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Review Article

Testosterone therapy for sexual dysfunction in men with Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials

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What's new?

- We have performed the first meta-analysis evaluating the effectiveness of testosterone therapy on a range of sexual function domains in men with Type 2 diabetes.
- Evidence to date suggests that testosterone therapy may improve sexual desire and erectile function in men with Type 2 diabetes; however, heterogeneity among the results of included studies, limited participant numbers, and possible reporting bias greatly weaken these inferences.
- We conclude that testosterone therapy could be considered for men with Type 2 diabetes non-responsive to phosphodiesterase-5 inhibitors when risks and benefits of therapy are carefully considered, and other therapeutic options are unsuitable.

Abstract

Aim To evaluate the effectiveness of testosterone therapy on a range of sexual function domains in men with Type 2 diabetes.

Method Electronic databases were searched for studies investigating the effect of testosterone therapy on sexual function in men with Type 2 diabetes. All randomized controlled trials were considered for inclusion if they compared the efficacy of testosterone therapy with that of placebo and reported sexual function outcomes. Statistical analysis was performed using a random-effects model, and heterogeneity was expressed using the I^2 statistic.

Results A total of 611 articles were screened. Six randomized control trials, in a total of 587 men with Type 2 diabetes, were eligible for inclusion. The pooled data suggested that testosterone therapy improves sexual desire (random-effects pooled effect size 0.314; 95% CI

0.082–0.546) and erectile function (random-effects pooled effect size 0.203; 95% CI 0.007–0.399) when compared with control groups. Testosterone therapy had no significant effect on constitutional symptoms or other sexual domains compared with control groups. No studies have investigated the incidence of prostate cancer, fertility and cardiovascular disease after testosterone therapy in men with Type 2 diabetes.

Conclusion Testosterone therapy may moderately improve sexual desire and erectile function in men with Type 2 diabetes; however, available data are limited, and the long-term risks of testosterone therapy are not known in this specific patient group. We conclude that testosterone therapy is a potential treatment for men with Type 2 diabetes non-responsive to phosphodiesterase-5 inhibitors. Testosterone therapy could be considered for men with Type 2 diabetes when potential risks and benefits of therapy are carefully considered and other therapeutic options are unsuitable.

Introduction

Erectile dysfunction affects 35–90% men with Type 2 diabetes, and has important clinical consequences, including reduced quality of life for people with diabetes [1–5]. Phosphodiesterase-5 (PDE-5) inhibitors are an effective and generally safe treatment for men with erectile dysfunction [6], but a significant proportion of men with Type 2 diabetes have ongoing sexual dysfunction which is refractory to PDE-5 inhibitor therapy [7,8]. Furthermore, PDE-5 inhibitors have been reported to have significantly lower treatment success rates in men with diabetes when compared with men without diabetes [9]; thus, there exists a clinical need for second-line treatments for sexual dysfunction in men with Type 2 diabetes.

Hypogonadism is a cause of sexual dysfunction which is commonly defined as a total serum testosterone <3.2 ng/ml (11 nmol/l) and free testosterone <64 pg/ml (220 pmol/l), with

at least three sexual symptoms [6,10]. Cross-sectional studies have reported an association between low testosterone and Type 2 diabetes since the early 1990s [11]. Recent published studies have reported that up to 40% of men with Type 2 diabetes have testosterone deficiency. Type 2 diabetes might cause testosterone deficiency through several mechanisms. These include insulin resistance, hyperglycaemia, visceral fat, nutritional status and high triglyceride levels [11,12]. In summary, many men with diabetes and erectile dysfunction remain refractory to PDE-5 inhibitor treatment, but we know that concurrent hypogonadism is common in men with Type 2 diabetes. A strong theoretical argument exists, therefore, for using testosterone therapy to treat erectile dysfunction in men with diabetes unresponsive to PDE-5 inhibitors.

