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REVIEW ARTICLE

Testosterone therapy in diabetes and pre-diabetes

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Abstract

Background: Type 2 diabetes mellitus and pre-diabetes are associated with reduced circulating testosterone levels. However, the role of testosterone replacement therapy in these patients is still conflicting.

Objectives: To summarize and critically analyze available data on the possible effect of testosterone administration in men with glucose abnormalities.

Materials and methods: A comprehensive systematic review was performed. When available, meta-analytic data were preferred. To better analyze the relationship between testosterone and the pre-diabetes condition, a systematic analysis was performed and the data obtained with the latter search were used for a meta-analytic approach. Finally, clinical data derived from a consecutive series of 4682 patients seeking medical care for sexual dysfunction at the University of Florence were also considered.

Results: Patients with impaired fasting glucose were characterized by a 3 nmol/L lower level of total testosterone when compared to controls. Similarly, impaired fasting glucose was associated with a 1.8-fold increased risk of hypogonadism, when compared to subjects with normal glucose levels. Waist circumference and body mass index resulted as being the best predictors of reduced total testosterone levels. Secondary hypogonadism was two times higher in subjects with impaired fasting glucose when compared to rates observed in the general population. Testosterone replacement therapy was able to improve body composition, insulin resistance, and glucose profile both in impaired fasting glucose and type 2 diabetes mellitus whereas its role on body weight, lipid profile, and sexual function was less evident.

Discussion and conclusion: Weight loss and physical activities are able to improve both metabolic profile and testosterone levels. The combined approach of testosterone replacement therapy and lifestyle modifications could be suggested in symptomatic hypogonadal men to better motivate patients to perform physical activity which can eventually result in weight loss as well as metabolic profile and sexual function improvement. Whether or not these approaches can prevent the development of type 2 diabetes mellitus from pre-clinical conditions requires more studies.

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KEYWORDS
erectile dysfunction, pre-diabetes, testosterone, testosterone replacement therapy, type 2 diabetes

1 | INTRODUCTION

Pre-diabetes is an emerging construct able to define an altered glucose metabolism that is at high risk for future progression to overt diabetes.[1,2] Although a matter of debate, the condition "pre-diabetes" has been recently incorporated in the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM codes [https://www.icd10data.com]. The impaired fasting glucose (IFG) category, originally defined by fasting plasma glucose concentrations between 110 and 125 mg/dl (6.1 and 6.9 mmol/L), was proposed for the first time in 1997 by the American Diabetes Association (ADA) and thereafter confirmed by the World Health Organization in 1999.[1,2] In 2003, the ADA recommended that the diagnostic threshold should be lowered to 100 mg/dl (5.6 mmol/L) and introduced glycated hemoglobin A1c (HbA1c; as derived from a certified and standardized method) 39–47 mmol/mol (5.7-6.4%) as a new category for high risk of diabetes. There is less controversy on the definition of pre-diabetes using impaired glucose tolerance (IGT), defined as a 2 h post-load plasma glucose concentration 140–199 mg/dl (7.8–11 mmol/L) measured during a 75 g oral glucose tolerance test (OGTT[1,2]). It has been estimated that between 5%–10% of pre-diabetic subjects will become diabetic every year and that 70% of individuals with pre-diabetes will develop lifelong diabetes.[1–4] Several diabetic risk models are also available to predict incident diabetes. In particular, the Atherosclerosis Risk in Communities (ARIC) algorithm developed by Schmidt et al.[5] was shown to be one of the most efficient instruments for the prediction of incident T2DM.[6] By using ARIC score quartiles in a large series of men seeking medical care for sexual dysfunctions, we previously showed that almost 50% of those in the fourth score quartile had a total testosterone (T) below 12 nmol/L, as opposed to 16% in the first score quartile.[7] Similarly, in a further study related to the same population, we also showed the pre-diabetes condition, defined as IFG, was associated with a sharp decline in total T and cFT, along with an increase in ANDROTEST score, a symptom-based algorithm able to predict male hypogonadism.[8] In addition, subjects with overt diabetes, but also those with IFG, were more often affected by severe ED and by loss of spontaneous erection, along with reduced penile blood flow.[8]

An association between type 2 diabetes mellitus (T2DM) and low total T has been apparent for more than 40 years[9,10] and has essentially been reconfirmed in all subsequent studies.[11–13]Availabe data indicated that T decline is more apparent in obese T2DM subjects[12,13] and in the youngest ones.[12] However, in a multivariate regression model, the negative relationship between T and T2DM retained significance even after adjusting for body mass index (BMI[12]). This suggests that obesity does not completely explain the negative effect of having T2DM on total T. Considering that hyperinsulinemic states are often associated with a decrease in the protein that tightly binds circulating T (sex hormone binding globulin; SHBG[14]), it is possible to speculate that the T2DM-related decline in total T is more apparent than real, due to the SHBG decrease. However, available meta-analyses showed that – either measured[12] or calculated[13] free T levels – were lower in the diabetic population than in controls (i.e., −9.17 and −32 pmol/L). Results from meta-analyses of cross-sectional studies were confirmed in the longitudinal trials performed so far,[12,13] showing that total T is lower in those developing diabetes at follow-up,[12,13] and both free T and SHBG are lower as well.[13]

Irrespective of the cut-off used to define male hypogonadism,[15–17] there is universal agreement that bothersome clinical symptoms should be present to define a real hypogonadal state.[15] Data derived from the European Male Aging Study (EMAS) showed that the most genuine symptoms clustering significantly with low T are sexual symptoms, i.e. reduced libido and loss of erections.[18] Similar results were derived from subjects consulting for sexual symptoms.[8]

Considering that almost 20%–30% of pre-diabetic and diabetic subjects, respectively, show T deficiency and that in a meta-analysis on the general population[19] T supplementation to hypogonadal subjects was able to improve body composition and glucose levels, it is possible to hypothesize a beneficial effect of T replacement therapy (TRT) in hypogonadal men with diabetes or pre-diabetes. Hence, the aim of the present systematic review is to scrutinize available evidence on the possible effect of T administration in men with glucose abnormalities.

