estimated prevalence or incidence in the general population (incidence rate of 43.1 per 10,000 per year).[9] Furthermore, it remains controversial which treatment modality produces the most benefit for men with functional hypogonadism. It is without doubt that in obese or overweight men, a weight reduction should be aspired. Life style changes comprising of lowering calorie intake and increasing

physical activity remains the first-line treatment, despite the difficulties in obtaining and preserving weight loss through lifestyle changes.[2,10] The addition of new treatment modalities for weight reduction should be investigated, since they are associated with other health benefits (e.g., glycemic control). In addition, recent data have shown that the presence of obesity predicted the development of low testosterone levels and that this group of men reported more erectile dysfunction, decreased libido and decreased morning erections, compared to men with normal testosterone levels.[9] Apart from other health benefits (e.g., cardiovascular disease, type 2 diabetes,…), the risk of developing functional hypogonadism could provide an additional motivation to men at risk in order to change their life style. Furthermore, recent advances with respect of the knowledge of the molecular background of obesity have led to an enormous progress in the development of medications for obesity and type 2 diabetes.[46] For instance, the recently developed dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonist Tirzepatide has shown to induce a weight loss of ≥15% in 15%–40% of patients with type 2 diabetes after 40 weeks of treatment.[47] Other therapeutic options, for example, GLP1/glucagon dual agonists, GIP/GLP1/glucagon tri-agonists, leptin sensitizers, amylin analogues and amylin/calcitonin dual agonists, are currently under study for the treatment of obesity and/or type 2 diabetes. Whether these new agents have beneficial effects on testosterone levels, and/or symptoms of androgen-deficiency are yet to be discovered but the preliminary promising results on weight loss could provide a new approach for the treatment of low testosterone secondary to obesity. In this line of thinking, a recent controlled study with GLP1-R analogues has already shown a beneficial effect on the severity of erectile dysfunction in men with type 2 diabetes with a high cardiovascular risk.[48] We would like to encourage future studies on these new agents to add the assessment of symptoms of hypogonadism.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

J.V.C. carried out the literature survey, analyzed the data, and drafted the manuscript. All authors contributed to critical revision of the manuscript and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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How to cite this article: Van Cauwenberghe J, De Block C, Vanderschueren D, Antonio L. Effects of treatment for diabetes mellitus on testosterone concentrations: A systematic review. *Andrology*. 2023;11:225–233. https://doi.org/10.1111/andr.13318