Metabolism and Target Organ Damage

Systematic Review

Male hypogonadism and pre-diabetes interplay: association or causal interaction? A systematic review

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Abstract

Aim: The association between type 2 diabetes mellitus (T2DM) and male hypogonadism has been largely demonstrated. Testosterone (T) serum levels are often lower in men with T2DM compared to the general population, and, conversely, men with higher T serum levels have shown lower risk of T2DM. On the contrary, the association between pre-diabetes and male hypogonadism has been less investigated thus far. Pre-diabetes is a common clinical condition preceding T2DM and has been recognized as a potential risk factor for other metabolic disorders and cardiovascular diseases. Therefore, the aims of this review are to investigate the association between pre-diabetes and male hypogonadism and to evaluate the potential effect of T treatment on glucose metabolism and anti-diabetic therapy on T serum levels.

Methods: We conducted this systematic review developing different literature searches, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol.

Results: In our analysis, male hypogonadism has a prevalence of around 24%-35% in pre-diabetic men. Moreover, we observed improvement of metabolic parameters in pre-diabetes with T treatment. On the contrary, anti-diabetic therapy seems to have no particular effects on T serum levels.

Conclusion: Overall, we demonstrated that, although T administration could be considered in pre-diabetic men, pre-diabetes-related treatments should be confined to the control glucose metabolism, since no evidence for a positive effect on total T serum levels is available. Future research should be oriented to study the role of new anti-diabetic drugs in the sex hormonal status in hypogonadal men.

Keywords: Hypogonadism, testosterone, pre-diabetes

INTRODUCTION

The association between diabetes mellitus (DM) and male hypogonadism has been largely claimed and proved[1,2]. Indeed, testosterone (T) deficiency and male hypogonadism are often found in patients with chronic metabolic diseases[3]. In the setting of type 2 DM (T2DM), T serum levels are lower in affected men compared to the general population[4], and men with higher T levels (7.4-15.5 nmol/L) have shown a 42% lower risk of T2DM development[4]. A threshold of 16 nmol/L of T serum levels was described to potentially predict the T2DM onset[5]. Despite this evidence, the association between low T serum levels and the initial impairment of the glucose metabolism (i.e., pre-diabetes) is less clear and still debated.

The term "pre-diabetes" was introduced in 1997, indicating a condition in which glucose serum levels do not meet diagnostic criteria for T2DM but are too high to be considered normal[6]. Currently, pre-diabetes indicates a clinical condition characterized by: (1) impaired fasting glucose (IFG) (defined by a fasting glucose level between 100 and 125 mg/dL); (2) impaired glucose tolerance (IGT) [defined by a glucose level between 140 and 199 mg/dL 2 h after receiving a 75 g oral glucose tolerance test (OGTT)]; or (3) glycated hemoglobin (HbA1c) level between 39 and 47 mmol/mol[6]. Despite these thresholds, the World Health Organization still considers 110 mg/dL as the upper reference limit for normal fasting glucose serum levels[7]. In line with international guidelines, pre-diabetes represents the buffer period before T2DM onset, during which impaired β-cell function and increased insulin resistance result in mild hyperglycemia[8]. The progression of pre-diabetes to frank T2DM is estimated to occur in up to 80% of the individuals with pre-diabetes[8,9]. However, the natural history of pre-diabetes is extremely variable, although an increased co-prevalence of metabolic syndrome, abdominal obesity, hypertension, and dyslipidemia is suggested[10,11]. Similarly, pre-diabetes seems to be related to microvascular changes-related comorbidities, such as nephropathy, neuropathy, retinopathy, erectile dysfunction, and obstructive sleep apnea[12-14].

Male hypogonadism is a clinical condition characterized by reduced T and/or impaired spermatogenesis, usually associated with other signs and symptoms. The diagnosis of hypogonadism requires serum T levels lower than normal and confirmed twice, together with the presence of specific signs and symptoms[15,16]. Among hypogonadism-related symptoms, sexual dysfunction (i.e., reduced libido, reduced spontaneous or stimulated penile erection, and erectile dysfunction), hot flashes, reduced semen volume, and decreased hair in androgen-dependent areas are reported[17-19]. However, no validated serum T cutoff level exists, and different thresholds have been proposed by the guidelines of several international scientific societies[18,20-23]. Large epidemiological studies suggested that serum T levels below 12.1 nmol/L could be considered a diagnostic threshold to diagnose hypogonadism[24-27]. However, several authors suggested the occurrence of functional hypogonadism in middle-aged and older men[28]. This condition is assumed when clinical features compatible with androgen deficiency are present, without evidence of organic hypothalamic-pituitary-testicular axis pathology[28].

Considering the association between endogenous sex hormones and glucose metabolism, longitudinal and population-based studies confirmed the T reduction in overweight/obese men, who, in turn, are more susceptible to develop T2DM[29-33]. Accordingly, low serum T levels increase the risk of insulin resistance independently of age[34-36], and T is directly related to insulin sensitivity[37]. Moreover, insulin resistance is found to be associated with reduced serum levels of total T and sex hormone binding globulin (SHBG)[38-40]. However, the cause-effect relationship direction linking endogenous sex hormones and impaired glucose metabolism remains to be clarified. Indeed, the main evidence in favor to this link simply identifies that low T levels are associated with higher T2DM risk[4,41], but which of T reduction or alteration of glucose metabolism occurs first in these patients is yet to be defined.