2 | METHODS

A comprehensive systematic review was performed using Medline, Embase, and Cochrane search and including the following words: ((“testosterone”[MeSH Terms] OR “testosterone”[All Fields] OR “testosteron”[All Fields] OR “testosterones”[All Fields] OR “testosterone s”[All Fields]) AND (“therapeutics”[MeSH Terms] OR “therapeutics”[All Fields] OR “therapies”[All Fields] OR “therapy”[MeSH Subheading] OR “therapy”[All Fields] OR “therapy s”[All Fields] OR “therapys”[All Fields]) AND (“diabetes mellitus”[MeSH Terms] OR (“diabetes”[All Fields] AND “mellitus”[All Fields]) OR “diabetes mellitus”[All Fields])) AND ((male[Filter]) AND (english[Filter])). Publications from January 1, 1969, up to April 30, 2022, were included. When available, meta-analytic data were preferred.

Clinical data were derived from a consecutive series of 4682 patients seeking medical care at the University of Florence as previously described.[7,8,20]

In addition, to better analyze the relationship between T and the pre-diabetes condition, a further specific search was performed using the following words: (“testosterone”[MeSH Terms] OR “testosterone”[All Fields] OR “testosteron”[All Fields] OR “testosterones”[All

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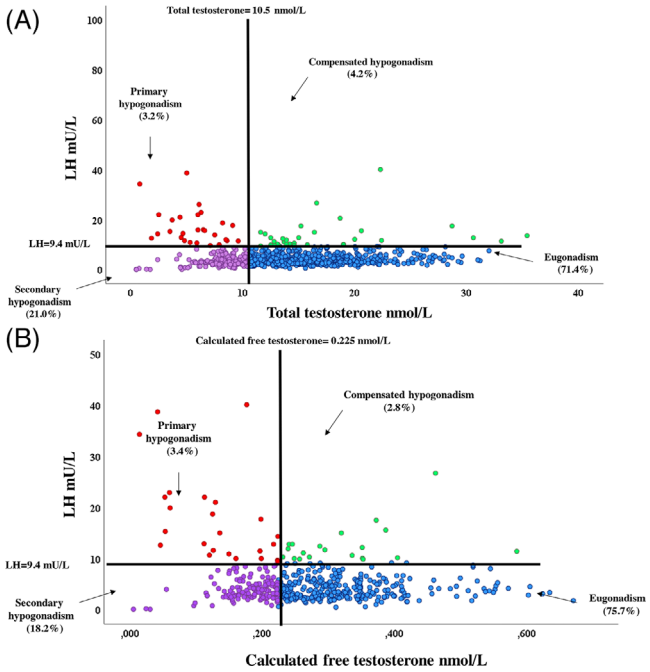


FIGURE 1 Relationship between luteinizing hormone (LH) and testosterone (T) (A) and calculated free T (B) levels according to the presence of pre-diabetes (fasting glucose levels were between 100 and 125 mg/dl, or 6.1-6.9 mmol/L and no previous history of diabetes mellitus or use of anti-diabetic medication). The prevalence of eugonadism (total T ≥ 10.5 mM or calculated free T ≥ 0.220 nM, and LH ≤ 9.4 U/L, blue circles), compensated hypogonadism (total T ≥ 10.5 mM or calculated free T ≥ 0.220 nM, and LH > 9.4 U/L, green circles), primary hypogonadism (total T < 10.5 mM or calculated free T < 0.220 nM, and LH > 9.4 U/L, red circles) and secondary hypogonadism (total T < 10.5 mM or calculated free T < 0.220 nM, and LH ≤ 9.4 U/L, purple circles) according to the European Male Aging Study criteria[21] is also reported. Data are derived from a cohort of subjects [$n = 4682$ and $n = 2611$ for TT and calculated free T, respectively] complaining of sexual dysfunction studied at the University of Florence

Fields] OR "testosterone s"[All Fields]) AND ("prediabetic state"[MeSH Terms] OR ("prediabetic"[All Fields] AND "state"[All Fields]) OR "prediabetic state"[All Fields] OR "prediabetes"[All Fields] OR "prediabetic"[All Fields] OR "prediabetics"[All Fields])) AND ((male[Filter]) AND (english[Filter])).Data obtained with the latter search were used for a meta-analytic approach as previously reported[12] (Appendix S1).

