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Effects of testosterone therapy in adult males with hypogonadism and T2DM: A meta-analysis and systematic review

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ABSTRACT

Background and aims: Testosterone supplementation therapy (TST) is a longstanding treatment for hypogonadal men with type 2 diabetes mellitus (T2DM), even though the benefits of TST are variable among trials. This meta-analysis was done to determine the specific role of TST in hypogonadal men with T2DM.

Methods: PubMed, Embase, and Google Scholar were queried to discover eligible randomized controlled trials (RCTs) and observational studies. To quantify the specific effects of TST, we estimated pooled mean differences (MDs) and relative risks with 95% confidence intervals (CIs).

Results: Our meta-analysis included 1596 hypogonadal T2DM subjects from 12 randomized controlled trials and one observational study. TST can significantly enhance glycemic control compared to placebo by decreasing homeostatic model assessment of insulin resistance (WMD = −1.55 [-2.65, −0.45]; p = 0.26; I2 = 20.2%), fasting glucose (WMD = −0.35 [-0.79, 0.10]; p = 0.07; I2 = 69.7%), fasting insulin (WMD = −2.88 [-6.12, 0.36]; p = In addition, TST can decrease cholesterol (WMD = −0.28 [-0.47, −0.09] p = 0.0008; I2 = 91%) and triglyceride (WMD = −0.23 [-0.43, −0.03] p = 0.03; I2 = 79.2%). Furthermore, Testosterone therapy is related to a significant rise in total testosterone levels (WMD = 5.08 [2.90, 7.26] p = 0.0002; I2 = 92.9%). Pooling of free testosterone levels indicated a larger increase in the patients who got TST than placebo (WMD = 81.21 [23.87, 138.54] p = 0.07; I2 = 70%).

Conclusion: Our findings suggested that TST can enhance glycemic control and hormone levels and reduce total cholesterol, triglyceride, LDL cholesterol whereas increase HDL cholesterol in hypogonadal T2DM patients. Therefore, in these patients, we propose TST alongside anti-diabetic treatment.

1. Introduction

According to the 2018 Endocrine Society Clinical Practice Guidelines, hypogonadism is a clinical syndrome caused by the testis's inability to produce physiological testosterone levels or a normal percentage of spermatozoa due to pathology in one or more hormonal concentrations of the hypothalamic-pituitary-testicular axis [1]. The prevalence of hypogonadism in the general population ranges from 5 to 12.3% in men aged 30 to 79, with an incidence

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of 12.3 per 1000 inhabitants/year.2 Male hypogonadism is diagnosed when patients exhibit symptoms and signs of testosterone deficiency and consistently low serum total testosterone and free testosterone concentrations [1]. Free testosterone concentrations less than 225 pmol/l (65 pg/ml) are considered diagnostic and support the use of replacement therapy [2]. Hypogonadism can significantly impact patients' multiple organ functions and quality of life and has developed into a global medical issue. Numerous studies have recently established a link between type 2 diabetes mellitus (T2DM) and hypogonadism. This is because obesity is a strong risk factor for testosterone deficiency (TD), which further increases fat accumulation, insulin resistance (IR), and glycemic control deterioration, constructing a negative spiral [3]. Around 25%–33% of men with T2DM have hypogonadotropic hypogonadism, which has been implicated as a risk factor for developing T2DM. There is a growing and sometimes contradictory body of research examining whether testosterone should be used in the standard clinical management of T2DM [4].

Numerous studies have demonstrated that testosterone therapy improves metabolic syndrome (MetS) components, lipid profile, decreases fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) levels, improves insulin sensitivity, reduces inflammation, and decreases systolic as well as diastolic blood pressures in males with T2DM [5]. Additionally, long-term testosterone therapy has been proposed to prevent prediabetes progression to T2DM in men with hypogonadism and improve the quality of life as measured by the Aging Males' Symptoms (AMS) questionnaire [5]. Nevertheless, some studies produced contradictory findings. For example, several studies have shown that testosterone replacement therapy (TRT) can significantly reduce the homeostatic model assessment of insulin resistance (HOMA-IR) levels, fasting serum glucose (FSG), fasting serum insulin (FSI), and HBA1C percentage in hypogonadal patients with T2DM [6]. Moreover, other data indicated that these indicators did not decrease significantly in TRT groups. TRT has been associated with improvements in lipid panel variables such as total cholesterol (TC), triglycerides (TG), and serum low-density lipoprotein (LDL) cholesterol, as well as an increase in serum high-density lipoprotein (HDL) cholesterol in some studies [7,8]. Other studies failed to demonstrate a statistically significant improvement in lipid metabolism.