Effects of exogenous testosterone on glucose metabolism

In this intriguing glucose-androgen crosstalk, several issues remain to be solved. The effects of T therapy on glucose metabolism have been investigated in some studies[42]. T administration in euglycemic men leads to a lean body mass increase, together with a reduction in fat mass, with a favorable net metabolic effect[43,44]. In particular, the comprehensive evaluation of existing data reveals that androgen therapy leads to a total body fat mass reduction and fat-free mass increase, together with a small decrease in total cholesterol[45]. Similarly, a potential glucose metabolism improvement after androgen replacement therapy is suggested in diabetic men[46-48]. Indeed, T replacement therapy reduced HbA1c, fasting plasma glucose levels, and homeostasis model assessment of insulin resistance (HOMA-IR) in T2DM subjects[49]. Briefly, 90% of T2DM patients achieved an HbA1c of less than 7%, and 34% had total T2DM remission[49]. Thus, it seems clear that treating male hypogonadism could have significant metabolic effects, useful to prevent or improve glucose metabolism dysregulation. These effects could be explained by the inhibitory action of T on the incorporation of dietary fat into adipose tissue, especially intra-abdominal fat[49]. Male subjects receiving 250 mg of T intramuscularly five days prior to abdominal surgery showed a significant reduction in the amount of labeled omental and retroperitoneal fat[50]. Moreover, *in vitro* experiments showed that T suppresses adipocytic differentiation of preadipocytes, activating the Wnt pathway with an increased expression of β-catenin[51]. Moreover, T seems to promote the conversion of mesenchymal pluripotent stem cells into myogenic lineage and inhibit their conversion to adipocytes[52]. Although these mechanisms have yet to be confirmed in humans, they contribute to the T-related loss of adiposity, through increased oxidation of fatty acids by the skeletal muscle[42]. International guidelines for the management of male hypogonadism suggest starting androgen replacement therapy when T serum levels are low (i.e., below 8 nmol/L) or slightly reduced in the case of hypogonadism-related symptoms, particularly decreased morning erections, limitation in vigorous activity, and fatigue[16]. Thus, the evidence available suggests starting androgen replacement therapy in men with T2DM and low or only slightly reduced T serum levels[18]. The question remains whether these treatments should be considered also in the case of pre-diabetes.

Effects of T2DM treatment on testosterone levels

Weight loss by lifestyle intervention is the cornerstone treatment for T2DM and still represents the first-line approach. In this setting, diet-induced weight loss is demonstrated to also have a modest reversal effect on total T serum levels in diabetic men[53]. Moreover, some of the anti-diabetic drugs currently used in T2DM seem to influence T serum levels in an experimental setting[54,55]. Thus, a potential action of T2DM-related therapies on hypogonadism could be expected. However, whether these therapeutic approaches are really useful in pre-diabetic men with hypogonadism is still controversial.

Collectively, it seems clear that T2DM and male hypogonadism are strictly associated, and, when co-existing, both disease-specific therapeutic approaches should be considered. The first aim of this review is to evaluate the evidence available in the literature, combining male hypogonadism and pre-diabetes. Then, our

goal is to evaluate the potential effect of hypogonadism and anti-diabetic therapies on glucose metabolism and T serum levels, respectively.

METHODS

This systematic review was conducted developing three different literature searches, following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocol [Supplementary Material]. The first literature search was conducted to evaluate the prevalence of male hypogonadism in pre-diabetes and vice versa. The second search was done to evaluate the effect on glucose metabolism of androgen replacement treatment in male hypogonadism. Finally, a third literature search evaluated the effect of pre-diabetes treatment on endogenous T serum levels.

Data sources and search strategies

We identified original research papers by searching MEDLINE and EMBASE until May 20, 2021. Terms used for the first literature search were: "male hypogonadism", "testosterone", "pre-diabetes", "impaired fasting glucose (IFG)", and "impaired glucose tolerance (IGT)". In the second search, the following terms were used: "androgen replacement therapy", "testosterone", "male hypogonadism", "pre-diabetes", "impaired fasting glucose (IFG)", and "impaired glucose tolerance (IGT)". Finally, the third search was performed using the terms: "lifestyle", "antidiabetic drugs", "metformin", "male hypogonadism", "pre-diabetes", "impaired fasting glucose (IFG)", and "impaired glucose tolerance (IGT)". These terms were intentionally chosen to be broad to increase sensitivity and capture all relevant studies and were mixed with Boolean functions "AND" and "OR". Only studies in English were considered.
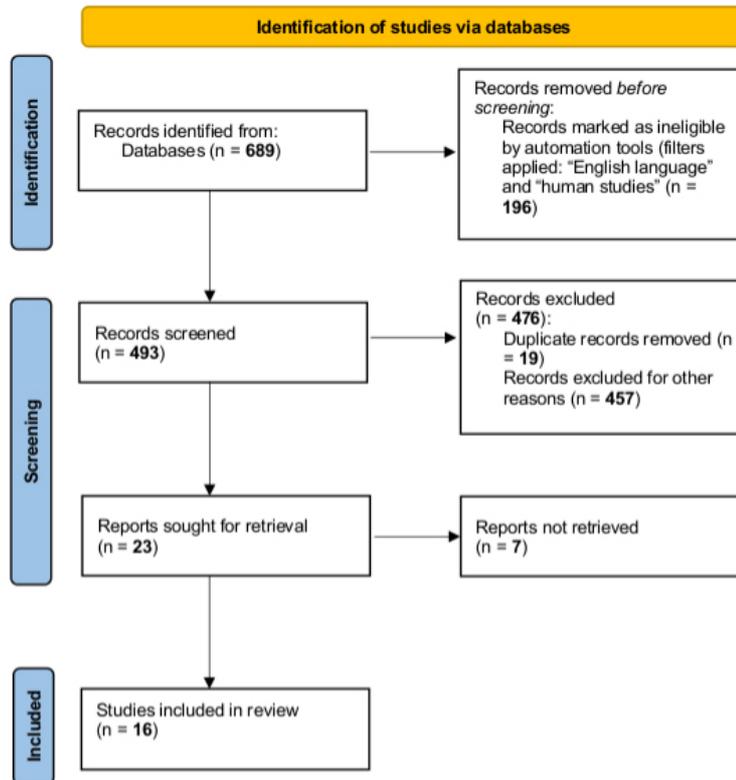
Study selection

All study designs were considered eligible, and both observational and interventional studies were considered. The following criteria were considered. In the first literature search, papers must report the percentage of patients with male hypogonadism and with pre-diabetes. For the second search, we considered studies in which (1) hypogonadal men (2) were treated with exogenous testosterone and (3) blood glucose levels were reported. For the third search, only studies enrolling (1) patients with pre-diabetes; (2) treated for pre-diabetes; and (3) in whom T serum levels were reported were considered eligible. For all three literature selections, it was required that the study reported the criteria used for the definition of both male hypogonadism and pre-diabetes.