3 | EPIDEMIOLOGY

3.1 | Pre-diabetes and low T

Only a limited number of studies have investigated the differences in T levels in subjects with or without pre-diabetes. By applying the EMAS thresholds for hypogonadism definition,[21] we here originally report data derived from a large sample of patients seeking medical care at our Unit for ED (Figure 1). Out of 4682 subjects with a mean age of 54.6 ± 12.4 years, 789 (16.9%) were defined as IFG as previously reported (fasting glucose levels were between 100 and 125 mg/dl, or 6.1–6.9 mmol/L and no previous history of DM or use of anti-diabetic medication).[8] Information related to the HbA1c measuring method was limited. Among subjects with IFG, the observed prevalence of secondary hypogonadism was two times higher when compared to that observed in the general population,[21] either when total T or free T was considered (See also Figure 1, Panels A and B). A slight increase in primary hypogonadism was also observed, whereas no difference in compensated hypogonadism was detected. In line with these data after the adjustment for age, BMI and waist were the best predictors of IFG-related reduction of total T (adj. $r = -0.271$ and -0.276 for waist and BMI, respectively vs. -0.053 for IFG).

To better clarify the impact of pre-diabetes on T levels, we collected all available studies comparing patients with IFG according to the ADA criteria and defined as fasting plasma glucose between 100 and 125 mg/dl (6.1–6.9 mmol/L), or 2-h plasma glucose levels after OGTT between 140 and 199 mg/dl (7.8–11.1 mmol/L) or HbA1c between 5.7% and 6.4%. Out of 72, eight studies included 3625 subjects with IFG and 6205 normal individuals (Table 1).[8,22–28] I^2 for IFG compared to non-IFG was 99.07, $p < 0.0001$. The funnel plot and Begg-adjusted rank correlation test suggested no major publication bias (Kendall's τ: -0.46; $p = 0.11$). Similar to what was previously reported for T2DM (see also Figure 2), IFG was characterized by a 3 nmol/L lower level of total T when compared to controls (Figure 3, panel A). Accordingly, IFG was associated with a 1.8-fold increased risk of hypogonadism, when compared to subjects with normal glucose levels (Figure 3, Panel B). Interestingly, when meta-regression analysis was applied, waist circumference (S = -0.092 [-0.111; -0.074] and I = 6.565 [4.765; 8.365]; both $p < 0.0001$) and BMI (S = -0.092 [-0.111; -0.074], and I = 6.565 [4.765; 8.365]; both $p < 0.0001$), resulted as being the best predictors of reduced total T levels (Figure S1).

3.2 | T2DM and low T

Several studies have reported a higher prevalence of hypogonadism in patients with T2DM when compared to controls. The specific prevalence ranged from 20% to more than 50% depending on the type of population and the thresholds used for defining hypogonadism.[29] In order to better clarify the latter association we collected available meta-analyses analyzing the difference in T levels between T2DM and controls. Three meta-analyses, published so far, have investigated the effects of T2DM on T levels.[12,13,30] (Table 2). The number of studies included were 20, 24, and 56, respectively. In addition, subjects with diabetes were 1355, 1822, and 6856 compared to 5745, 10,009, and 23,572 controls, respectively (Table 2). All studies reported cross-sectional data, whereas longitudinal analyses were provided by only two meta-analyses (Table 2). Overall, when compared to controls, patients with T2DM showed significantly lower total and free-T levels despite a significant reduction of SHBG (Figure 2). When longitudinal results were analyzed, those patients who developed T2DM at follow-up had significantly lower total T levels at

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TABLE 1 Characteristics of observational studies describing subjects with impaired fasting glucose (IFG) or normal fasting glucose (NFG) included in the meta-analysis. BMI, body mass index; WC, waist circumference; T, testosterone; HbA1c, glycated hemoglobin

Author	Subjects with IFG (n°)	Subjects with NFG (n°)	Age (years)	BMI (kg/m^2)	WC (cm)	Serum T (nmol/L)	HbA1c (%)	Serum glucose (mmol/L)
Corona et al., 2012[11]	446	2238	58.5	28,6	103.2	16.0	NR	5.3
Ho et al., 2013[23]	543	577	54.3	24.8	87.9	14.6	5.5	5.4
Rabijewski et al., 2015[24]	196	184	67.1	28.4	101.1	13.9	5.8	5.9
Zhu et al., 2016[25]	907	1405	52.5	24.3	81.8	15.1	5.4	5.3
Liu et al., 2019[27]	355	355	59.9	23.6	82.9	7.5	5.6	5.1
Lu et al., 2019[26]	495	545	75.3	24.5	90.4	17.2	NR	5.3
Boeri et al., 2020[28]	105	253	56.2	25.3	NR	14.7	5.3	5.1
Beckmann et al., 2022[29]	578	648	41.2	26.1	93.8	17.6	5.1	5.4

