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# Diagnosis and Effectiveness of Treatment of Male Hypogonadism in Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis

## ABSTRACT

**Objective:** Variations exist in the diagnosis and management of male hypogonadism in patients with type 2 diabetes mellitus (T2DM). These variations necessitated the need to review the diagnosis and effectiveness of treatment of male hypogonadism in patients with T2DM. The objective of the study was to systematically review the approach to the diagnostic workup and treatment of male hypogonadism in patients with T2DM.

**Methods:** This was a systematic review and meta-analysis of randomized controlled trials. A systematic search was done using PubMed/Medline, Embase, Google Scholar, and the Cochrane Central Library. This was followed by a manual evaluation of the literature. Two independent reviewers used a standardized data extraction tool to obtain data from the included studies in the review. Articles were pooled, and statistical meta-analysis was conducted using RevMan-5 version 5.a.4 software.

**Results:** The global prevalence of hypogonadism ranged from 4.4% to 80.4%. Twelve studies were included in the analysis to find the best diagnostic option for hypogonadism. Three studies used a total testosterone (TT) level of <11 nmol/L to diagnose hypogonadism, 5 used a TT level of <12 nmol/L, and 2 studies each used free testosterone levels of <11.8 pg/mL and <6.5 ng/L. From the analysis, studies that used a TT level of <11 nmol/L had the best glycemic control [pooled standardized mean difference (SMD) = −0.65, 95% CI (−0.95)-(−0.35), $P < .001$ (with low heterogeneity: $Q = 2.83$; $I^2 = 29\%$)]. Seven studies were analyzed to find the best treatment option for male hypogonadism. Three of these used intramuscular testosterone undecanoate, 3 used transdermal testosterone gel, and 1 used intramuscular testosterone enanthate. However, the use of TT gel was found to be the best treatment option as it produced pooled SMD (95% CI) that is most precise with the lowest *P*-value ($P < .001$) and absence of heterogeneity (Cochran *Q*-test = 1.11; $I^2 = 0\%$).

**Conclusion:** Male hypogonadism is best diagnosed using a serum TT of <11 nmol/L. The best treatment option for hypogonadal men with T2DM was daily TT gel.

**Keywords:** Diagnosis, effectiveness of treatment, hypogonadism, type 2 diabetes mellitus

## Introduction

Type 2 diabetes is linked to a higher prevalence of male hypogonadism, associated with an increased risk of cardiovascular events and death.[1] Testosterone therapy has been recommended for type 2 diabetes mellitus (T2DM) patients with hypogonadism because it improves libido and insulin sensitivity.[2] However, variations exist in its diagnosis and treatment.[3-6] This, therefore, necessitated a review of the various diagnostic workups and the effectiveness of different formulations of testosterone therapy for male hypogonadism in T2DM patients. The objectives of this study were to review the best approach to the diagnostic workup and the most effective treatment formulation for male hypogonadism in patients with T2DM.

## Materials and Methods

### *Eligibility Criteria/Inclusion Criteria*

This evaluation included studies focusing on male patients with type 2 diabetes who had hypogonadism and were treated with testosterone replacement therapy (TRT). We also looked at studies that employed TRT to treat male hypogonadism in type 2 diabetic patients. We included cross-sectional studies (for assessing the prevalence of hypogonadism in men with type 2 diabetes) and randomized controlled trials (for meta-analyses).

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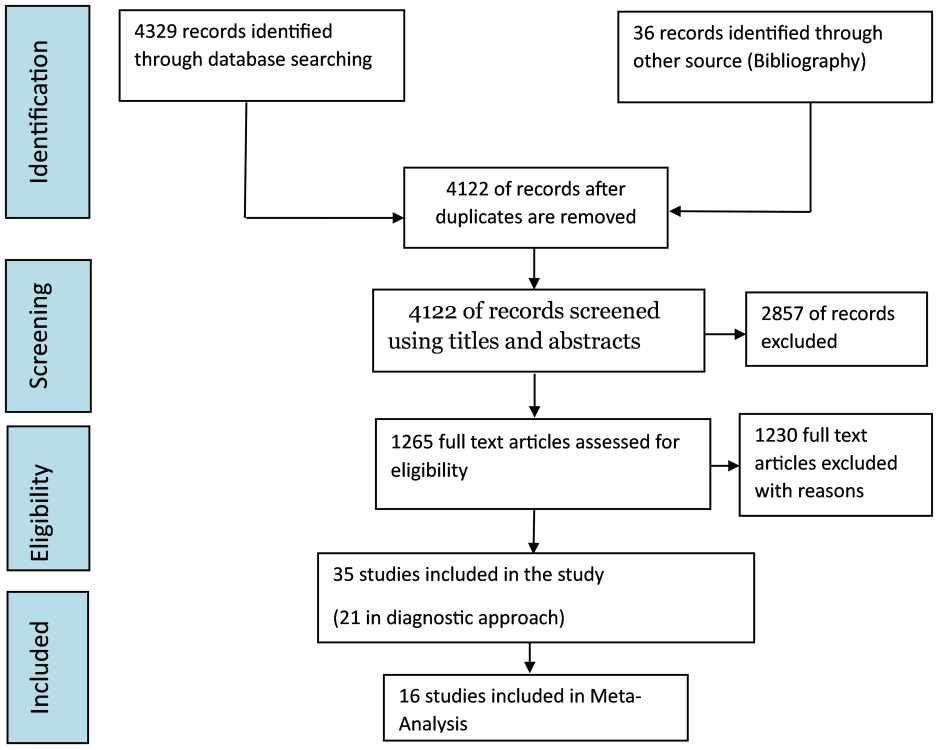


**Figure 1. Flow diagram summarizing the screening strategy for studies included for meta-analysis.**

### *Information Sources*

This review's information sources included electronic databases, hand searching, internet searching, and reference lists. PubMed/Medline, Embase, Google Scholar, Scopus, Web of Science, and the Cochrane Central Library were among the databases searched (the last search was in March, 2022). Dissertation abstracts, the Index to Scientific and Technical Proceedings, conference listings, popular media sources, and portals for relevant gray literature were all searched for unpublished studies (the last search was in March, 2022). The keywords used first were diagnosis, male hypogonadism, TRT, and type 2 diabetes mellitus. EndNote, a bibliography management software package, handled the records.