Data extraction

Two authors (Corleto R and Ebert R) independently searched databases, extracted works, and reviewed titles and abstracts. Data were independently extracted from the included studies using a standardized Excel form. The following parameters were extracted for each manuscript: author, journal, year of publication, study design, aim of the study, inclusion criteria, male hypogonadism and pre-diabetes diagnostic criteria used, number of patients enrolled, and patients' age, body mass index (BMI), androgen replacement therapies, T2DM-related therapies, T serum levels, and glucose serum levels.

Data synthesis and analysis

A meta-analytic approach was added when more than three case-control studies were detected. When the same author published different works on the same cohort, only the most recent one was included in the meta-analysis. Using the Review Manager (RevMan) 5.4 Software (Version 5.4.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), continuous variables were comprehensively evaluated as inverse variance of mean variables. When data were reported in the original manuscript as median or logarithm, they were transformed in mean ± standard deviation. However, since these parameters could be obtained using different approaches, the meta-analyses were performed using standard

First search, performed on databases MEDLINE and EMBASE until May 20, 2021, using the terms "male hypogonadism", "testosterone", "prediabetes", "IFG", "impaired fasting glucose", "IGT", "impaired glucose tolerance".

Figure 1. Flow chart of the first literature search.

mean difference. The degree of heterogeneity among the studies included in each analysis was examined by inspecting both the scatter in the data points and the overlap in their confidence intervals (CIs), as well as by performing I^2 statistics. The inverse variance with the fixed model was initially chosen, whereas the random effect model was preferred in the case of I^2 higher than 60%.

RESULTS

Male hypogonadism prevalence in pre-diabetes

Considering the first literature search, 16 cross-sectional studies were retrieved [Figure 1], reporting either total T serum levels or hypogonadism prevalence in men with pre-diabetes [Table 1]. The mean hypogonadism prevalence was 29%, ranging from 30%, when T below 12 nmol/L was considered as diagnostic threshold[56], to 24.1%-34.8%, when hypogonadism was defined by total serum T levels lower than 10.4 nmol/L[57-60]. Overall, pre-diabetic men showed significantly (P = 0.002) higher BMI compared to euglycemic controls [Supplementary Figure 1], whereas no difference (P = 0.870) in patients' age was found [Supplementary Figure 2].

In eleven studies, pre-diabetic patients were compared to euglycemic controls. Overall, total T serum levels were significantly lower (of about 2.90 nmol/L; 95%CI: 1.01-3.60 nmol/L) in pre-diabetic men compared to euglycemic controls, applying a meta-analytic approach (P < 0.001) [Figure 2]. Moreover, some of these studies tried to distinguish pre-diabetes in IFG and IGT. Goodman-Gruen *et al.*[61] evaluated 266 pre-diabetic subjects, highlighting either total T serum levels or bioavailable T serum levels lower in IFG

Table 1. Characteristics of studies considered in the first literature search: male hypogonadism prevalence in pre-diabetes. Data are expressed as mean 4 standard deviation

Author, year	Aim of the study	Diagnostic criteria		Pre-diabetic			Controls		
		Hypogonadism	Pre-diabetes	Subjects	BMI (kg/m^2)	Age (years)	Subjects	BMI (kg/m^2)	Age (years)
Goodman-Gruen *et al.*[61], 2000	To evaluate sex differences in the association between endogenous estrogen and testosterone levels and glucose tolerance status	NA	FPG 100-126 mg/dL 2 h OGTT 140-199 mg/dL	IFG 60 IGT 206	IFG 26.7 ± 2.8 IGT 25.7 ± 3.3	IFG 68.6 ± 8.5 IGT 74.2 ± 7.5	397	25.8 ± 3.3	70.5 ± 8.6
Colangelo *et al.*[63], 2009	To assess associations of sex hormones with IFG and T2DM in men	NA	FPG: 100-126 mg/dL	1046	NA	NA	NA	NA	NA
Corona *et al.*[12], 2012	To evaluate the impact of IFG on sexual health in men	TT < 8 nmol/L	FPG: 100-125 mg/dL	659	28.6 ± 5.0 (all)	58.5 ± 9.7 (all)	2045	NA	NA
Ho *et al.*[59], 2013	To investigate whether pre-diabetes was associated with an increased risk of testosterone deficiency	TT < 10.4 nmol/L	FPG: 100-125 mg/dL 2 h OGTT 140-199 mg/dL HbA1c 39-46 mmol/mol	543	25.2 ± 3.1	55.8 ± 8.5	577	24.4 ± 3.0	52.6 ± 8.6
Chen *et al.*[65], 2014	To investigate the associations of serum total osteocalcin and undercarboxylated osteocalcin with glucose and lipid metabolism	NA	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL	52	27.6 ± 1.0	50.0 ± 10.0	46	26.3 ± 4.8	48.0 ± 10.0
Rabijewski *et al.*[56], 2015	To investigate the prevalence of LOH in men with pre-diabetes	TT < 12 nmol/L or calculated free T < 0.25 nmol/L	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL HbA1c 39-46 mmol/mol	196	29.6 ± 1.5	68.4 ± 3.1	184	27.1 ± 0.9	65.8 ± 3.4
Arthur *et al.*[40], 2016	To investigate whether serum sex steroid hormone concentrations differ between men with and without pre-diabetes	NA	FPG: 100-125 mg/dL; 2 h OGTT 140-199 mg/dL HbA1c 39-46 mmol/mol	411	27.5 ± 12.2	38.3 ± 12.2	728	25.4 ± 5.4	47.5 ± 32.4
Rabijewski *et al.*[46], 2016	To investigate the relationships between anabolic hormones and body composition in middle-aged and elderly men with pre-diabetes	TT < 12 nmol/L	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL HbA1c 39-46 mmol/mol	84	28.6 ± 1.2	66.5 ± 3.8	58	27.8 ± 0.9	65.7 ± 3.8
Zhu *et al.*[60], 2016	To investigate whether androgens were associated with the prevalence of pre-diabetes in men	NA	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL HbA1c 39-46 mmol/mol	907	24.7 ± 26.3	57.3 ± 10.4	1405	24.1 ± 31.7	45.5 ± 8.2
Boeri *et al.*[57], 2018	To assess the association between pre-diabetes and erectile function in men with ED	TT < 10.4 nmol/L	FPG: 100-125 mg/dL; 2 h OGTT 140-199 mg/dL HbA1c 39-46 mmol/mol	86	25.9 ± 4.7	56.9 ± 10.7	286	25.1 ± 3.4	54.2 ± 13.4
Lu *et al.*[62], 2018	To investigate the relationship of testosterone and different glucose tolerance state, and its association with osteocalcin	NA	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL HbA1c 39-46 mmol/mol	495	24.6 ± 2.8	77.2 ± 9.1	545	24.4 ± 2.8	73.6 ± 9.2
Boeri *et al.*[58], 2019	To study the prevalence and the risk associated with pre-diabetes in primary infertile men	TT < 10.4 nmol/L	FPG:100-125 mg/dL 2 h OGTT 140-199 mg/dL HbA1c 39-46 mmol/mol	114	26 ± 2.5	40.4 ± 6	630	25.3 ± 2.8	38 ± 4.5