Consistent with the physiological actions of testosterone, testosterone therapy is known to inhibit spermatogenesis, increase haematocrit levels and stimulate prostatic growth; it is therefore imperative to ensure that any indication of testosterone therapy avoids the potential risks of fertility, cardiovascular disease and prostate cancer [13,14]. Men with Type 2 diabetes and erectile dysfunction are often middle-aged or elderly, so have an *a priori* increased risk of cardiovascular disease and prostate cancer. Recently, a number of studies have been published investigating the effects of testosterone therapy on sexual dysfunction in men with Type 2 diabetes. The aim of the present systematic review and meta-analysis was to assess collectively the available evidence to determine the suitability of testosterone therapy for the treatment of sexual dysfunction in men with Type 2 diabetes [15].

Materials and methods

Study search strategy and selection

We registered our protocol in advance on the PROSPERO database (reference: 2017:CRD42017060835). A systematic search was performed in accordance with the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. To identify eligible studies, we conducted a systematic search of the literature using the electronic databases MEDLINE (1966 to August 2016), EMBASE (1988 to August 2016), Cochrane CENTRAL (inception to August 2016), Google Scholar, WHO international Clinical Trials Registry Platform Search Portal and clinicaltrials.gov. Recent conference proceedings and article references were also hand searched for all relevant studies. The search terms used were 'diabetes mellitus', 'impotence, 'erectile dysfunction', 'hypogonadism', 'testosterone' and 'trial OR RCT'. The search was rerun in April 2017. Articles published in any language were included if: (i) they included adult men (aged ≥18 years) with Type 2 diabetes, irrespective of disease duration or background antidiabetic therapy, who were either eugonadal or hypogonadal; (ii) they were randomized controlled clinical trials (RCTs) comparing testosterone with placebo; and (iii) the outcomes of each study included sexual measurements. We excluded studies that compared testosterone therapy with other agents or included people with metabolic syndrome or without diabetes.

Data extraction and quality assessment

Two independent authors (M.A. and P.M.) screened abstracts, titles and full-text publications for eligibility. Discrepancies were adjudicated by a third author (C.J.). Authors were emailed to obtain unpublished data and, where possible, these were included. For each study, the following data were identified: study reference details; publication date; study location; study design; number of participants; intervention; dose and route of administration; duration of treatment; randomization; allocation; blinding; withdrawals and drop-outs; and mean and SD values at baseline and post-treatment for all variables related to sexual function. In some cases, the mean and SD values were not reported, so the authors were contacted and the information retrieved [17]. The methodological quality of the included studies was

assessed using the criteria proposed by Jadad *et al*. [18].

Statistical analysis

Statistical analysis was performed using Comprehensive Meta-Analysis Version 2 by an independent statistician. Applying the method of Hedges and Olkin, the treatment effect size and 95% CI was calculated for each study [19]. The mean difference for each study was divided by the pooled estimate of the SD in order to define the effect size in each study by a common metric, most notably the standardized mean difference (SMD), as different scales were used among the studies. Effect sizes were then reported as SD units. Compared with control groups, this measure expresses the amount of active treatment and how it influences the distribution in the outcome of interest. Cohen offers these guidelines in assessing treatment effect size: small ~0.2; medium ~0.5; and a large effect size ~0.8. Cohen's guidelines can be used both in judging the treatment effect size of individual studies and/or the treatment effect size of all studies combined. As heterogeneity was expected in the effect between studies, we used the random-effects model. Statistical heterogeneity was assessed using the chi-squared test and was expressed as the I^2 index, as described by Higgins and Green. P values < 0.05 and I^2 values >50% were taken to indicate statistical significance [20].

Results

Search results

A total of 611 articles were identified from the literature search (Fig. 1) with 14 studies confirmed to be eligible. Of these, eight studies were excluded for the reasons shown in Fig. 1 and six RCTs were identified [17,21–25], with four eligible for inclusion in the meta-analysis [17,23–25]. The risk of bias of the studies is shown in Table 1 [17,23–25].

Authors of all studies included in the meta-analysis were contacted; two authors replied [17,22], and one author was able to provide further data requested (mean and SD summary data) [17].

Study characteristics

Six RCTs including a total of 587 men with Type 2 diabetes were assessed to evaluate the effectiveness of intramuscular testosterone therapy on sexual function between mid-2006 and 2016 (Table 2 [17,21–25]). Placebo-controlled double-blind trials were used in six of the studies (two of them were crossover studies) [17,21–25]. Three trials were conducted in Europe [21,23,24] and the remaining three were conducted in India [22], Australia [17] or the USA [25]. The mean follow-up ranged between 3 and 12 months. Participants ages were similar across the studies, ranging between 44 and 64 years. Testosterone therapy was administered in different regimens (Table 2). The mean level of testosterone in participants ranged from 9 to 10.6 nmol/l. Researchers used questionnaires and scales investigating the character of one or more sexual functions, with adequate evidence of validity and reliability [26,27]. All the relevant data provided in the trials were reported as mean with SD values.