Meta-analysis is a research method used to systematically synthesize or merge the findings of single, independent studies, using statistical methods to calculate an overall or absolute effect, and test how sensitive their results are to their own systematic review protocol (study selection and statistical analysis). Only a few randomized control trials and observational studies have been conducted to investigate the role of TRT in male hypogonadism associated with TDM, and the majority of them have produced inconsistent findings. As a result, we conducted a systematic review and meta-analysis to ascertain the exact role of TRT in hypogonadal men with T2DM. To the best of our knowledge, this is the first recently updated meta-analysis that compares the various effects of testosterone therapy versus the control arm having placebo or no treatment.

2. Materials and methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) [9].

2.1. Search strategy

A thorough search was conducted on PubMed (Medline) and Cochrane from the study's beginning until the 5th of May 2022. Grey literature and preprints were identified by searching Clinical Trials.gov, Google Scholar, and Medrxiv. Utilizing Medical Subject Headings (MESH terms) and keywords, a search strategy was developed that contained ['Testosterone' OR 'TST' OR Testosterone undecanoate] AND ['Hypogonadism' OR 'Hormonal deficit'] AND [Diabetes Mellitus']. The search approach is specified in Table S1. The search results were not filtered or restricted in any way. Using Google's translate function, non-English language text was translated. Manual searches of review articles extracted relevant studies. Titles, complete texts, and abstracts of papers were separately examined by two reviewers (MK and SK). Relevant studies were imported into Endnote X9 (Clarivate Analytics, US) to eliminate duplications.

2.2. Eligibility criteria

2.2.1. Inclusion criteria

Studies included were selected based on the following: language, study design, patient population, intervention, comparison, outcomes of interest, and definition.

- English publications;
- Study design: Eligible completed randomized clinical trials or observational studies were extracted to perform the meta-analysis.
- Patient population: patients with confirmed type 2 diabetes who met the criteria of hypogonadism.
- Exposure: Patients who received testosterone therapy.
- Comparison: This includes the non-TST group, which received the usual standard of care or placebo.
- Outcomes of interest: effects on glucose metabolism, cholesterol levels, BMI, waist circumference, body fat, systolic and diastolic blood pressure, and post-treatment hormonal levels.

2.2.2. Exclusion criteria

To preserve the quality of this meta-analysis, the following significant exclusion criteria were outlined:

- No clear definitions of the diagnosis of late-onset hypogonadism and T2DM, population, amount and serving method of testosterone, or outcome assessment
- No placebo or treatment groups
- Insufficient data for estimating a mean difference (MD) with a 95% confidence interval (CI)
- Duplicates of previous publications

In addition, all included RCTs were evaluated based on the 25-item CONSORT checklists, which emphasize describing how the trials were conceived, analysed, and interpreted (Table S2). The quality of the included RCTs was evaluated based on the number of the 25 items that were reported. A correlation exists between the number of reported items and the quality of an RCT. High-quality research will report all 25 criteria.

2.3. Data Extraction

Two researchers (MK and SK) independently assessed the selected studies to determine whether a particular article should be included. A dialogue examined and resolved uncertain data. The following essential variables were retrieved from each study: first author's name, publication year, country, ethnicity, testosterone cut-off point, diabetes duration, testosterone regimen, drugs on comparators, mean age, Hba1c percentage, and total serum testosterone level. Table 1 details the previously mentioned data. Homeostatic model assessment of insulin resistance (HOMA-IR),

Table 1
Baseline characteristics of included studies.