| Boeri *et al.*[58], 2019 | To assess rates of and predictors of response to oral treatment in a cohort of ED men naïve for PDE5i with normo-glycemia, Pre-DM, or diabetes mellitus | TT < 10.4 nmol/L | FPG:100-125 mg/dL 2 h OGTT 140-199 mg/dL HbA1c 39-46 mmol/mol | 105 | 26 ± 11.4 | 58.2 ± 34.9 | 253 | 25.2 ± 14.9 | 50.2 ± 82.8 |
| Liu *et al.*[64], 2019 | To investigate the association of serum testosterone with IFG and T2DM and calculate the proportion explained by obesity status on the relationship | NA | FPG 110-125 mg/dL; HbA1C 39-46 mmol/mol | 355 | 24.2 ± 3.3 | 59.9 ± 9.0 | 355 | 23.1 ± 3.1 | 59.8 ± 9.0 |

BMI: Body mass index; DM: diabetes mellitus; ED: erectile disfunction; FPG: fasting plasma glucose; HbA1c: hemoglobin glycated; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; LOH: late-onset hypogonadism; NA: not available; OGTT: oral glucose tolerance test; PDE5i: phosphodiesterase-5 inhibitors; T2DM: type 2 diabetes mellitus; TT: total testosterone.

compared to controls and IGT. This large population-based study confirmed that men with IFG and IGT have reduced total T serum levels, similarly to T2DM, regardless of total body fat, body fat distribution, physical activity, and smoking[61]. This result, although interesting, is partly in contrast with a previous work of Rabijewski *et al.*[46], which reported lower T in IGT compared to IFG patients. In this scenario, Corona *et al.*[12] detected a stepwise increase in hypogonadism prevalence as a function of glucose abnormalities. Similarly, Lu *et al.*[62] reported a direct correlation between glucose tolerance status impairment and serum T decrease. Again, Colangelo *et al.*[63] observed a significant inverse association between total T serum levels and IFG, and similar results were also reported by Liu *et al.*[64]. Zhu *et al.*[60] confirmed lower T in pre-diabetic compared to euglycemic men, highlighting an inverse relationship between T and pre-diabetes by multinomial and logistic regression analyses. Some other biochemical or anthropometric parameters were found to be significantly different between pre-diabetic and non-pre-diabetic patients. Despite this extensive demonstration of reduced total T serum levels in pre-diabetic men, some studies detected only a slight, but not statistically significant, increase of T levels in pre-diabetes compared to euglycemic controls[65]. However, it is suggested that low T concentrations in men are associated with progression from normoglycemia to pre-diabetes, but not from pre-diabetes to diabetes[66].

SHBG serum levels were available in nine studies[12,40,46,56,58,60,62,63]. Arthur *et al.*[40] and Boeri *et al.*[58] reported significantly lower SHBG levels in pre-diabetic patients compared to controls. Similarly, a significant, inverse correlation between SHBG and glucose homeostasis was detected in pre-diabetic men[12] as well as in the subgroup of patients with IFG[61]. However, five studies reported lower SHBG concentrations in euglycemic controls compared to pre-diabetic patients, leaving the association between SHBG serum levels and pre-diabetes unclear[46,56,57,60,62]. In particular, Zhu *et al.*[60] highlighted low SHBG as an independent predictor of pre-diabetes incidence, especially in elderly men and irrespective of total T serum levels.

Finally, estradiol serum levels were reported in eight studies, showing a significant direct relationship with IFG[12,40,46,56-58,61-63]. In detail, estradiol serum levels were significantly lower in pre-diabetic patients compared to controls in three studies[46,56,58], whereas five studies did not detect any significant difference[40,57,61,62].
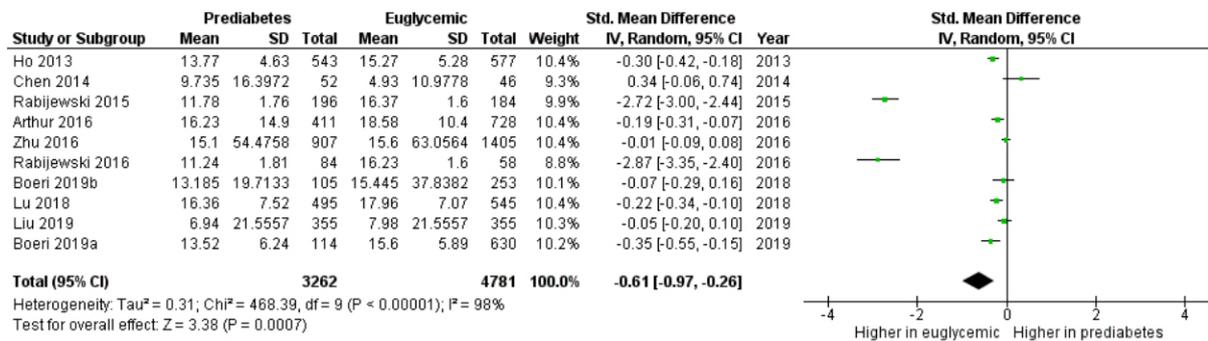
Study or Subgroup	Prediabetes Mean	SD	Total	Euglycemic Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Ho 2013	13.77	4.63	543	15.27	5.28	577	10.4%	-0.30 [-0.42, -0.18]	2013
Chen 2014	9.735	16.3972	52	4.93	10.9778	46	9.3%	0.34 [-0.06, 0.74]	2014
Rabijewski 2015	11.78	1.76	196	16.37	1.6	184	9.9%	-2.72 [-3.00, -2.44]	2015
Arthur 2016	16.23	14.9	411	18.58	10.4	728	10.4%	-0.19 [-0.31, -0.07]	2016
Zhu 2016	15.1	54.4758	907	15.6	63.0564	1405	10.4%	-0.01 [-0.09, 0.08]	2016
Rabijewski 2016	11.24	1.81	84	16.23	1.6	58	8.8%	-2.87 [-3.35, -2.40]	2016
Boeri 2019b	13.185	19.7133	105	15.445	37.8382	253	10.1%	-0.07 [-0.29, 0.16]	2018
Lu 2018	16.36	7.52	495	17.96	7.07	545	10.4%	-0.22 [-0.34, -0.10]	2018
Liu 2019	6.94	21.5557	355	7.98	21.5557	355	10.3%	-0.05 [-0.20, 0.10]	2019
Boeri 2019a	13.52	6.24	114	15.6	5.89	630	10.2%	-0.35 [-0.55, -0.15]	2019
Total (95% CI)			**3262**			**4781**	**100.0%**	**-0.61 [-0.97, -0.26]**	