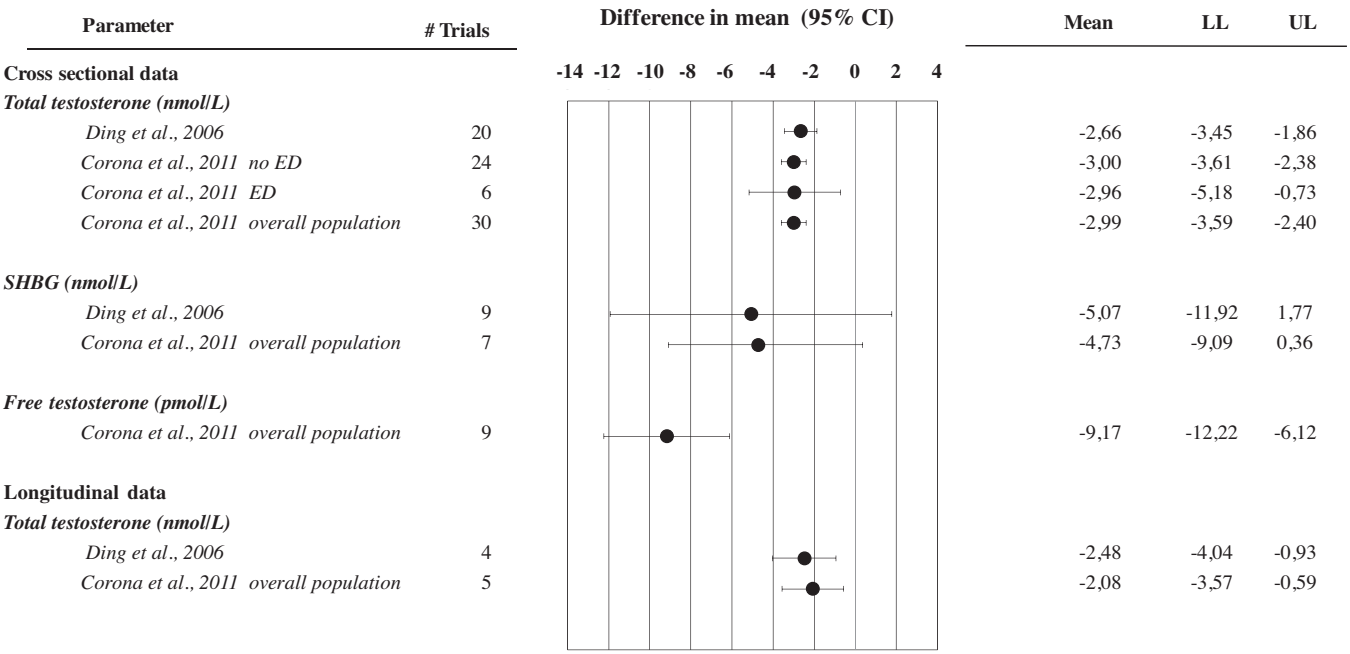


FIGURE 2 Available meta-analyses summarizing weighted mean differences (with 95% confidence interval [CI]) between patients with or without type 2 diabetes mellitus of different hormonal parameters as derived from cross-sectional or longitudinal studies. ED, erectile dysfunction

baseline (Figure 2). Similar data were reported for free-T and SHBG by Zhang et al.[13]

3.3 | Influence of TRT on body composition and glycometabolic control

3.3.1 | Pre-diabetes

Only a limited number of studies have evaluated the impact of TRT in hypogonadal patients with pre-diabetes. In the first open-label, observational study, 229 hypogonadal (total T < 12 nmol/L) subjects (mean age 58.2 ± 9.6 years) with pre-diabetes (defined as HbA1c 5.7%–6.4%) were treated with a long-acting injectable T undecanoate for up to 8 years (mean 6.6 ± 2.2 years).[31] When compared to 87 controls with similar characteristics, 90% of patients who received TRT achieved normal HbA1c (< 5.7%) during follow-up. Conversely, among the untreated group, 40.2% progressed to T2DM (HbA1c > 6.5%). In addition, the active treatment group, upon normalizing T levels, showed significant improvement in body composition (BMI; waist circumference, and body weight), lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides levels) as well as fasting glucose when compared to controls.[31] Finally, TRT resulted also in a significant improvement of hypogonadism-related symptoms, including sexual function, as derived from the Aging Male Scale score.[31]

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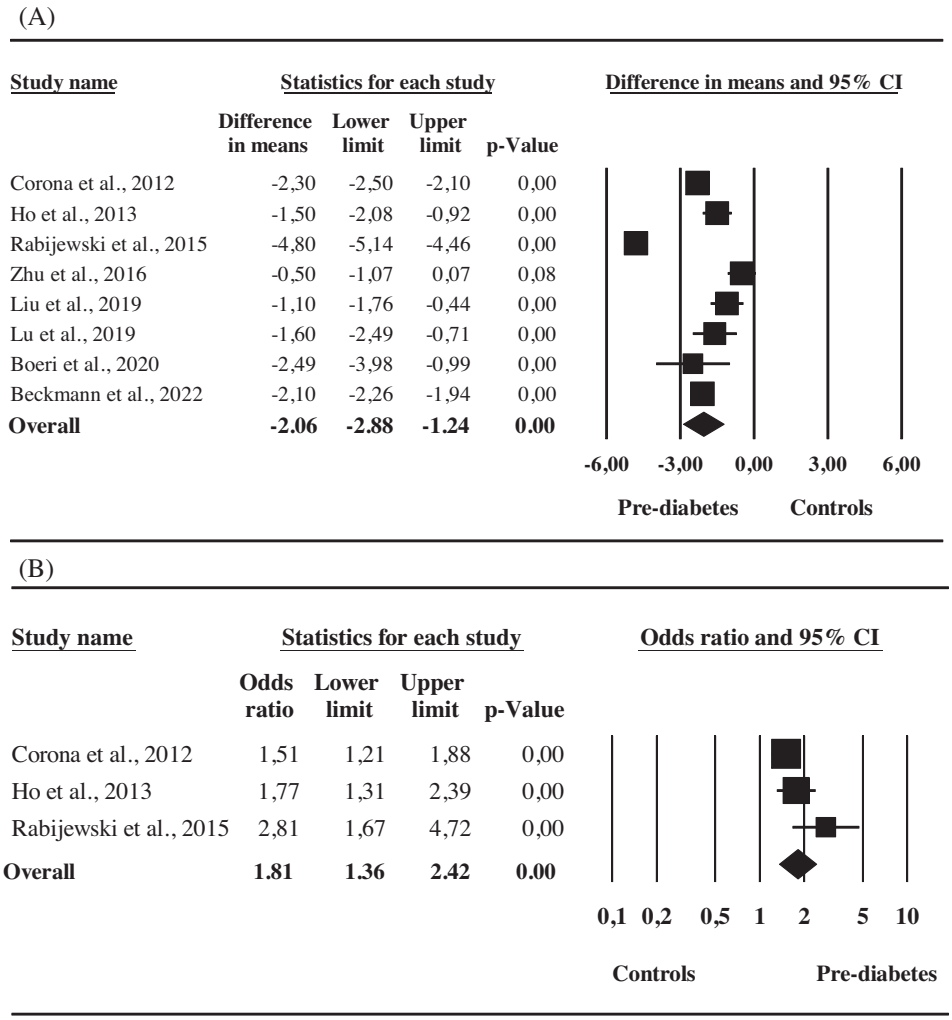