Study	Study design	Total no of patients	Hypogonadism cut off point	No of patients		Age (Mean ± SD)		Waist circumference (cm) (Mean ± SD)		BMI (kg/m2) (Mean ± SD)	
				TRT	Placebo	TRT	Placebo	TRT	Placebo	TRT	Placebo
Dhindsa (2015) [13]	RCT	34	FT < 225 pmmol/L	20	14	**54.6 ± 7.9**	**54.6 ± 7.9**	**128 ± 20**	**124 ± 30**	**39.0 ± 7.6**	**39.4 ± 7.9**
Gianatti (2014) [8]	RCT	67	TT < 12 nmmol/L	37	30	62 ± 2.5	62 ± 2.5	110 ± 4.2	115 ± 2.75		
Hackett (2014) [14]	RCT	186	TT < 12 nmmol/L	91	95	61.2 ± 10.5	62.0 ± 9.3	115.1 ± 13.1	112.6 ± 13.3	33.0 ± 6.1	32.4 ± 5.5
Jones (2011) [15]	RCT	137	TT < 11 nmmol/L	68	69	59.9 ± 9.1	59.9 ± 9.4	112.7 ± 13.35	111.7 ± 15.23	32.76 ± 6.12	31.56 ± 5.87
Gopal (2010) [16]	RCT crossover	22	FT < 225 pmmol/L	22	22	44.23 ± 3.29	44.23 ± 3.29	93.25 ± 7.03	84.10 ± 13.86	25.44 ± 3.57	22.10 ± 4.93
Heufelder (2009) [17]	RCT	32	TT < 11 nmmol/L	16	16	57.3 ± 1.4	55.9 ± 1.5	107.9 ± 1.3	105.7 ± 1.4	32.1 ± 0.5	32.5 ± 0.6
Kapoor (2006) [18]	RCT crossover	27	TT < 12 nmmol/L	24	24	64 ± 1.34	64 ± 1.34	115.1 ± 2.4	115.1 ± 2.4	33 ± 0.86	33 ± 0.96
Boyanov (2003) [19]	RCT	48	TT < 15 nmmol/	24	24	57.5 ± 4.8	57.5 ± 4.8	N/A	N/A	31.08 ± 4.79	31.01 ± 4.90
Hackett (2018) [20]	RCT	537	TT < 12 nmmol/L	175	362	58.3 ± 11	65.5 ± 11.8	N/A	N/A	32.6 ± 6.4	31.7 ± 5.9
Yassin (2019) [12]	Observational study	316	TT < 12.1 nmol/L	229	87	58.2 ± 9.6	66.4 ± 7.2	104.2 ± 7	101.1 ± 9.9	30.7 ± 4.1	29.8 ± 3
Khirpun (2018) [21]	RCT	80	serum levels of total testosterone two times below 12.1 nmol/L or serum levels of free testosterone two times below 243 pmol/L in combination of at least two symptoms or complaints of sexual or psychological nature	40	40	53.3 ± 5.4	54.1 ± 5.6	114.3 ± 9.5	114.7 ± 9.8	34.0 ± 2.6	33.6 ± 2.9
Groti (2020) [5]	RCT	55	(total testosterone [TT] below 11 nmol/L and free testosterone below 220 pmol/L) on at least two separate morning measurements after an overnight fast in addition to exhibiting at least two symptoms of sexual dysfunction (less frequent morning e	28	27	58.21 ± 7.94	62.19 ± 5.90	116.48 ± 5.07	115 ± 1.47	34.03 ± 4.37	32.63 ± 3.67
Groti (2018) [22]	RCT	55	total testosterone (TT) level <11 nmol/l and/or free testosterone (FT) level <220 pmol/l	28	27	N/A	N/A	116.48 ± 5.07	116.64 ± 4.96	34.03 ± 4.37	32.63 ± 3.67

SD: Standard deviation, Ft: free testosterone, TT: total testosterone.

fasting plasma glucose (FSG), fasting serum insulin (FSI), HbA1c, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholestreol, body fat, BMI index, systolic and diastolic blood pressure (SBP and DBP), Aging male score (AMS) and international (IIEF).