Heterogeneity: Tau² = 0.31; Chi² = 468.39, df = 9 (P < 0.00001); I² = 98%
Test for overall effect: Z = 3.38 (P = 0.0007)

Higher in euglycemic   Higher in prediabetes

Figure 2. Forest plot reports total T serum levels comparing pre-diabetic men with controls.

Pre-diabetes prevalence in male hypogonadism

Considering still the first literature search, two studies reported the pre-diabetes prevalence in male hypogonadism [Figure 1 and Table 2]. Rabijewski *et al.*[67] showed that hypogonadal men were older, with higher BMI and waist circumference compared to euglycemic controls. In this cohort, pre-diabetes prevalence was higher in hypogonadal patients (41.5%) than in controls (13%)[67]. Among hypogonadal patients, serum T was significantly lower in patients with pre-diabetes compared to euglycemic controls, and patients with IGT had significantly lower T than the subgroups with IFG and elevated HbA1c. Similarly, Pitteloud *et al.*[37] detected a slightly higher pre-diabetes prevalence in hypogonadal than eugonadal men (30% *vs.* 18%, respectively), showing that hypogonadal patients were more insulin resistant than their eugonadal counterparts (insulin sensitivity = 3.6 ± 0.6 mg·kg⁻¹·min⁻¹ *vs.* 7.3 ± 3 mg·kg⁻¹·min⁻¹, respectively; *P* < 0.007).

Effects of androgen-replacement therapy on glucose metabolism in pre-diabetic males

Considering the second literature search [Figure 3], only three studies were retrieved. Wittert *et al.*[48] performed a randomized, double-blind, placebo-controlled, phase 3b trial, treating men with hypogonadism and impaired glucose tolerance and proving that T treatment for two years can prevent progression to T2DM or reverse early T2DM, beyond the effects of a lifestyle program. Even though the authors considered patients with early T2DM (20%) and pre-diabetes (80%) together, it is possible to estimate a similar effect in both in reducing the proportion of participants T2DM after T treatment showing OGTT normalized in 43% and 52% in control and study groups, respectively[48]. Krysiak *et al.*[68] treated 14 hypogonadal-IGT men with a combination of metformin (1.7 g daily) and oral T undecanoate (120 mg daily) for 24 weeks [Table 3]. As expected, T significantly improved after 24 weeks of T administration compared to baseline and patients treated with metformin alone[68]. Moreover, serum glucose levels at 120 min during OGTT were significantly reduced after 24 weeks of combined metformin and T therapy compared to baseline, although no significant differences were observed compared to metformin alone[68].

Yassin *et al.*[69] followed 229 hypogonadal men with pre-diabetes receiving parenteral T undecanoate (1000 mg every 12 weeks) over eight years. Total T levels normalized after the first injection[69]. Fasting glucose and HbA1c were significantly lower in the treated compared to the control group throughout the entire follow up[69]. Fasting blood glucose and HbA1c were reduced in the T group and increased in the control group at eight years[69]. All treated patients showed HbA1c below 48 mmol/mol at eight years and 205 patients had HbA1c lower than 39 mmol/mol, achieving normal glucose control, while 40.2% in the untreated group developed T2DM[69].

Table 2. Characteristics of studies considered in the first literature search: male hypogonadism prevalence in pre-diabetes and pre-diabetes prevalence in male hypogonadism. Data are expressed as mean 4 standard deviation

Author, year	Aim of the study	Diagnostic criteria		Hypogonadal			Eugonadal con-trols		
		Hypogonadism	Pre-diabetes	Subjects	BMI (kg/m²)	Age (years)	Subjects	BMI (kg/m²)	Age (years)
Pitteloud *et al.*[35], 2005	To examine the relationship between serum testosterone levels and insulin sensitivity and mitochondrial function in men	TT < 9.7 nmol/L	2 h OGTT 140-200 mg/dL	10	32 ± 2	57 ± 3.5	50	26 ± 0.5	61 ± 1
Rabijewski *et al.*[67], 2014	To investigate the prevalence of pre-diabetes in men with LOH	TT < 12 nmol/L or calculated free T < 0.25 nmol/L	FPG: 100-125 mg/dL 2 h OGTT 140-200 mg/dL HbA1c 39-46 mmol/mol	246	32.4 ± 1.4	67.3 ± 3.2	184	27.6 ± 1.2	65.8 ± 3.4