### *Search Strategy*

This review employed a 3-step search method. A preliminary search of PubMed/MEDLINE and CINAHL was conducted, followed by examining the text words in the title and abstract and the index keywords used to characterize the article. Second, a search was conducted across all included databases using all the indicated keywords and index phrases. Lastly, all recognized reports and papers' reference lists were searched for additional studies (Figure 1). There were no geographical or linguistic constraints.

## MAIN POINTS

- A serum total testosterone of 11 nmol/L is the most effective way to diagnose male hypogonadism.
- Hypogonadism is common among male patients with type 2 diabetes mellitus.
- Transdermal testosterone gel is the most effective treatment for male hypogonadism in type 2 diabetic patients.

### *Selection Process*

Before inclusion in the review, all papers selected for retrieval were examined for methodological validity by 2 independent reviewers using a validated review tool. The 2 reviewers assessed each eligibility criterion in an article as eligible, not eligible, or possibly eligible. Following discussion between the 2 independent reviewers, a study was judged relevant if it could not be dismissed based on its title and abstract. The entire study text was collected and read for abstracts with insufficient information or when the 2 reviewers disagreed. It was included when both reviewers independently determined that a study met the inclusion criteria in the full text. Studies with duplicate or overlapping data and articles whose full texts were unavailable were eliminated. Any differences between the reviewers are handled through discussion or with the assistance of a third reviewer. The IBM StatisticalPackage for the Social Sciences Statistics, version 25.0, software (IBM corp., Armonk, NY, USA) was used to calculate kappa agreement (Cohen's *k*) between reviewers when choosing research for this study.

### *Data Collection Process*

Two independent reviewers used a standardized data extraction tool to obtain data from the included studies in the review. The retrieved data contained detailed information regarding the demographics, interventions, study procedures, and outcomes relevant to the review questions and specified objectives.

### *Data Items*

Data for the primary and secondary outcomes, as well as additional variables, were sought. The primary outcomes addressed in this analysis were improvement in glycemic control, as measured by glycated hemoglobin (HbA1c), and reduction in insulin resistance, as measured by the homeostasis model assessment of insulin resistance (HOMA-IR). However, improvements in erectile function (EF)

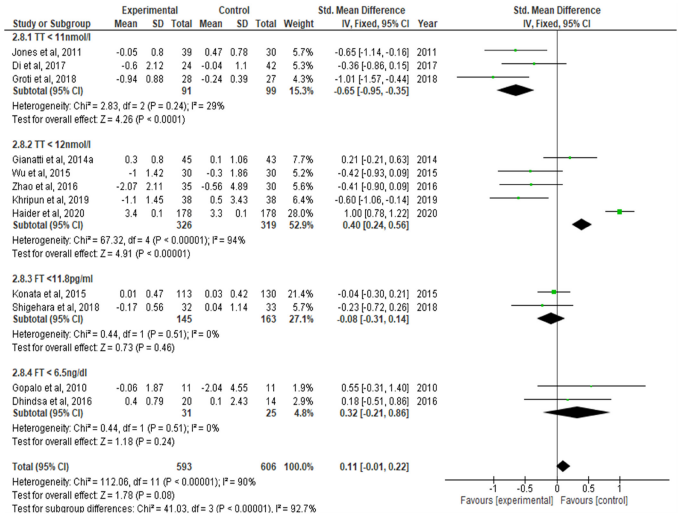


**Figure 2. Hypogonadism diagnostic workup among patients with type 2 diabetes mellitus**

as measured by the International Index of Erectile Function 5 (IIEF-5) scores, libido, quality of life as measured by the aging male syndrome (AMS) score and the 36-item Short Form (SF-36), and depression as measured by the Hospital Anxiety and Depression Scale were considered secondary outcomes. Other additional variables sought were the studies' population, the studies' design, the studies' intervention criteria, the studies' inclusionary and exclusionary criteria, the follow-ups of the participants in the studies, the type(s) of intervention, and the age group examined. All results from each study that were compatible with each outcome domain were sought. If data are lacking, the lead reviewer tries to contact the study's authors to account for the missing information. When the authors failed to respond, the study was removed from the meta-analysis but kept for discussion.

### *Risk of Bias Assessment*

Two independent reviewers used the Cochrane Risk of Bias form to assess the risk of bias (Figure 2). The template is divided into a predefined set of bias domains focusing on various aspects of trial design, conduct, and reporting. Each evaluation created using the template focuses on a specific outcome of a randomized experiment. A set of questions (called "signaling questions") within each domain aims to gather information on trial factors important to the risk of bias. The answers to the signaling questions provided by 2 independent reviewers were used to decide on the possibility of discrimination arising from each area. Decisions can have a "low" or "high risk of bias," or they can reflect "some worries" (Table 1).[7-22]

### *Effect Measure*

The standardized mean difference (SMD) was the effect size used to synthesize and present results for both primary and secondary outcomes.