2.4. Study quality assessment

The modified Cochrane Collaboration's risk of bias tool was used to assess the quality of published RCTs [10], observational studies were assessed using New Castle Ottawa scale [11].

2.5. Statistical analysis

Review Manager 5.4 (Cochrane Collaboration) software was used to conduct the proposed meta-analysis. Relative risks (RRs) and their respective 95% confidence intervals (CI) were retrieved for dichotomous outcomes. Continuous outcomes were given with mean values and standard deviations. This meta-analysis presents a pooled effect of relative risks (RRs) and weighted mean differences (WMDs) calculated using the generic-inverse variance and continuous outcome functions with a random-effects model. All p values less than 0.05 were deemed statistically significant. Funnel plots for all outcomes were visualized to assess publication bias.

Using I2 statistics, heterogeneity between trials was measured and reported as a percentage. Low heterogeneity was indicated by an I2 value of 25%, moderate heterogeneity between 25% and 50%, and high heterogeneity by an I2 value above 50%. Results from studies with a significant proportion of heterogeneity were subjected to sensitivity analysis to determine how each study affected the pooled estimate.

Table 2
Baseline glucometabolic, lipid and blood pressure parameters.

Study	Fasting plasma glucose (mmol/L) (Mean ± SD)		Fasting serum insulin (Mean ± SD)		HbA1c %		Free testosterone (Mean ± SD)		Total testosterone (Mean ± SD)		HOMA-IR (Mean ± SD)		Mean total cholesterol (Mean ± SD)		Systolic blood pressure (Mean ± SD)		Diastolic blood pressure (Mean ± SD)	
	TRT	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**	**TRT**	**Placebo**
Dhindsa (2015) [13]	**6.99 ± 0.44**	**6.60 ± 0.55**	**13.6 ± 3**	**11.8 ± 2.2**	**6.8 ± 0.9**	**7 ± 1.4**	**156.5 ± 45.11**	**145.74 ± 41.6**	**9 ± 2.9**	**8.3 ± 2.8**	**9 ± 2.9**	**8.3 ± 2.8**	**4.06 ± 0.98**	**4.03 ± 0.95**				
Gianatti (2014) [8]	9.57 ± 3.78	9.11 ± 3.65	N/A	N/A	7.7 ± 1.3	7.5 ± 1.2	187.7 ± 57.0	181.2 ± 63.6	9.2 ± 3.1	8.9 ± 3.8	4.1 ± 2.0	3.7 ± 2.6	4.15 ± 0.90	4.08 ± 0.9	140.2 ± 15.9	137.1 ± 13.0	79.4 ± 9.4	77.5 ± 8.9