BMI: Body mass index; FPG: fasting plasma glucose; HbA1c: hemoglobin glycated; LOH: late-onset hypogonadism; OGTT: oral glucose tolerance test; TT: total testosterone.
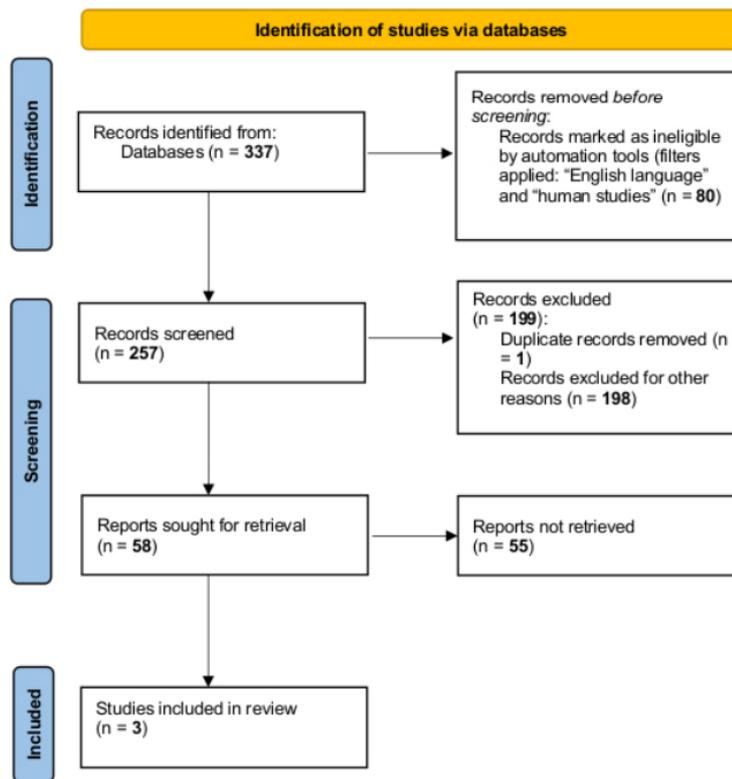
Strollo *et al.*[70] treated 48 overweight patients with hypogonadism and IFG with oral, transmucosal, and transdermal T formulations for six months. Metabolic parameters, such as fasting glucose levels and HOMA-IR, improved after treatment, with a greater reduction with transmucosal and transdermal deliveries, compared to oral formulations[70].

Effects of anti-diabetic treatment on male hypogonadism
Considering the third literature search [Figure 4], only two studies were retrieved. Krysiak *et al.*[71] evaluated 29 pre-diabetic men, 10 with hypergonadotropic hypogonadism and 19 with normal total T serum levels, treated with metformin (2.55-3 g/daily) for 16 weeks [Table 4]. The treatment significantly reduced fasting glucose and HbA1c in both groups, with lower values in hypogonadal compared to eugonadal men[71]. Total T serum levels did not significantly change after 16 weeks of treatment in both groups, although a significant gonadotropin decrease was detected in hypogonadal men[71]. This result is consistent with a previous study in which 14 hypogonadal-IGT men were treated with metformin for 16 weeks[68]. Glucose tolerance assessed by OGTT significantly improved after treatment, without improvement of total T serum levels[68].

DISCUSSION
According to our review of the literature, male hypogonadism has a prevalence of around 24%-35% in pre-diabetic men. Indeed, total T serum levels are lower in pre-diabetic patients compared to healthy controls, confirming that T decrease is a characteristic of pre-diabetes as well as T2DM. However, the exact timing of the T decline in the natural history of pre-diabetes/T2DM is still not fully understood. Considering the pathophysiology of pre-diabetes and the role of increased body fat and insulin resistance, a higher prevalence of hypogonadism could be expected in IFG compared to IGT. This correlation was detected in some but not all studies. Indeed, some authors detected a reduction of serum total T levels more evident in IGT than in IFG pre-diabetic patients. In particular, total T serum levels in pre-diabetic patients seemed to be related to the glycemic control, although it is not clear whether a threshold of glucose metabolism impairment resulting in T reduction exists. This contrasting result confirms the need to perform an accurate evaluation of both metabolic and hormonal status

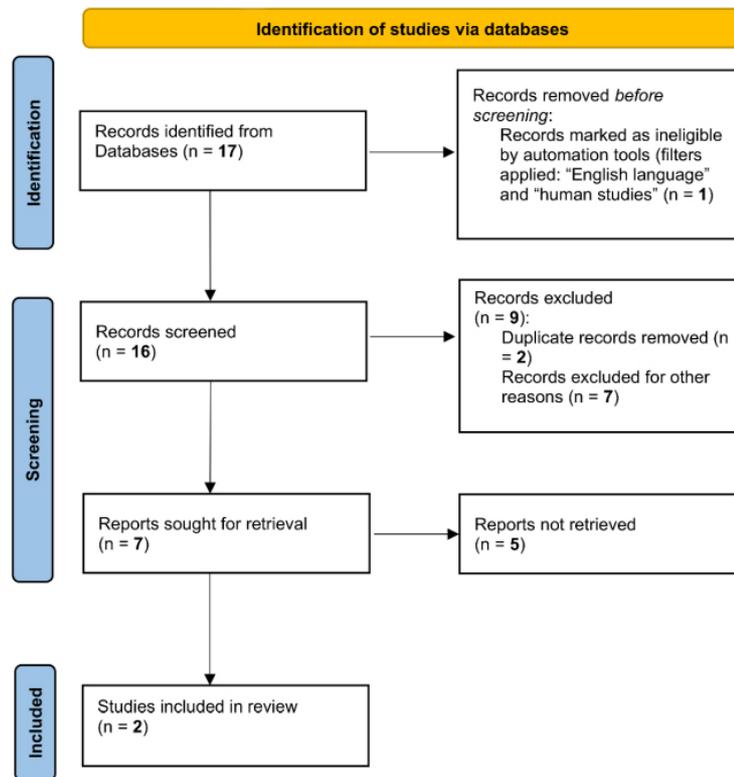**Figure 3.** Flow chart of the second literature search.

in these patients.

Overall, a bidirectional association between male hypogonadism and pre-diabetes has been identified[72,73]. Similarly to what happens for other chronic diseases[3], recommendation statements[74] and guidelines[16] on male hypogonadism management recognize T2DM as one of the main determinants of T decline. Our systematic review suggests that pre-diabetes should also be considered among risk factors of T reduction and male hypogonadism development. Consistently with this hypothesis, the mildest forms of glucose impairment are associated with a reduced sexual response[75], resulting in erectile dysfunction[12] and confirming that glucose homeostasis dysregulation could influence many aspect of male hypogonadism[76]. While a stepwise T decrease as a function of glucose abnormalities was strongly suggested[12,62,63], the change in SHBG serum levels occurring in DM and pre-diabetes is still debated. Particularly, the association of T2DM with the metabolic impairment of liver function can interfere with SHBG levels. However, it is not clear whether pre-diabetes results in SHBG reduction[12,40,58,63] or not[40,46,56,62]. Thus, despite the association between reduced total T serum levels and pre-diabetes, there is no clear evidence of a reduction in bioavailable T. Similarly, estradiol serum levels were described to be reduced[46,56,58] or not[40,57,61,62] in pre-diabetic patients, leaving doubts about the clinical consequences of the reduction of total T serum levels in pre-diabetes.