FIGURE 3 **Panel A**: random-effects pooled mean difference of total testosterone (nmol/L) between pre-diabetes cases and controls from cross-sectional studies. **Panel B**: Odds ratio for hypogonadism (Total T below 12 nM) between pre-diabetes mellitus and controls. Pre-diabetes was defined as fasting plasma glucose between 100 and 125 mg/dl (6.1–6.9 mmol/L), or 2-h plasma glucose levels after oral glucose tolerance test between 140 and 199 mg/dl (7.8–11.1 mmol/L) or glycated hemoglobin (HbA1c) between 5.7% and 6.4%.

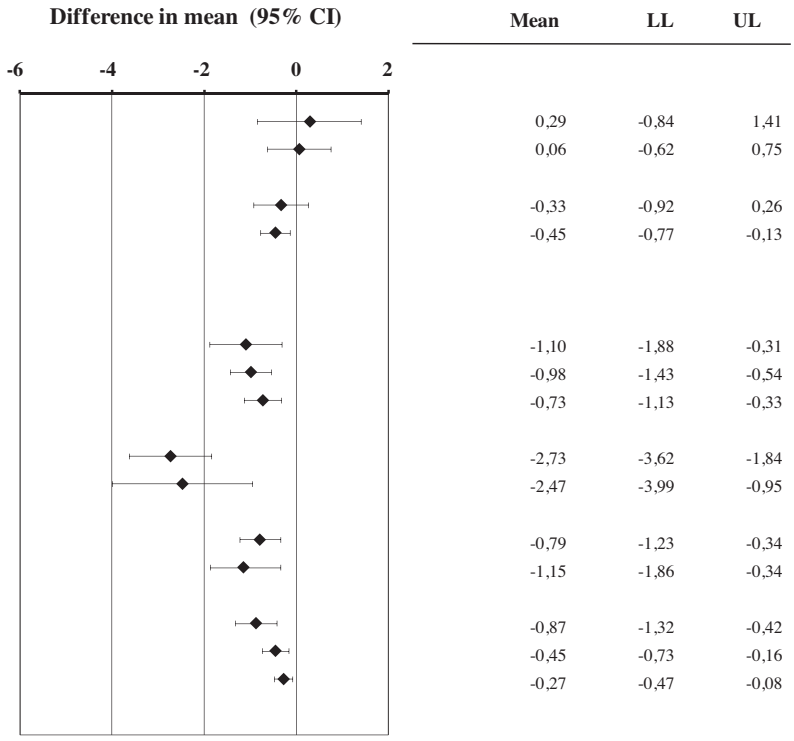
Only one randomized, placebo-controlled trial has investigated the role of TRT in patients with pre-diabetes.[32] The testosterone for diabetes mellitus is a 2-year, phase 3b, a trial involving 1007 subjects (aged 50–74 years) – with a waist circumference ≥95 cm and total T ≤ 14.0 nmol/L – who had either IGT – that is, OGTT 2-h glucose ≥ 140–199 mg/dl or 7.8–11.0 mmol/L) – or newly diagnosed T2DM-OGTT 2-hglucose ≥200–270 mg/dl or 11.1–15.0 mmol/L. After the pre-enrolment screening, only 20% were classified as T2DM whereas the vast majority of the included patients had pre-diabetes. All the included subjects were allocated to a lifestyle program and randomly assigned (1:1) to receive an intramuscular injection of T undecanoate (1000 mg) or placebo at baseline, 6 weeks, and then every 3 months for 2 years.[32] At the study endpoint, the active treatment group showed a significant improvement in body composition parameters including fat mass, lean mass, and waist circumferences, whereas no significant modification of body weight was reported.[32] In addition, a significant reduction of fasting glucose, but not of HbA1c levels, was also reported in those subjects receiving TRT.[32] Similarly, there was no difference between T and placebo in OGTT parameters at 2 years. Finally, all the International Index of Erectile Function (IIEF) domain scores were ameliorated by TRT.[32] Regarding the latter study,[32] no data on lipid profile is available yet.

3.4 | Type 2 DM

Four meta-analyses, published so far, have investigated the role of TRT in patients with DM as derived from RCTs.[33–36] The number of studies included ranges from 5 to 12 and the considered patients from 351 to 899 (Table 3). Independently from the meta-analysis considered, TRT resulted in a significant improvement in fasting glucose and HbA1c levels; similarly, an improvement of fasting insulin levels and insulin resistance parameters, as derived from the Homeostasis Model Assessment Index, was also observed (Figure 4, Panel A).