Hackett (2014) [14]	9.05 ± 3.18	8.49 ± 2.84	20.88 ± 22.83	18.17 ± 15.7	N/A	N/A	198 ± 49.3	202.4 ± 62.1	9.2 ± 2.6	9.5 ± 3.3	5.9 ± 3.8	4.9 ± 3.3	4.51 ± 1.17	4.55 ± 1.01	138.6 ± 17.30	136.7 ± 17.12	82.5 ± 10.23	81.6 ± 9.50
Jones (2011) [15]	7.9 ± 4.3	9.2 ± 3.4	12.80 ± 8.95	17.86 ± 24.72	6.43 ± 2.20	7.69 ± 2.77	177.57 ± 60.19	177.57 ± 60.19	10.1 ± 3.7	10.1 ± 3.7	5.50 ± 6.82	6.45 ± 8.75	4.7 ± 0.9	4.0 ± 1.0	115.83 ± 5.15	118.40 ± 9.97	82.00 ± 6.93	79.00 ± 3.16
Gopal (2010) [16]	7.9 ± 0.2	8.3 ± 0.2	19.03 ± 0.63	16.8 ± 0.87	7.5 ± 0.1	7.5 ± 0.1	200 ± 0.00	200 ± 0.00	10.5 ± 0.2	10.4 ± 0.2	5.6 ± 0.3	6.1 ± 0.4	N/A	N/A	104.5 ± 2.6	143.5 ± 2.1	85.6 ± 0.9	85.0 ± 1.0
Heufelder (2009) [17]	7.83 ± 0.49	7.6 ± 0.43	13.68 ± 1.95	12.37 ± 1.87	7.28 ± 0.19	7.28 ± 0.19	N/A	N/A	8.63 ± 0.51	8.63 ± 0.51	N/A	N/A	5.11 ± 0.17	4.95 ± 0.15	127.6 ± 2.8	131 ± 3.1	74 ± 1.4	74 ± 1.4
Kapoor (2006) [18]	8.0 ± 2.6	8.4 ± 2.8	N/A	N/A	10.4 ± 1.6	10.3 ± 1.6	N/A	N/A	9.56 ± 2.33	10.76 ± 3.0	N/A	N/A	5.50 ± 1.41	5.59 ± 1.49	122 ± 8	120 ± 8	80 ± 4	76 ± 6
Boyanov (2003) [19]	N/A	N/A	N/A	N/A	7.6 ± 1.3	7.5 ± 1.5	210 ± 124.5	175 ± 67.9	9.7 ± 4.4	8.9 ± 3.2	N/A	N/A	4.5 ± 1.1	4.1 ± 1.0	141.8 ± 16.1	139.4 ± 16.8	81.4 ± 10.4	78.2 ± 10.4
Hackett (2018) [20]	5.3 ± 0.8	4.9 ± 1.3	N/A	N/A	5.9 ± 0.2	5.9 ± 0.2	N/A	N/A	8.2 ± 2.1	9.6 ± 2.4	N/A	N/A	6.9 ± 1.2	6.4 ± 1.4	136.9 ± 13.5	129.8 ± 12.7	81.2 ± 8.9	84.7 ± 6.7
Yassin (2019) [12]	8.1 ± 3.7	8.7 ± 5.0	N/A	N/A	7.8 ± 2.4	7.9 ± 2.4	208 ± 142	223 ± 140	9.6 ± 2.7	9.9 ± 2.6	N/A	N/A	6.1 ± 1.2	5.9 ± 1.5	N/A	N/A	N/A	N/A
Khirpun (2018) [21]	10.06 ± 1.44	9.77 ± 1.40	N/A	N/A	8.12 ± 1.04	7.89 ± 0.77	208 ± 142	223 ± 140	7.24 ± 1.97	7.96 ± 1.34	11.45 ± 7.34	10.82 ± 6.52	5.31 ± 0.91	5.11 ± 0.85	134.64 ± 10.71	138.15 ± 13.24	77.50 ± 5.85	78.89 ± 5.25
Groti (2020) [5]	10.06 ± 1.44	9.60 ± 1.44	26.03 ± 15.86	24.89 ± 13.90	8.12 ± 1.04	7.89 ± 0.77	N/A	N/A	7.24 ± 1.97	7.96 ± 1.34	11.45 ± 7.34	10.70 ± 6.52	5.31 ± 0.91	5.31 ± 0.97	134.64 ± 10.71	138.15 ± 13.24	77.50 ± 5.85	78.89 ± 5.25
Groti (2018) [22]	10.06 ± 1.44	9.60 ± 1.44	26.03 ± 15.86	24.89 ± 13.90	8.12 ± 1.04	7.89 ± 0.77	N/A	N/A	7.24 ± 1.97	7.96 ± 1.34	11.45 ± 7.34	10.70 ± 6.52	5.31 ± 0.91	5.31 ± 0.97	134.64 ± 10.71	138.15 ± 13.24	77.50 ± 5.85	78.89 ± 5.25

SD: Standard deviation, HOMA-IR: Homeostasis model of insulin resistance, HbA1c: glycated hemoglobin.