Effects of testosterone treatment on sexual function

Three RCTs in our analysis measured sexual behaviour and/or dysfunction [23–25]. Hackett *et al.* [24] and Jones *et al*. [23] enrolled men with Type 2 diabetes and confirmed hypogonadism in addition to other symptoms attributed to androgen deficiency; however, Dhindsa *et al.* [25] included men with Type 2 diabetes and confirmed biochemical hypogonadism, without any selection for symptoms of sexual dysfunction.

Meta-analysis was performed to examine if testosterone therapy improved each of five questionnaire-based indices of sexual function in men with Type 2 diabetes (Fig. 2) [23–25]. Testosterone therapy significantly improved erectile function (pooled effect size 0.203,

95% CI 0.007–0.399; P=0.042, I^2=0%) and sexual desire (pooled effect size 0.314, 95% CI 0.082–0.546; P=0.008, I^2=21.5%); however, it did not significantly improve orgasmic function (pooled effect size 0.236, 95% CI 0.604 to –0.132; P=0.209, I^2=69%), intercourse satisfaction (pooled effect size 0.453, 95% CI 0.937 to –0.032; P=0.067, I^2=79%) or overall satisfaction (pooled effect size 0.0085, 95% CI 0.289 to –0.118; P=0.41, I^2=0%).

Effects of testosterone treatment on constitutional symptoms

The Aging Male Symptom score was used to assess constitutional symptoms in three RCTs [17,23,24], which included a total of 452 men (224 for testosterone therapy and 228 for control). Across all three trials, the pooled estimate suggested a consistent, non-significant effect of testosterone on symptom scores [pooled effect size, –0.115; 95% CI –0.299 to 0.070; I^2=0% (Fig. 3)].

Safety of testosterone treatment

Testosterone therapy stimulates haemopoiesis and therefore may be associated with thromboembolic disease. Furthermore, controversy surrounds the potential association of testosterone therapy with prostate cancer. No cases of thromboembolic disease, fertility or prostate cancer were reported in any of the included studies; however, most of the retrieved studies investigated a duration of testosterone therapy of ≤6 months, so cannot address the long-term safety of testosterone therapy in men with Type 2 diabetes [21,22,25].

Discussion

This is the first meta-analysis of randomized studies investigating the effects of testosterone therapy on sexual function in men with Type 2 diabetes, and the results suggest that testosterone therapy may increase sexual desire and erectile function in men with Type 2

diabetes; however, we recognize that evidence supporting these conclusions is only moderate in strength.

Levels of serum total and free testosterone decline gradually with age in the general male population, but there remains considerable debate as to the severity of hypogonadism appropriate for the initiation of testosterone therapy [14]. Symptoms of sexual dysfunction play an important role in helping clinicians decide if testosterone therapy should be initiated; however, it can be more challenging to diagnose symptomatic hypogonadism in men with Type 2 diabetes, who commonly have erectile dysfunction for reasons other than testosterone deficiency. The mainstay of treatment of sexual dysfunction in men with Type 2 diabetes is PDE-5 inhibitor administration. A large number of men with Type 2 diabetes, however, are refractory to PDE-5 inhibitor treatment [6,7]. Considering that Type 2 diabetes is reported to increase the risk of hypogonadism, it is plausible that a proportion of men with Type 2 diabetes refractory to PDE-5 inhibitor treatment would be responsive to testosterone therapy.

Serum levels of testosterone are subject to diurnal variation, and are suppressed by ingestion of food. None of the studies included in the present analysis used the 'gold standard' method of measuring serum testosterone during two, fasted 09:00 h serum venepunctures [28,29]. We therefore cannot exclude the possibility that some participants in the included studies had artefactually subnormal serum testosterone levels (so called 'afternoon clinic' or 'postprandial' hypogonadism). Published evidence on osteoporosis, anaemia and reduced testicular volume is needed to support the low serum testosterone levels reported in men with Type 2 diabetes who present with hypogonadism.