### *Data Synthesis*

Two investigators independently verified and compiled the extracted data for each study to provide a descriptive synthesis of key characteristics by comparing the extracted information from each study with the list of eligibility criteria for each outcome domain. The cleaning of the data on the extraction sheet followed this. The data were then organized in a form that could be read by analytical software. Quantitative papers were pooled in statistical meta-analysis using RevMan 5 software version 5.4 to conduct meta-analysis when appropriate and feasible (i.e., when at least 2 studies that used the same design provided sufficient outcome data on the same construct that permitted estimation of effect sizes). Effect sizes were calculated and displayed in forest plots as weighted SMDs with 95% CIs. Heterogeneity was assessed statistically using the standard chi-square (Cochrane's *Q* statistic) and $I^2$. The results were tested for consistency and the effects of certain confounders on the outcome using sensitivity, subgroup, and cumulative analyses. An assessment

**Table 1. Risk of Bias Assessment**

| | Random Sequence Generation (Selection Bias) | Allocation Concealment (Selection Bias) | Blinding of Participants and Personnel (Performance Bias) | Blinding of Outcome Assessment (Detection Bias) | Incomplete Outcome Data (Attrition Bias) | Selective Reporting (Reporting Bias) | Other Bias |
|---|---|---|---|---|---|---|---|
| Gopal et al[7] | ? | + | + | ? | ? | ? | ? |
| Jones et al[8] | + | + | + | ? | + | ? | ? |
| Hackett et al[9] | + | + | + | ? | + | ? | ? |
| Mitkov et al[10] | + | + | – | – | – | ? | ? |
| Hackett et al[11] | + | + | ? | ? | + | ? | ? |
| Gianatti et al[12] | + | + | + | – | ? | ? | ? |
| Konaka et al[13] | + | ? | + | – | + | + | ? |
| Wu et al[14] | ? | ? | – | – | ? | ? | ? |
| Dhindsa et al[15] | + | + | + | ? | – | ? | ? |
| Magnussen et al[16] | + | + | + | – | + | + | ? |
| Zhao et al[17] | ? | – | – | – | ? | ? | ? |
| Di et al[18] | – | – | – | – | + | + | ? |
| Groti et al[19] | ? | ? | + | ? | + | ? | ? |
| Shigehara et al[20] | ? | ? | + | ? | + | ? | ? |
| Khripun et al[21] | + | + | ? | ? | + | ? | ? |
| Haider et al[22] | – | – | – | – | + | ? | ? |

Nine (56.3%) of the 16 studies that were used to assess the risk of bias had low risk in terms of random sequence generation while 10 had low rik of bias in terms of allocation concealment. However, most of the studies (13) had unclear risk of reporting bias.

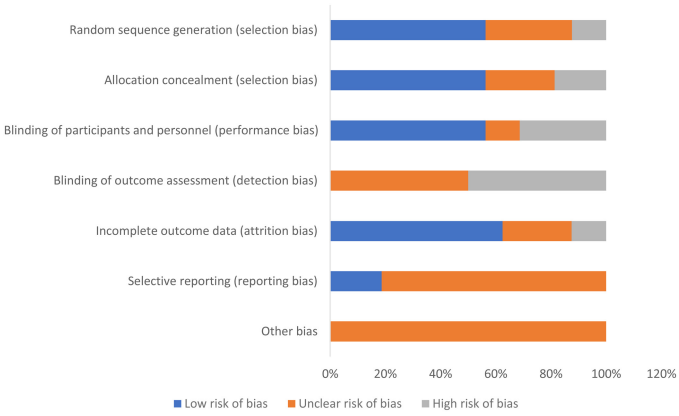


**Figure 3. Risk bias assessment. FT, free testosterone; TT, total testosterone.**

of publication bias was made to investigate the presence of missing studies. The funnel plot showed studies scattered on either side of the dotted line in nearly a symmetrical manner, indicating the absence of publication bias (Figure 3).

## Results

### *Approach to the Diagnostic, Workup of Hypogonadism in Patients with Type 2 Diabetes Mellitus*

The operational definition of hypogonadism used across studies varied considerably. The studies by Ogbera et al,[23] Al Hayek et al,[24] and Anderson et al,[25] in Nigeria, Saudi Arabia, and the UK, respectively, used the most liberal definition of hypogonadism [total testosterone (TT) <300 ng/dL, no symptom criteria] and reported the prevalence as 36%, 22.9%, and 4.4%, respectively (Table 2).[21,23-40]

### *Best Diagnostic Workup for Hypogonadism in Men with Type 2 Diabetes Mellitus*

Four meta-analyses were performed to evaluate the best diagnostic approach for hypogonadism in men with T2DM using a change in glycemic control (by HbA1c) as an outcome of interest after TRT. Overall, 12 studies were included in the analysis; of these, 3 used a TT level of <11 nmol/L to diagnose hypogonadism, 5 studies used a TT level of <12 nmol/L, and 2 studies each used free testosterone (FT) levels of <11.8 pg/mL and <6.5 ng/L, respectively. From the analysis, studies that used a TT level of <11 nmol/L showed a significant reduction in HbA1c (i.e., had good glycemic control), pooled SMD = −0.65 (95% CI (−0.95)-(−0.35); $P < .001$), and low heterogeneity ($Q = 2.83$; $I^2 = 29\%$; $P = .24$). However, subgroup analysis of the studies that used TT levels of <12 nmol/L as diagnostic criteria revealed a significant increase in HbA1c (i.e., poor glycemic control) and SMD = 0.40 (95% CI, 0.24-0.56; $P < .001$) with significantly high heterogeneity ($Q = 67.32$; $I^2 = 94\%$; $P < .001$). There was no significant change in the level of HbA1c among studies that used FT levels of either <11.8 pg/mL or < 6.5 ng/L (Figure 4).