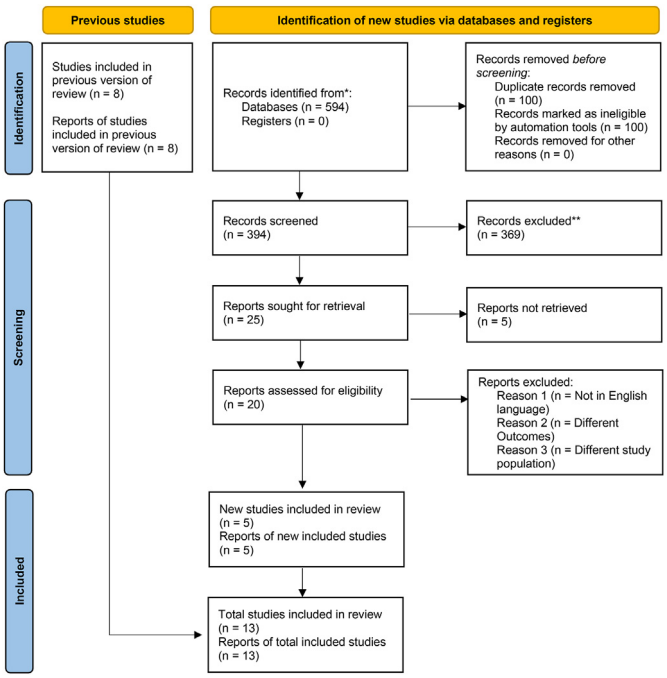


Fig. 1. Prisma flow chart.

3. Results

3.1. Study selection

A total of 247 articles were identified from the preliminary literature search. After eliminating duplicated articles and based on title and abstract, a total of 13 studies (1 observational [12] and 12 RCTs [5,8,13–22]) were included in this meta-analysis. Characteristics of included studies are reported in (Supplementary Tables S2 and S3)

3.2. Baseline characteristics

Totalling 1596 participants, the 13 studies included people who met the clinical definition of hypogonadism, with 802 receiving testosterone and 837 receiving a placebo. At least three sexual symptoms and total testosterone (TT) or TT12 nmol/L were considered hypogonadism in five studies [8,12,14,18,20], while TT15 nmol/L or free testosterone (FT) 225 pmol/L was defined as hypogonadism in other studies [5,13,15–17,19,21,22]. The primary testosterone regimen varied among the studies that were enrolled. One [19], three [15,17,21], and nine [5,8,12–14,16,18–20,22] studies respectively used oral testosterone, testosterone gel by intradermal injection, and testosterone by deep intramuscular injection. There were a variety of dosages and timings for testosterone use in these investigations. Double-blind placebo-controlled studies accounted for ten [5,8,13–16,18,20–22] of the 12 RCTs, whereas the other two [17,19] was conducted with no control group. As indicated by the research type, Tables 1 and 2 provides information on participants' baseline characteristics, medical conditions, hormone levels, and glycaemic indices.

3.3. Quality assessment and publication bias

Using the New Castle Ottawa scale to assess the quality of studies, it was determined that the observational study had a low risk of bias (Supplementary Table 4). The Cochrane method of evaluating RCTs indicated trials of fair to good quality (Supplementary Table 5). The funnel plots demonstrated that the quantitative results were not affected by publication bias (Supplementary Fig. S1) (see Fig. 1).

3.4. The effects on glucometabolism (Fig. 2)

The effects of testosterone on glucometabolism were evaluated using the variables HOMA-IR, HbA1c, fasting serum glucose (FSG), and fasting serum insulin (FSI). The data on HOMA-IR was reported by 8 [5,8,13,14,16,17,21,22] out of 13 studies and revealed that therapy with testosterone lowered HOMA-IR levels to a greater level than placebo (WMD = −1.55 [−2.65, −0.45]; p = 0.26; I2 = 20.2%). Similarly, 12 [5,8,12–19,21,22] out of 13 studies recorded FSG, and patients in the testosterone group showed a higher reduction in FSG following treatment than those in the placebo group (WMD = −0.35 [−0.79, 0.10]; p = 0.07; I2 = 69.7%). Seven [8,13,15–18,22] out of thirteen studies found that post-treatment patients in the testosterone group had a higher reduction in FSI levels (WMD = −2.88 [−6.12, 0.36]; p = 0.38; I2 = 0%). Eleven [5,8,12–14,16,17,19–22] of thirteen studies provided HbA1c levels, and pooled analysis found that testosterone treatment was linked with a greater reduction in post-treatment HbA1c levels (WMD = −0.35 [−0.64, −0.06] p = 0.17; I2 = 47.5%).