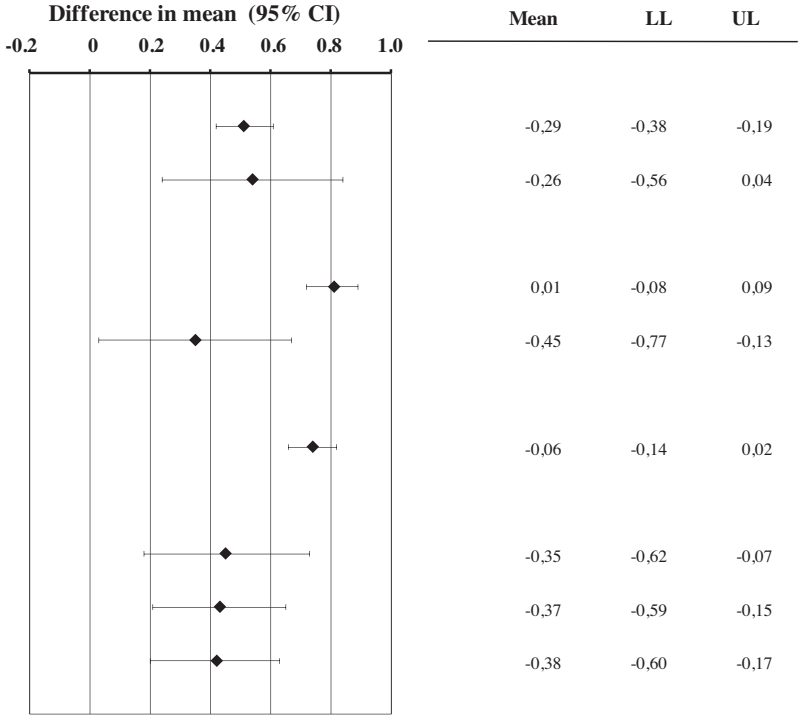
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(A)



Parameter	# Trials	Mean	LL	UL
Body composition				
Body mass Index (kg/m²)				
Zhang et al., 2018	7	0,29	-0,84	1,41
Corona et al., 2021	10	0,06	-0,62	0,75
Fat Mass				
Zhang et al., 2018 (kg)	3	-0,33	-0,92	0,26
Corona et al., 2021*	7	-0,45	-0,77	-0,13
Glyco-metaboilic profile				
Fasting glycemia (mmol/L)				
Cai et al., 2014	5	-1,10	-1,88	-0,31
Zhang et al., 2018	8	-0,98	-1,43	-0,54
Corona et al., 2021	12	-0,73	-1,13	-0,33
Fasting insulin (mmol/L)				
Cai et al., 2014	4	-2,73	-3,62	-1,84
Zhang et al., 2018	6	-2,47	-3,99	-0,95
HOMA IR				
Zhang et al., 2018	6	-0,79	-1,23	-0,34
Corona et al., 2021	10	-1,15	-1,86	-0,34
HbA1c (%)				
Cai et al., 2014	3	-0,87	-1,32	-0,42
Zhang et al., 2018	6	-0,45	-0,73	-0,16
Corona et al., 2021	12	-0,27	-0,47	-0,08

(B)



Parameter	# Trials	Mean	LL	UL
Total cholesterol (mmol/L)				
Zhang et al.,	7	-0,29	-0,38	-0,19
Corona et al.,	10	-0,26	-0,56	0,04
HDL cholesterol (mmol/L)				
Zhang et al.,	8	0,01	-0,08	0,09
Corona et al., 2021	10	-0,45	-0,77	-0,13
LDL cholesterol (mmol/L)				
Zhang et al.,	7	-0,06	-0,14	0,02
Triglycerides (mmol/L)				
Cai et al.,	4	-0,35	-0,62	-0,07
Zhang et al.,	8	-0,37	-0,59	-0,15
Corona et al.,	11	-0,38	-0,60	-0,17

FIGURE 4 Weighted mean differences (with 95% confidence interval [CI]) on body composition and glycometabolic profile (A) or lipid profile (B) as derived from available meta-analyses investigating the effect of testosterone replacement therapy in patients with type 2 diabetes mellitus. LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; UL, upper levels; LL, lower levels

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TABLE 2 Comparisons of the available meta-analyses evaluating the relationship between total testosterone, free testosterone, and sex hormone binding globulin differences between subjects with or without diabetes mellitus (DM); –, not available. Both cross-sectional and prospective analyses were reported

Inclusion criteria	Ding et al., 2006[30]	Corona et al., 2011[12]	Zhang et al., 2019[35]
Number of trials included	20	24	56
Number of patients with DM analyzed	1,355	1,822	6,856
Number of patients without DM analyzed	5,745	10,009	23,573
Outcomes evaluated			
Cross-sectional studies			
Total testosterone	X	X	X
Free testosterone	–	X	X
Sex hormone-binding globulin	X	X	X
Prospective studies			
Total testosterone	–	X	X
Free testosterone	–	–	X
Sex hormone-binding globulin	–	–	X

Conversely, data on body composition and lipid profile were more conflicting (Figure 4, Panels A and B). In particular, no modification in BMI was reported, whereas only the largest available meta-analysis confirmed an improvement in fat mass (Figure 4, Panel A). When the lipid profile was investigated, all available meta-analyses were consistent in an improvement of triglyceride levels whereas data on other lipid parameters were more conflicting (Figure 4, Panel B). Finally, when the sexual function was analyzed, erectile function and libido domain was ameliorated in one study, but the data were not confirmed when only those studies using IIEF were considered (Figure 5).