### *Treatment Options for Hypogonadism in Men with Type 2 Diabetes Mellitus*

A total of 16 studies with 1851 participants (936 for the TRT group and 915 for the control group) were included in the meta-analysis. From these, 3 studies were conducted in China, 2 in Japan, 2 in the UK, and others in different parts of the world, including Germany, Belgium, the USA, Denmark, Russia, and India. Ten studies used the

**Table 2. Approach to the Diagnostic Workup of Hypogonadism in Patients with Type 2 Diabetes Mellitus**

| Author (Year) | Country | Study Population | Sample Size | Definition of Hypogonadism Used |
|---|---|---|---|---|
| Biswas et al[26] | UK | Hospital based | 115 | TT < 11.9 nmol/L |
| Anderson et al[25] | UK | Hospital based | 353 | TT < 8.0 nmol/L<br>TT 8-11.99 nmol/L |
| Ogbera et al[23] | Nigeria | Hospital based | 203 | TT < 8 nmol/L |
| Al Hayek et al[24] | Saudi Arabia | Hospital based | 157 | TT ≤ 8 nmol/L |
| Musa et al[27] | Nigeria | | 358 | TT ≤ 12 nmol/L. |
| Musa et al[28] | Nigeria | Hospital based | 358 | Testosterone < 8 nmol/L with or without symptoms or TT 8-12 nmol/L with symptoms |
| Awe et al[29] | Nigeria | Hospital based | 30 | Testosterone < 3 ng/mL |
| Etawo and Aleme[30] | Nigeria | Hospital based | 142 | Testosterone < 3 ng/mL |
| Mohamed et al[31] | Egypt | Hospital based | 140 | Testosterone ≤ 300 ng/dL |
| Al-Hayek et al[24] | Saudi Arabia | Hospital based | 157 | Testosterone ≤ 8 nmol/L + positive ADAM score |
| Khripun et al[21] | Russia | Hospital based | 40 | TT ≤ 12 nmol/L |
| Anupam et al[32] | India | Hospital based | 150 | FT < 6.35 ng/dL + positive ADAM score |
| Al Hayek et al[33] | Jordan | Hospital based | 1049 | Testosterone < 3 ng/mL + positive ADAM score |
| Li et al[34] | China | Hospital based | 100 | TT of < 3 ng/mL |
| Teka et al[35] | Ethiopia | Hospital based | 115 | TT < 12.1 nmol/L + presence of clinical symptoms |
| Raza et al[36] | Pakistan | Hospital based | 108 | TT of <3 ng/mL + erectile dysfunction |
| Antonic et al[37] | Slovenia | Hospital based | 165 | TT < 11 nmol/L |
| Ho et al[38] | Taiwan | Hospital based | 105 | TT < 300 ng/dL |
| Liu et al[39] | China | Population based | 766 | TT < 300 ng/dL |
| Di Luigi et al[40] | Italy | Population based | 183 | TT < 230 ng/dL |
| Anderson et al[25] | UK | Population based | 253 | TT < 8.0 nmol/L |

ADAM, androgen deficiency in the aging male; FT, free testosterone; TT, total testosterone.

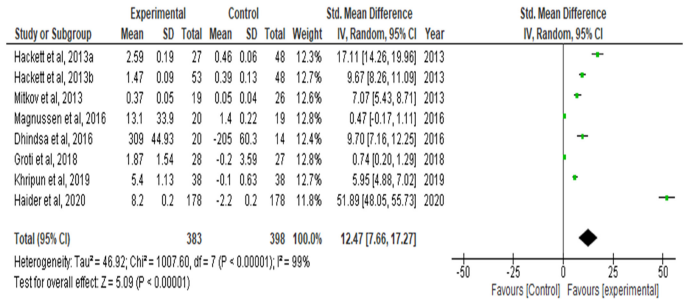


**Figure 4. Effect of testosterone replacement therapy on total testosterone level in hypogonadal men with type 2 diabetes mellitus**

TT level to diagnose hypogonadism, while 5 used the FT level. In these studies, different treatment options were employed to treat hypogonadism in the TRT group. Seven studies used intramuscular testosterone undecanoate, 3 used intramuscular testosterone enanthate, 4 used transdermal testosterone gel, and 2 employed oral testosterone undecanoate. The duration of TRT ranged between 3 and 13 months across studies, with 6 of the studies using 6 months each (Table 3).[7-22]

### *Effect of Testosterone Replacement Therapy on Serum Testosterone levels in Hypogonadal Men with Type 2 Diabetes Mellitus*

A total of 8 studies were included (383 patients in TRT and 398 patients in control) for the evaluation of TRT's effects on TT level. It was found that testosterone therapy significantly increases the testosterone level (SMD 12.47, 95% CI, 7.66-17.27, and $P < .00001$), indicating that TRT improves the TT level. However, heterogeneity was high ($I^2 = 99\%$) (Figure 5).

A total of 5 studies (158 patients in TRT and 167 patients in control) were included to evaluate TRT's effect on the FT levels. Overall, it was found that TRT significantly increased FT levels (SMD 9.50, 95% CI, 5.47-13.52) (Figure 6).