The mechanistic, molecular link between pre-diabetes and male hypogonadism is still undefined. Animal models showed that mild hyperglycemia and glucose intolerance are associated with hypertension,

Table 3. Characteristics of studies considered in the second literature search: effects of androgen-replacement therapy on glucose metabolism in pre-diabetic males. Data are expressed as mean 4 standard deviation

Authors, year	Aim of the study	Diagnostic criteria	Study group						Control group					
			Treatment	Subjects	Age (years)	BMI (kg/m²)	Baseline 2 h OGTT (mg/dL)	2-OGTT after treatment (mg/dL)	Treatment	Subjects	Age (years)	BMI (kg/m²)	Baseline 2 h OGTT (mg/dL)	2 h OGTT after treatment (mg/dL)
Krysiak *et al.*[68], 2015	To investigate the effect of metformin, alone or with testosterone, on cardiometabolic risk factors in hypogonadal men	**Hypogonadism** TT < 10.4 nmol/L **Pre-diabetes** FPG: < 100 mg/dL 2 h OGTT 140-199 mg/dL	Oral testosterone undecanoate (120 mg daily) + metformin (1.7 g daily) for 24 weeks	14	65 ± 4	29.2 ± 3.2	182 ± 10	145 ± 12	Metformin (1.7 g daily) for 24 weeks	14	64 ± 5	29 ± 3	178 ± 11	153 ± 14
Yassin *et al.*[69], 2019	To investigate whether testosterone therapy in men with hypogonadism and pre-diabetes prevents progression to T2DM	**Hypogonadism** TT ≤ 12.1 nmol/L **Pre-diabetes** HbA1c 39-46 mmol/mol	Parenteral testosterone undecanoate (1000 mg every 12 weeks) for eight years	229	58.2 ± 9.6	30.7 ± 4.1	41 ± 6.1	NA	No treatment	83	66.4 ± 7.2	29.8 ± 3	41 ± 7.2	NA
Strollo *et al.*[70], 2013	To verify whether oral, buccal, and transdermal TRT administered at a dosage lower than that commonly utilized in young hypogonadal men improves frailty symptoms in elderly men with visceral adiposity, IFG, and LOH	**Hypogonadism** TT < 8 nmol/L **Pre-diabetes** FPG > 100 mg/dL	(a) Oral testosterone undecanoate 80 mg daily (b) Buccal testosterone 60 mg daily (c) Transdermal testosterone 30 mg daily	(a) 15 (b) 18 (c) 15 (all 48)	(a) 70.0 ± 3.1 (b) 69.3 ± 3.0 (c) 70.1 ± 2.9	(a) 27.7 ± 1.3 (b) 29.4 ± 2.4 (c) 28.6 ± 2.0	(a) 108 ± 5 (b) 111 ± 5 (c) 110 ± 6	(a) 101 ± 6 (b) 103 ± 8 (c) 100 ± 9	No treatment	16	68.5 ± 3.7	28.4 ± 1.9	109 ± 6	107 ± 8

BMI: Body mass index; IFG: impaired fasting glucose; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; LOH: late onset hypogonadism; NA: not available; T2DM: type 2 diabetes mellitus; TRT: testosterone replacement therapy; TT: total testosterone.

Third search, performed on databases MEDLINE and EMBASE until May 20, 2021, using the terms "lifestyle", "antidiabetic drugs", "metformin", "male hypogonadism", "prediabetes", "IFG", "impaired fasting glucose", "IGT", "impaired glucose tolerance".

Figure 4. Flow chart of the third literature search.

increased visceral adiposity, and a reduced number of gonadotropin-releasing hormone (GnRH) neurons in the hypothalamus of the pre-diabetic rabbit[77]. In this model, pre-diabetic conditions created by a long-term, high-fat diet could induce a hypogonadotropic hypogonadism comparable to that obtained with a long-acting GnRH analog[77]. Similarly, impaired insulin secretion could induce a hypogonadotropic hypogonadism in other animal models[78-80], suggesting that either glucose homeostasis impairment or the lack of insulin signaling within the brain could be the pathogenic mechanism connecting hypogonadism and diabetes. Moreover, increased body fat and adiposity have been considered the hidden link between glucose homeostasis impairment and low total T serum levels[42]. Indeed, total and bioavailable T levels in men were inversely associated with total body fat[81,82]. This suggestion was confirmed even after statistical adjusting for BMI, which reduces but does not eliminate the T-diabetes associations[61]. Moreover, serum T levels are inversely related to BMI in obese men, and androgen administration increases insulin sensitivity[83,84]. Accordingly, insulin resistance decreases after T replacement in T2DM patients[85,86]. This T-related effect on insulin sensitivity is probably multifactorial[42]. Our systematic review is not able to clarify the cause-effect relationship between T and glucose metabolism, but it clearly confirms this potential association.

Limited evidence is available considering male hypogonadism. Indeed, only two studies evaluated the association between total T serum levels and pre-diabetes enrolling hypogonadal men[37,67]. Hypogonadal men show a higher degree of insulin resistance and pre-diabetes compared to eugonadal men. This result

Table 4. Characteristics of studies considered in the third literature search: effects of anti-diabetic treatment on male hypogonadism. Data are expressed as mean 4 standard deviation