4 | DISCUSSION

Both overt T2DM and pre-diabetic conditions are characterized by significantly reduced T levels, which were tightly related to the degree of BMI and central obesity. TRT is able to ameliorate some of the metabolic derangements, whereas data on sexual function are more conflicting.

Data derived from pre-clinical models have clearly documented that the aforementioned metabolic derangements can support the development of chronic low-grade inflammation, involving the entire hypothalamus-pituitary-testis axis, and leading to an impairment of gonadotropin secretion supporting the presence of secondary or mixed hypogonadism.[37–39] Accordingly, in an animal model of metabolic syndrome – characterized also by IFG, IGT along with low levels of LH and T – we originally described a hypothalamic metaflammation with several alterations of the complex network of neurotransmitters controlling GnRH secretion.[37] It is also nowadays quite clear that the association between metabolic derangements and low T is bidirectional. Accordingly, whereas low T is a risk factor for a forthcoming metabolic condition, any metabolic condition is a risk factor for developing low T. In line with these views, data derived from available meta-analyses showed that those people who experienced the development of T2DM at follow up have a significantly lower level of T at baseline. Similarly, a community-based prospective cohort study including 903 normoglycemic men aged 30–70 years showed up to a 10% increased risk for developing T2DM per unit decrease (ng/ml) in total T concentration over a median follow-up of 12 years.[40] The specific molecular mechanisms through which T can play a protective role in pre-clinical and clinical diabetic conditions are far to be completely elucidated. Experimental models have shown that T exerts anti-inflammatory effects on several tissues[41–43] which represent a key element in the pathogenesis of insulin resistance and T2DM.[44] Pro-inflammatory adipocytokines, impaired insulin, and leptin signaling can contribute to hypothalamic gonadotropic suppression, at least partially, via effects on KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the arcuate nucleus of the hypothalamus (see for review[29]). In addition, at a cellular level, T is involved in the expression of the glucose carrier GLUT4, the insulin receptor, and the insulin receptor substrate 1, supporting insulin sensitivity proprieties.[45] In line with these hypotheses, in the aforementioned animal model of MetS, T administration to hypogonadal rabbits was able to improve FPG and glucose tolerance to the same extent as metformin administration, with a more drastic effect than metformin on visceral fat accumulation that resulted almost undetectable upon T administration (reviewed in[34]). In addition, we previously demonstrated that in vivo T administration to MetS rabbits ameliorates the overall functioning of cultured adipocytes by increasing insulin-stimulated triglyceride synthesis and glucose uptake, along with GLUT4 membrane translocation and expression of adipocyte-specific genes.[38] Similar results were recently replicated in obese men undergoing bariatric surgery and treated with T, if symptomatic and hypogonadal.[46] Accordingly, available data indicate that TRT results in improved fasting glucose and insulin resistance in both pre-diabetes and T2DM. The latter observations were recently confirmed by our group when only placebo-controlled RCTs on T2DM were considered.[47]

Obesity and insulin resistance are well-known risk factors for the development of male hypogonadism and metabolic derangements.[3,4,29] However, whether or not TRT can play a direct effect on metabolically active visceral adipose tissue has not yet been completely clarified. Studies performed on a limited number of subjects have shown that T might regulate insulin sensitivity directly and acutely, before the appearance of changes in body composition.[48–50] Accordingly, no modifications in BMI were observed after TRT in the available meta-analyses and a significant improvement in fat mass was observed only in one of the provided meta-analyses. The latter finding, however, was confirmed even when only placebo RCTs were considered.[34] Similar data have been reported from placebo-controlled RCTs performed in the general population.[19,51–53] In

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TABLE 3 Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several body composition and glycometabolic parameters in patients with type 2 diabetes mellitus. TT, total testosterone; –, not reported; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance. * only data derived from the International Index of Erectile Function were considered

Inclusion criteria	Cai et al., 2014[33]	Zhang et al., 2018[35]	Algeffari et al., 2012[36]	Corona et al., 2021[34]
Number of trials included	5	8	6	12
Number of patients analyzed	351	596	587	889
Hypogonadism definition (TT)	11–15 nmol/L	11–15 nmol/L	8–11 nmol/L	8–15 nmol/L
Outcomes evaluated				
Body composition				
Fat mass	–	X	–	X
Lean mass	–	–	–	–
Waist (cm)	–	–	–	–
BMI (kg/m^2)	–	X	–	X
Glycometabolic parameters				
Fasting glycemia (mmol/L)	X	X	–	X
Fasting insulin (	X	X	–	–
HOMA index	–	X	–	X
HbA1c (%)	X	X	–	X
Total cholesterol (mmol/L)	–	X	–	X
LDL cholesterol (mmol/L)	–	X	–	–
HDL cholesterol (mmol/L)	–	X	–	X
Triglycerides (mmol/L)	X	X	–	X
Sexual function parameters				*
Overall Erectile function domain	–	–	X	X
Libido domain	–	–	X	–
Orgasm domain	–	–	X	–
Intercourse satisfaction domain	–	–	X	–
Overall satisfaction domain	–	–	X	–

apparent contrast with the latter observations, several long-term observational registry studies have shown that TRT is able to improve body composition allowing for a body weight reduction.[54,55] Differences in the population characteristics, baseline T levels, and duration of follow-up can explain, at least partially, the differences observed.[55]