### *Hypogonadism Treatment Options in Men with Type 2 Diabetes Mellitus*

A subgroup analysis was performed according to the types of TRT employed by the studies to treat hypogonadism. Three studies used intramuscular testosterone undecanoate which showed a significant increase in serum testosterone levels among respondents in the intervention group (pooled SMD = 2.39; 95% CI, 0.89-2.50; $P = .002$). Similarly, 3 studies used transdermal testosterone gel in the treatment of hypogonadism, with their pooled analysis also showing a

**Table 3. Characteristics of Randomized Controlled Studies Included in the Meta-Analysis**

| Author (Year) | Country of Study | Mean Age ± SD (Years) | | Sample Size | | Diagnosis of Hypogonadism | Treatment Given | Duration of Treatment |
|---|---|---|---|---|---|---|---|---|
| | | TRT | Control | TRT | Control | | | |
| Gopal et al[7] | India | 44.23 ± 3.29 | 44.23 ± 3.29 | 11 | 9 | FT < 64.8 pg/mL | IM TU 400 mg 12 weekly | 3 months |
| Jones et al[8] | Multicenter | 59.9 ± 9.1 | 59.9 ± 9.4 | 108 | 112 | TT < 11 nmol/L | Td T-gel 60 mg daily | 6 months |
| Hackett et al[9] | UK | 64 (38-83) | 60 (41-74) | 53 | 48 | TT < 12 nmol/L | IM TU 1000 mg 6 weekly | 7.5 months |
| Mitkov et al[10] | Belgium | 51.58 ± 0.92 | 50.40 ± 1.04 | 19 | 26 | Not available | Td T-gel 50 mg per day | 4 months |
| Hackett et al[11] | UK | 61.2 ± 10.5 | 62.0 ± 9.3 | 91 | 95 | FT < 225 pmol/L | IM TU 1000 mg 6 weekly | 7.5 months |
| Gianatti et al[12] | Australia | 62 (58-68) | 62 (57-67) | 45 | 43 | TT < 12 nmol/L | IM TU 1000 mg 6 weekly | 10 months |
| Konaka et al[13] | Japan | 65.65 ± 9.01 | 67.55 ± 9.36 | 169 | 165 | FT < 11.8 pg ml/L | IM TE 250 mg 4 weekly | 13 months |
| Wu et al[14] | China | 52.63 ± 3.15 | 53.26 ± 4.53 | 30 | 30 | TT < 12 nmol/L | IM TU 259 mg monthly | 6 months |
| Dhindsa et al[15] | USA | 54.6 ± 7.9 | 51.5 ± 8.9 | 20 | 14 | FT < 6.5 ng/dL | IM TE 250 mg 2 weekly | 6 months |
| Magnussen et al[16] | Denmark | 61 ± 6 | 59 ± 6 | 20 | 19 | TT < 7.3 nmol/L | T-gel 5 g daily | 6 months |
| Zhao et al[17] | China | 50.7 ± 5.6 | 52.5 ± 3.2 | 35 | 30 | TT < 12 mmol/L | Oral TU 20 mg tds | 6 months |
| Di et al[18] | China | 44.5 ± 5.7 | 45.5 ± 5.2 | 42 | 40 | TT < 11 nmol/L | Caps TU 80 mg bd x 2 weeks then 40 mg bd | 6 months |
| Groti et al[19] | Slovenia | 60.15 ± 7.23 | 60.15 ± 7.23 | 28 | 27 | TT < 11 nmol/L | IM TU 1000 mg 10 weekly | 12 months |
| Shigehara et al[20] | Japan | 67.0 ± 9.4 | 69.3 ± 9.7 | 47 | 39 | FT ≤ 11.8 pg/mL | IM TE 250 mg 4 weekly | 12 months |
| Khripun et al[21] | Russia | 53.3 ± 5.4 | 54.1 ± 5.6 | 40 | 40 | TT ≤ 12.1 nmol/L | Td T-gel 50 mg per day | 9 months |
| Haider et al[22] | Germany | 61.5 ± 5.4 | 63.7 ± 4.9 | 178 | 178 | TT ≤ 12.1 nmol/L | IM TU 1000 mg every 12 weeks | 5 years |

FT, free testosterone; IM, intramuscular; Td, transdermal; T-gel, testosterone gel; TRT, testosterone replacement therapy; TT, total testosterone; TU, testosterone undecanoate; TE, testosterone enanthate; bd, twice daily; tds, three times daily.

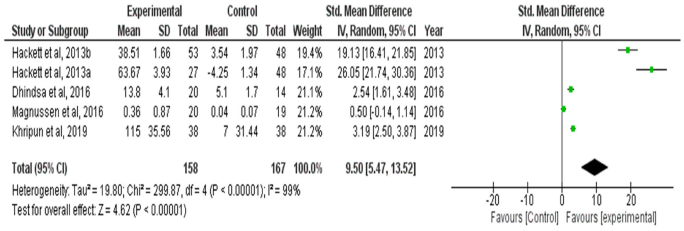


**Figure 5. Effect of testosterone replacement therapy on free testosterone level in hypogonadal men with type 2 diabetes mellitus. IM, intramuscular.**

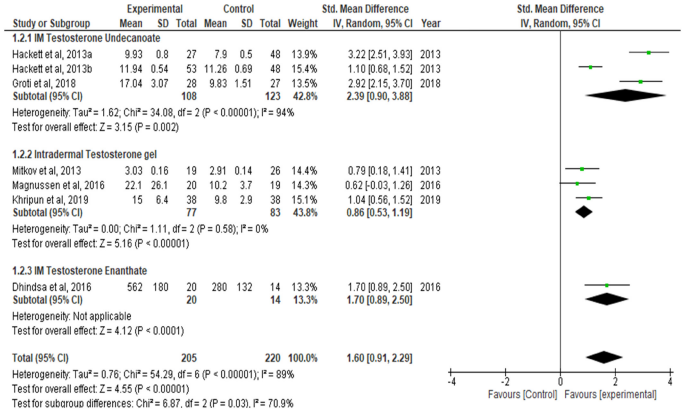


**Figure 6. Options for the treatment of hypogonadism in men with type 2 diabetes mellitus**

significant increase in serum testosterone level among respondents in the intervention group (SMD = 0.85; 95% CI: 0.5-1.19; $P < .001$). The subgroup analysis showed that the use of transdermal testosterone gel produced the pooled SMD (95% CI) that is most precise with the lowest *P*-value ($P < .001$) and absence of heterogeneity (Cochran *Q*-test = 1.11; $I^2 = 0\%$) (Figure 7).