For instance, unlike men with objective hypogonadism, there are no data to suggest that men with a single randomly low serum testosterone level associated with T2DM (representing the preponderance of men recruited to these studies) exhibit either low bone density, anaemia or reduced testicular volume at baseline (although testicular volume

probably shrinks with testosterone therapy).

Testosterone promotes male sexual desire. Our results indicate that testosterone therapy significantly improved sexual desire in men with Type 2 diabetes, which is consistent with previous studies on the general male population [30,31] and men with either Type 2 diabetes or metabolic syndrome [23,24]. For instance, Hackett *et al.* [24] observed that testosterone therapy improved sexual function in 68 men attending routine clinic appointments for Type 2 diabetes who had no sexual activity in the last 12 months.

Erectile dysfunction can arise during Type 2 diabetes for several reasons other than hypogonadism. It is therefore important to consider if testosterone therapy effectively improves erectile function in men with Type 2 diabetes. One study in our analysis concluded that testosterone therapy significantly improved erectile function [24]; Hackett *et al*. [24] observed, for instance, that testosterone therapy increased International Index of Erectile Function (IIEF) score by 4.31 points from baseline. Furthermore, the IIEF score still improved by 2.9 points during testosterone therapy after patients taking PDE-5 inhibitors were removed from the analysis. Other studies observed no significant effect between testosterone therapy and erectile function [17,23,25]. Overall, our analysis suggests that testosterone therapy significantly improved erectile function in men with Type 2 diabetes with an effect size 0.203 (95% CI 0.007–0.399), but results of individual studies were heterogeneous. Furthermore, there are no long-term data investigating whether testosterone therapy confers an increased risk of fertility, prostate cancer or cardiovascular disease. We therefore recommend caution when considering long-term testosterone therapy for erectile dysfunction in men with Type 2 diabetes.

A recent meta-analysis evaluating the effect of testosterone therapy on sexual function in the general population, concluded that testosterone therapy significantly improved erectile function and other aspects of sexual dysfunction compared with placebo, but these effects

were less prominent in the presence of metabolic derangement such as diabetes and obesity. This result is not surprising as diabetes is often associated with the presence of other diabetes-related complications, such as peripheral neuropathy, vasculopathy and endothelial dysfunction, which are not directly attributable to androgen deficiency [32,33]. Conversely, testosterone therapy is able to improve body composition and insulin resistance in men with obesity-related metabolic syndrome and Type 2 diabetes [34,35]. Further studies are required to compare directly the effectiveness of testosterone therapy for sexual dysfunction in men with and without diabetes.

In two RCTs included in our analysis, it was observed that testosterone therapy improved orgasm or satisfaction with intercourse using the Androgen Deficiency Symptom score (ADMS) in men with Type 2 diabetes [21,22]; however, when considering all studies in our analysis, there was no overall improvement in orgasm or satisfaction with intercourse during testosterone therapy in men with Type 2 diabetes [23–25]. A systematic review of RCTs among men without diabetes did show an improvement of orgasm or satisfaction with intercourse following testosterone therapy [30,31,36]. Larger studies using a unified questionnaire methodology will be important to determine whether people with diabetes do have improved orgasm or satisfaction with intercourse using testosterone therapy, or are refractory to treatment when compared with men who have normal glucose tolerance.

Several limitations should be recognized in this systematic review. All studies included men with Type 2 diabetes with low levels of serum testosterone, but no unifying threshold was used to define testosterone deficiency in the individual studies; this limitation reflects the notable clinical controversy that currently surrounds the indications for testosterone therapy prescribing, and the potential risks of associated thromboembolic disease, fertility and prostate cancer associated with therapy [37–39]. Most of the retrieved studies investigated a duration of testosterone therapy of ≤6 months [21,22,25] and involved

a small number of participants. It is therefore imperative to conduct large trials further delineating the effects of testosterone therapy on sexual function, with long-term follow-up to determine adverse events. Published studies seldom report all study outcomes, and often under-report outcomes (e.g. describing them as 'non-significant' without presenting the data). This reporting bias was addressed by contacting the authors of all included studies and requesting the relevant data [17].