Only limited or not significant improvement in lipid profile has been reported in all the available meta-analyses. Conversely, a consistent improvement in triglyceride levels, a surrogate marker of insulin resistance, has been observed. Similar data have been reported in the general population.[19] However, when the latter analysis was limited only to those studies enrolling hypogonadal subjects (total T < 12 nmol/L) at baseline, TRT also resulted in a significant improvement in total cholesterol.[19]

The reported data on sexual function deserves a better explanation. A significant improvement in erectile function and libido domain was reported by Algeffari et al.,[36] but not confirmed by our group.[34] It should be clarified that we restricted our meta-analysis only to those trials using IIEF as sexual function outcome. In line with our observation, a previous meta-analysis performed in the general population, and using the IIEF as the outcome, showed that TRT alone improved in a significant and clinically effective manner only milder forms of ED.[56] Conversely, its role in more complicated patients, such as those with obesity and T2DM is more limited.[56] Interestingly, recent data showed that the combination of PDE5i and TRT can work better in T2DM.[53,57]

In conclusion, experimental and clinical evidence clearly indicates that metabolic derangements even in pre-clinical stages are characterized by significantly lower T circulating levels. In the latter circumstances, TRT can improve body composition, metabolic profile, and insulin resistance, whereas the data on body weight are more conflicting. The effects seem to be more evident in less complicated conditions, whereas the role of TRT in patients enriched with associated morbidities is still more conflicting. A large body of evidence has also documented that weight loss and physical activities are able to improve both metabolic profile and T levels.[58] Interestingly, preliminary data suggest that the combination of TRT and lifestyle modifications can result in better outcomes.[59] Hence, considering the role of TRT on

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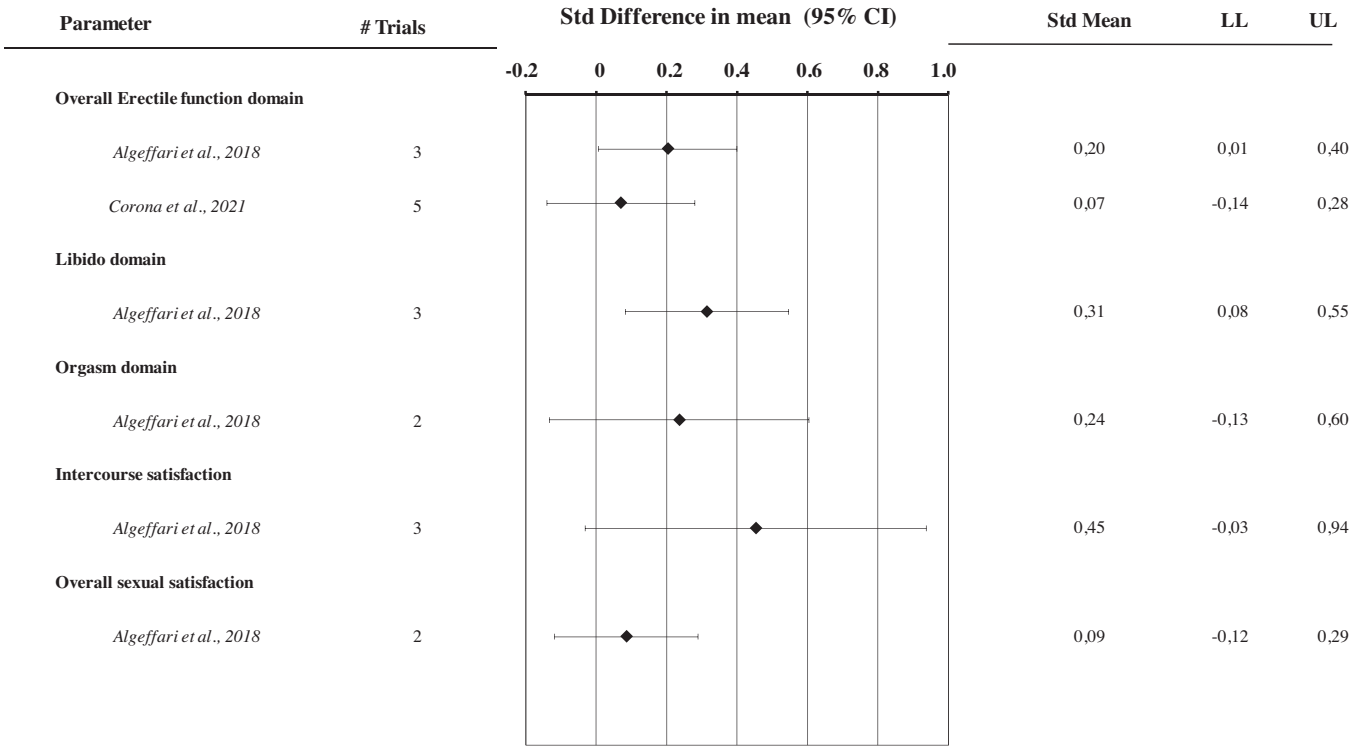


FIGURE 5 Standardized mean differences (with 95% confidence interval [CI]) on several sexual parameters as derived from available meta-analyses investigating the effect of testosterone replacement therapy in patients with type 2 diabetes mellitus. UL, upper levels; LL, lower levels

sexual function and on body composition, it is our opinion that the combined approach of TRT and lifestyle changes should be used in symptomatic hypogonadal men to better motivate patients to perform physical activity eventually resulting in weight loss and sexual function improvement. Whether or not these approaches can prevent the development of T2DM from pre-clinical conditions require more longitudinal well-performed studies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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