### *Effect of Testosterone Replacement Therapy on Primary Outcomes (Glycemic Control and Insulin Resistance) in Men with Type 2 Diabetes Mellitus and Hypogonadism*

A total of 17 studies were included (803 patients in TRT and 845 patients in control) to evaluate TRT's effects on glycemic control (using HbA1c). It was found that testosterone therapy significantly reduced HbA1c (MD: −0.16, 95% CI (−0.31)-(−0.02), and $P = .03$) (Figure 8).

A total of 10 studies (374 patients in TRT and 368 patients in control) were included to evaluate TRT's effect on the insulin resistance index (HOMA-IR). Overall, it was found that TRT significantly reduced the insulin resistant index (SMD: −0.84, 95% CI (−1.54)-(−0.14), and $P = .02$) (Figure 9).

### *Effect of Testosterone Replacement Therapy on Secondary Outcomes (Erectile Function, Libido, Quality of Life, and Depression) in Men with Type 2 Diabetes Mellitus and Hypogonadism*

Six studies assessed the effect of TRT on EF using the IIEF-5 score. From these, 3 studies demonstrated a significant increase in EF among respondents in the intervention group; 1 reported a significant increase among respondents in both groups; 2 showed a significant decrease among respondents in the intervention group;

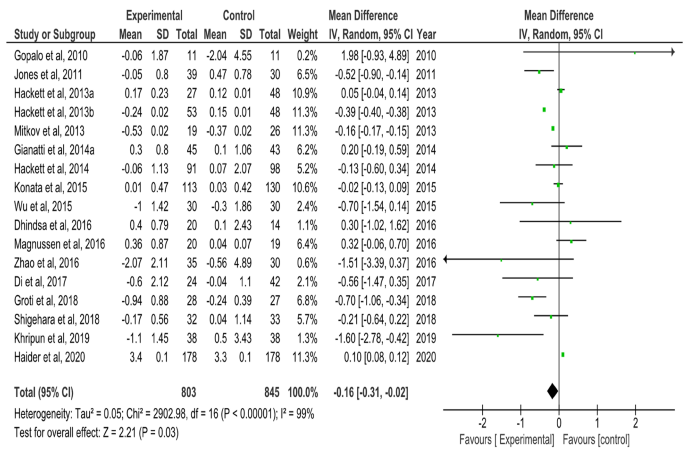


**Figure 7. Effect of testosterone replacement therapy on glycemic control (using glycated hemoglobin) in men with type 2 diabetes mellitus and hypogonadism**

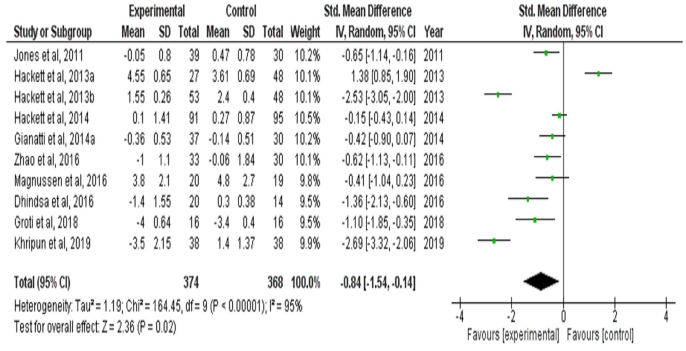


**Figure 8. Effect of testosterone replacement therapy on insulin resistance (using homeostasis model assessment of insulin resistance) in men with type 2 diabetes mellitus and hypogonadism**

and 1 demonstrated no significant change in both groups. The meta-analysis included 785 subjects (389 for TRT and 396 for control). The pooled estimate showed a significant increase in EF among subjects that received TRT [random-effect model SMD = 5.26 (95% CI, 2.92-7.60) ($P < .0001$)] (Figure 10).

Four studies evaluated the effect of TRT on libido, of which 3 demonstrated a significant increase in libido among respondents in the intervention group, while 1 reported a significant decrease among

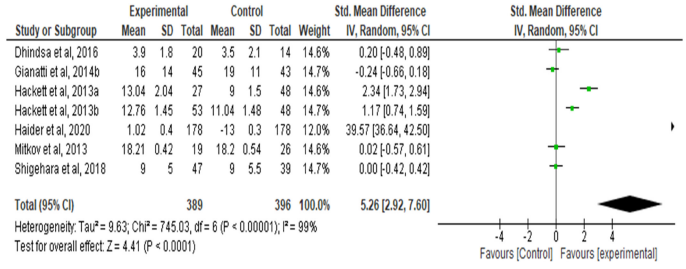


**Figure 9. Effect of testosterone replacement therapy on insulin resistance (using homeostasis model assessment of insulin resistance) in men with type 2 diabetes mellitus and hypogonadism**

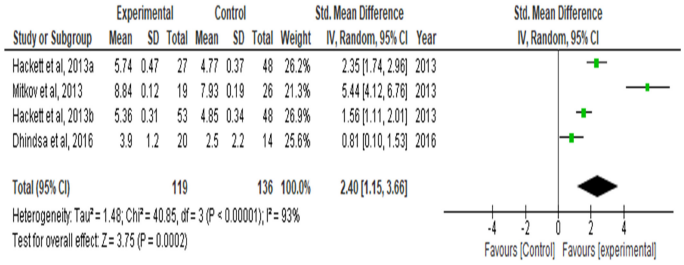


**Figure 10. Effect of testosterone replacement therapy on libido in men with type 2 diabetes mellitus and hypogonadism.**

respondents in the control group. The pooled analysis included a total of 225 subjects (119 for TRT and 136 for placebo). The pooled estimate showed a significant increase in libido among subjects that received TRT [random-effect model SMD = 2.40 (95% CI,1.15-3.66; *P* = .0002)] (Figure 11).