In conclusion, randomized placebo-controlled trials to date suggest that testosterone therapy has a moderate improvement on sexual desire, and a smaller effect on erectile function; however, we have highlighted the lack of long-term safety data on testosterone therapy in men with Type 2 diabetes. Further research is needed, using validated assessments of sexual dysfunction such as IIEF score, evaluation of nocturnal penile tumescence and penile colour Doppler ultrasonography, and Androgen Deficiency in the Aging Male (ADAM) questionnaires. We conclude that testosterone therapy is a potential treatment for men with Type 2 diabetes non-responsive to PDE-5 inhibitors. Testosterone therapy could be considered for men with Type 2 diabetes when the risks and benefits of therapy are carefully considered, and other therapeutic options are unsuitable. More studies in this area may better substantiate the role of testosterone therapy in men with Type 2 diabetes and sexual dysfunction, which is sufficient to warrant changes in clinical practice.

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Competing interests

None declared.

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FIGURE 1 Study selection, based on PRISMA guidelines. *n*, number of studies.

FIGURE 2

FIGURE 3

Table 1 Quality assessments of four randomized controlled trials using Jadad score

Items	Score standard			Study			
	0	**1**	**2**	**Dhindsa *et al.* (2016) [25]**	**Gianatti *et al.* (2014) [17]**	**Hackett *et al.* (2013) [24]**	**Jones *et al.* (2011) [23]**
Randomization	Not randomized	Study described as randomized	Randomization scheme described and appropriate	1	2	2	2
Double blinding	No blind or inappropriate method of blinding.	Study described as double-blind.	Method of double blinding described appropriately	1	2	2	2
Withdrawals and dropouts	Follow-up not described	Description of withdrawals and dropouts given	/	1	1	1	1
Score summaries	/	/	/	3	5	5	5

Table 2 Characteristics of the included randomized controlled trials

	Study (year)					
	Dhindsa *et al.* (2016) [25]	**Gianatti *et al.* (2014) [17]**	**Hackett *et al.* (2013) [24]**	**Jones *et al.* (2011) [23]**	**Gopal *et al.* (2010) [22]**	**Kapoor *et al.* (2006) [21]**
Study characteristic						
Location	New York, USA	Melbourne, Australia	Multicentre, UK	Multicentre, Europe	Mumbai, India	Sheffield, UK
Design	RCT	RCT	RCT	RCT	RCT crossover	RCT crossover
Drugs	i.m. testosterone cypionate	i.m. testosterone undecanoate	i.m. testosterone undecanoate	testosterone gel 2%	i.m. testosterone cyponate	i.m. sutanon
Dose	250 mg/2 weeks	1 g at 0, 6, 18 and 30 weeks	1 g at 0, 6 and 18 weeks	60 mg/day	200 mg/2 weeks	200 mg/2 weeks
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Trial duration, weeks	24	40	30	48	12	12
Number of participants: testosterone group/control group	20/14	45/43	97/102	108/112	22/22	24/24
Baseline testosterone therapy, nmol/l	N/A	N/A	N/A	9.4	10.2	8.6
Testosterone therapy: testosterone group/control group, nmol/l	9/8.3	10.6/11	10.5/10.8 7.4/7.2	9.2/9.5	N/A	8.8/8.1
Clinical score	IIEF	AMS	IIEF, AMS	IIEF, AMS	ADAM	ADAM
Mean age, years	55	62	62	60	44	64
Diabetes duration, years	9	8	N/A	N/A	N/A	N/A

HbA_{1c}: testosterone group/control group mmol/mol %	51/ 53 6.8/7	51/54 6.8/7.1	59/60 7.5/7.6	51/59 6.8/7.5	47/ 60 6.4/7.6	55/55 7.2/7.2
BMI: testosterone group/control group, kg/m^2	39/39.5	31.5/33.4	32.8/32.7	32.8/31.2	25.4/22.1	33.2/32.8

AMS, Aging Male Symptom; IIEF, International Index of Erectile Function; ADAM, Androgen Deficiency in the Aging Male; i.m., intramuscular; N/A, xxx; RCT, randomized controlled trial.

Figure 1: PRISMA diagram.