Authors, year	Aim of the study	Diagnostic Criteria	Treatment	Study group					Control group				
				Subjects	Age (years)	BMI (kg/m^2)	Baseline TT (nmol/L)	TT after treatment (nmol/L)	Subjects	Age (years)	BMI (kg/m^2)	Baseline TT (nmol/L)	TT after treatment (nmol/L)
Krysiak *et al*.[71], 2021	To investigate hypothalamic-pituitary-testicular axis activity in men with primary hypogonadism receiving metformin	**Hypogonadism** TT < 8.7 nmol/L **Pre-diabetes** FPG: 100-125 mg/dL 2 h OGTT 140-199 mg/dL	Metformin 2.55-3 g daily for 16 weeks	10	43 ± 8	28.1 ± 5.2	5.6 ± 3	5.7 ± 3.3	19	44 ± 7	27.6 ± 4.2	20.3 ± 8.7	21 ± 9.8
Krysiak *et al*.[68], 2015	To investigate the effect of metformin, alone or with testosterone, on cardiometabolic risk factors in hypogonadal men	**Hypogonadism** TT < 10.4 mol/L **Pre-diabetes** 2 h OGTT 140-199 mg/dL	Metformin 1.7 g daily for 24 weeks	14	64 ± 5	29 ± 3.0	6.2 ± 1.0	7.3 ± 1.7	12	67 ± 4	28.7 ± 3.4	NA	NA

BMI: Body mass index; FPG: fasting plasma glucose; OGTT: oral glucose tolerance test; NA: not available; TT: total testosterone.

indicates that low total T serum level is an independent risk factor of pre-diabetes, which most likely affects glucose tolerance during OGTT more than fasting plasma glucose concentrations[67]. Although these studies clearly demonstrate an indirect correlation between total T serum levels and glycemic control in hypogonadal men, the amount of evidence limits the robustness of this association. Similarly, the pathophysiological mechanisms causing pre-diabetes in T deficiency are still unknown.

Considering the treatment, it has been suggested that T administration in pre-diabetic hypogonadal men could prevent the pre-diabetes progression to overt T2DM, as suggested by the reduction in HbA1c[69] or insulin resistance[56]. The result of our systematic review, although limited for the low number of studies included, could be extremely useful in clinical practice. Indeed, the literature suggests that pre-diabetic hypogonadal men would develop T2DM in more than 40% of cases[69]. Thus, the clinical management of both conditions could be useful to slow down disease development and onset of complications. In particular, although the association between pre-diabetes and cardiovascular mortality risks is clearly demonstrated[87], high-quality studies are required to evaluate whether T administration could reduce this risk. According to our review, combined T and metformin administration may be useful in the management of men with hypogonadism coexisting with early glucose metabolism abnormalities. Indeed, while metformin improves glucose metabolism, the euglycemic state could be more efficiently obtained by T replacement[56]. Therefore, the question arises whether T treatment should be given to all patients with pre-diabetes and hypogonadism in order to prevent development into overt T2DM. The evidence currently available is still insufficient and future studies should be dedicated to this topic.

Similarly, speculatively, no clear conclusion could be drawn on the efficacy of anti-diabetic drugs in improving sex hormone status in pre-diabetic hypogonadal men. Indeed, this association has been even less and only superficially studied. Several studies suggested that weight loss improves T in obese T2DM men, more than glycemic control[88]. However, less information is available in pre-diabetic men, and only two studies evaluated the effect of metformin on T levels. Moreover, no studies evaluated the combined androgen and anti-diabetic approaches in this setting. In the studies available, chronic metformin administration did not improve serum T levels, leaving the field open for debate. In general, we can conclude that T administration reduces the T2DM risk beyond lifestyle intervention alone[88].

Clinical implications

Men with documented total T serum levels below 8 nmol/L or below 12.1 nmol/L with signs or symptoms related to hypogonadism[16] should be treated with exogenous T administration[18]. The treatment should be tailored to patient's health status, expectations, and potential adverse events[15]. T replacement therapy is surely effective in improving sexual function, body composition, and metabolic outcomes[44]. On the contrary, pre-diabetes-related treatments should be reserved aiming to control glucose metabolism, since the evidence of a positive effect on total T serum levels is not available yet. Therefore, T replacement therapy should not be considered a potential therapy to treat pre-diabetes, but positive effects on glucose metabolism may be expected in T-treated patients with male hypogonadism.

Conversely, the treatment of pre-diabetes status in men with hypogonadism may indirectly have positive effects on serum T levels since lifestyle changes (both dietary changes and increasing physical activity) are able to improve serum T levels[89-91].

Unresolved issues

Glucose metabolism disorders are an established risk factor for T decline in men. However, the influence of pre-diabetes on T deficiency is still not completely known. In particular, the first unresolved issue remains the exact moment of total T decline in the natural history of T2DM. Prospective studies are needed to determine the cause-effect relationship of sex hormone-glucose metabolism association and the timing of the onset of a condition in the presence of the other one. Clinically, it is important to establish exactly whether pre-diabetes can be considered as an early sign of male hypogonadism. Here, we describe a male hypogonadism prevalence ranging from 24% to 35% in pre-diabetic men, suggesting that detailed glucose metabolism investigation should be performed in every man with biochemical and/or symptomatic hypogonadism. The second main issue remains whether to implement a prevention program to reduce progression to T2DM in such men.

The third unresolved issue is the knowledge of the possible pathophysiological mechanism effecting pre-diabetes and T decline. This association is probably multifactorial and represented mainly by visceral adiposity and insulin resistance. However, concerning the hypothalamic function, the pathogenic role of the impairment of glucose homeostasis and insulin signaling directly in the brain and GnRH neurons remains to be clarified. The fourth unresolved issue is the accurate characterization of hypogonadism in pre-diabetic males. Indeed, it is not completely clear if the total T decline results in a decrease of bioavailable T. Future research should focus on the SHBG and estradiol changes in pre-diabetes. Moreover, the sex hormone measurement must be performed by the gold-standard technique, i.e., mass spectrometry[92,93]. Finally, the studies considered here were limited to biochemical hypogonadism, without information about gonadotropin serum levels. Thus, this analysis is unable to describe the pathomechanism (primary/secondary hypogonadism) and to distinguish whether the hypo- or hyper-gonadotropic form of hypogonadism would be the best responder to treatments. Similarly, no information about the severity of hypogonadism and its correlation with glucose metabolism alterations is available. Finally, future research

should be oriented to study the role of new anti-diabetic drugs (such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) in the sex hormonal status in hypogonadal men.

DECLARATIONS

Authors' contributions
Conceive the study: Greco C, Santi D
Extracted data: Greco C, Corleto R, Ebert R, Santi D
Revised the manuscript: Simoni M, Rochira V

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