Four studies evaluated the effect of TRT on quality of life [3 used the AMS scale, while 1 used the Short Form Survey (SF-36)]. Of these studies, 1 reported a significant decrease in both groups, 1 reported a significant decrease in the intervention group, 1 reported a significant increase in both groups, and 1 reported no significant change in either group following TRT intervention. The meta-analysis included 395 subjects (191 for TRT and 204 for control). Pooled estimates showed that quality of life (QOL) slightly decreased among subjects that received TRT [random-effect model SMD = −0.15 (95% CI, −0.49-0.19)], but the change was not statistically significant (*P* = .39) (Figure 12).

## Discussion

Male hypogonadism is usually treated with testosterone replacement to return testosterone levels to normal. The Endocrine Society recommends testosterone therapy in T2DM with symptomatic androgen deficiency because studies have shown that testosterone therapy improves libido and insulin sensitivity.[2] Testosterone is available in multiple formulations. It can be administered by deep intramuscular injection. It can be taken orally as tablets or capsules; it can be applied on the skin in the form of intradermal gel or a patch; it can be administered in the buccal mucosa (as an adhesive tablet), in the axilla (as 2% transdermal solution), or in the intranasal cavity (gel); or it can be implanted as pellets subcutaneously every 3 to 6 months. The choice of formulation and route of administration depends on different factors such as bioavailability, accessibility, affordability, patient preference, and formulation-specific advantages or side effects.[4,6]

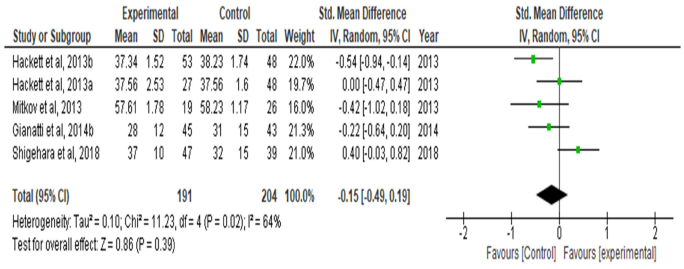


**Figure 11. Effect of testosterone replacement therapy on quality of life in men with type 2 diabetes mellitus and hypogonadism. MD, mean difference; SE, standard error**

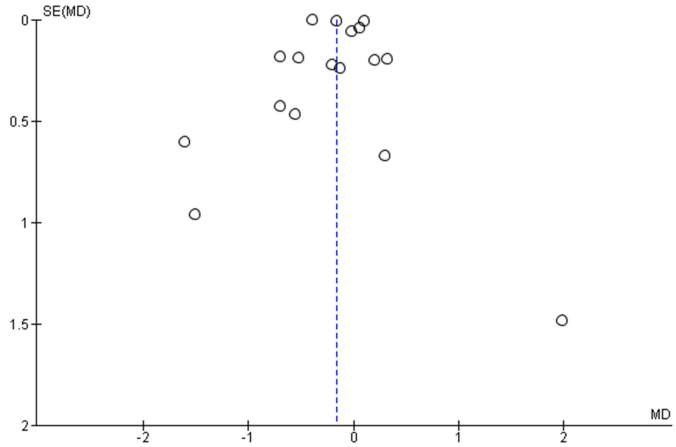


**Figure 12. Assessment of publication bias (by change of glycated hemoglobin after testosterone replacement therapy).**

This study found that a TT level of less than 11 nmol/L is the best diagnostic approach for hypogonadism in men with type 2 diabetes mellitus. This result is, however, not supported by the report of a systematic review by Majumdar et al,[4] which revealed that hypogonadism is only confirmed if TT is <8 nmol/L and that levels between 8 and 12 nmol/L require reevaluation by repeating the measurement of serum TT and SHBG. However, a serum TT level of 2.3 ng/mL (8 nmol/L) or FT of 46 pg/mL (160 pmol/L) is advised as the typical lower limit to diagnose hypogonadism in men with T2DM, per the consensus statement by the Integrated Diabetes and Endocrine Academy (IDEA) task force.[3]

es were included in the evaluation of TRT's effects on TT levels. It was found that testosterone therapy significantly increases testosterone levels, indicating that TRT improves TT levels. However, heterogeneity was high. Similarly, 5 studies were included to evaluate TRT's effect on FT levels. Overall, it was found that TRT significantly increased FT levels. The findings of this study indicated that TRT could improve glycemic control. This conclusion is supported by the result that TRT decreased HbA1c, fasting insulin, and the insulin resistance index (HOMA-IR). The meta-analysis of HbA1c and HOMA-IR indicated significant heterogeneity, and sensitivity analysis showed that the variability was mostly due to variations in treatment duration. The study showed that testosterone therapy significantly improved glycemic management as measured by HbA1c and HOMA-IR. Reductions in insulin resistance with testosterone treatment were primarily reported in randomized controlled trials (RCTs) that included males with metabolic syndrome who were not confirmed with type 2 DM.[8,41] This suggests that testosterone therapy may be more beneficial in improving glycemic outcomes in men with metabolic syndrome than in those with type 2 DM who have already developed the condition. This study found that the most effective treatment for hypogonadism in males with T2DM is transdermal testosterone gel. The consensus statement of the IDEA task force suggested the use of transdermal testosterone patches or gel (where available and affordable) in the treatment of hypogonadism among men with T2DM because it offers better bioavailability and a smoother pharmacoki netic/pharmacodynamics (PK/PD) profile and supports the findings of this study in a similar manner.[4]

The outcome of this study showed that males with T2DM and hypogonadism who underwent TRT experienced a significant improvement

in erectile performance. This finding is consistent with a related meta-analysis examining testosterone therapy's impact on sexual function in 587 T2DM males using data from 6 RCTs. The results revealed that hormone replacement had no effect on the other sexual function categories but somewhat enhanced libido and EF.[4,42] The findings of this investigation are consistent with the findings of several RCTs that evaluated the impact of TRT on the sexual function of type 2 diabetic males with hypogonadism, where a significant increase in EF was also noted.[8,9,10,15,22,43] For instance, Hackett et al,[9] found that TRT enhanced sexual function in 68 males who were attending routine clinic visits for type 2 diabetes but had not engaged in sexual activity in the previous 12 months. When men with type 2 diabetes and hypogonadism took TRT at 11$^{th}$ or 18$^{th}$ week or both, some studies saw a significant decline in EF.[9] The inconsistent nature of these findings could be explained by the fact that a combination of factors, including poor metabolic control, arteriopathy, and autonomic neuropathy, frequently causes erectile dysfunction (ED) in males with T2DM.[4]

This study revealed that TRT does not significantly affect the quality of life of men with T2DM, even though there was a slight reduction. However, individual studies reported conflicting results. Hackett et al[44] showed a significant decrease in QOL among type 2 diabetic men with severe hypogonadism who received TRT and placebo. Mitkov et al[10] found a significant improvement in QOL for both the TRT and control groups. These conflicting results support the pooled meta-analysis result of this study, which showed the absence of a relationship between TRT and QOL in hypogonadal men with T2DM. The result in this study is also comparable with another meta-analysis across 3 RTCs that revealed a consistent, nonsignificant effect of testosterone on quality-of-life scores among diabetic men with hypogonadism.[42] Contrasting results were also reported from studies conducted among nondiabetic patients with hypogonadism. For example, Behre et al,[45] in their RCT to assess the effect of testosterone gel on health-related QOL of men with hypogonadism, reported a significant improvement in QOL among hypogonadal men that received testosterone gel as compared to the placebo group. Another RCT by Giltay et al[46] found a similar result, where TRT was found to improve the QOL of hypogonadal men with metabolic syndrome. However, a different result was reported from a study that assessed the effect of TRT on QOL among testicular cancer survivors with mild Leydig cell insufficiency. The study showed that TRT did not improve the overall quality of life in patients with mild Leydig cell insufficiency compared to placebo.[47]

There is limited research on the impact of testosterone therapy on depressive symptoms in hypogonadal T2DM men. This meta-analysis has shown that TRT does not significantly affect depression among hypogonadal men with T2DM. However, individual RCTs reported conflicting results. For instance, Hackett et al[11] reported a significant improvement in depression among type 2 diabetic men with mild hypogonadism but no significant change among those with severe hypogonadism. Similarly, some RCTs among nondiabetic males with hypogonadism and depression have demonstrated conflicting outcomes. A small RCT with 23 men with depressive illness and mild hypogonadism discovered that testosterone therapy successfully reduced several depression severity scores.[48] Another small RCT among 33 men aged 50 years or older with moderate-to-severe hypogonadism found a significant improvement in depression among those treated with testosterone compared to the placebo group.[49] In contrast to the findings above, an RCT comprising 100 adult men with major depressive illness and mild hypogonadism found no evidence of a significant improvement in depression between the group receiving TRT and the group receiving placebo.[50] Overall, these RCTs support the conclusion of this study that testosterone replacement treatment does not significantly affect individuals with subnormal serum TT levels' mood.[4,48,49] Furthermore, a meta-analysis of 7 RCTs that assessed the effect of TRT on depression among nondiabetic men with hypogonadism or human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) showed a significant positive effect of TRT on depressed patients when compared with placebo in both hypogonadal and HIV/AIDS patients.[51]

The outcome of this meta-analysis showed that a blood TT level of less than 11 nmol/L is the best cutoff point for diagnosing hypogonadism in males with T2DM. Transdermal testosterone gel was the most effective treatment for hypogonadal men with T2DM. In type 2 diabetic males with hypogonadism, TRT significantly improved glycemic control and insulin resistance. Testosterone replacement therapy had no appreciable impact on depression or quality of life, but it significantly enhanced EF and libido in men with type 2 diabetes mellitus and hypogonadism.

In line with this study's findings, it is recommended that men with type 2 diabetes mellitus and symptoms of hypogonadism be screened for hypogonadism and diagnosed if their serum TT level falls below 11 nmol/L. However, all type 2 diabetic men with a TT of <11 nmol/L and or sexual dysfunction (erectile dysfunction or lack of sexual desire) should receive TRT, preferably using daily transdermal testosterone gel.

The small number and small size of included studies, the lack of access to patient-level data, and the fact that included studies only sometimes fully comply with CONSORT reporting guidelines, which may reduce the precision of some estimations, are all limitations of this analysis. Also, the meta-analysis included various testosterone therapy dosages and modes of administration, which could have affected how TRT affected the outcomes that were measured. Finally, only a small number of studies were considered when depression and quality of life were examined, which could have led to incorrect conclusions.

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