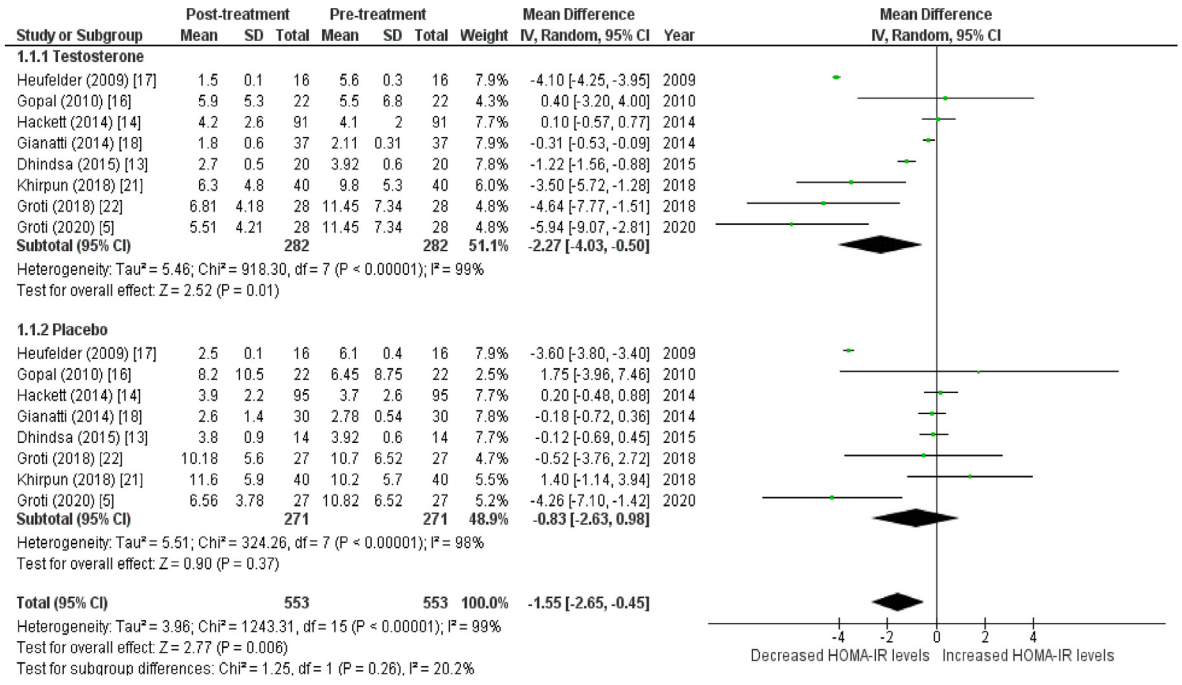
3.5. The effect on lipid parameters (Fig. 3)

All of the recruited studies have demonstrated the effect on lipid metabolism by TST. The effect on lipid metabolism was examined by considering the following parameters: total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol levels. Total cholesterol level was reported in 12 [5,8,12–16,18–22] out of 13 articles. Our meta-analysis demonstrated that cholesterol levels was reduced to a larger extent post-treatment in testosterone group compared to the placebo group (WMD = −0.28 [−0.47, −0.09] p = 0.0008; I2 = 91%). On the other hand, triglyceride levels and HDL cholesterol levels were studied in all 13 [5,8,12–22] studies and showed that treatment with testosterone was associated with a significant reduction in the levels of triglyceride (WMD = −0.23 [−0.43, −0.03] p = 0.03; I2 = 79.2%) and increase in the level of HDL cholesterol (WMD = 0.07 [0.00, 0.13] p = 0.80; I2 = 0%) after treatment with testosterone. LDL cholesterol level was specified in 11 [5,8,12–16,18,19,21,22] out of 13 studies, and there was no significant difference between the pretreatment and posttreatment values among the two groups (WMD = 0.03 [−0.42, 0.48] p = 0.77; I2 = 0%)

3.6. The effect on blood pressure, body fat percentages and BMI indexes (Fig. 4)

Diastolic (DBP) and systolic blood pressure (SBP) were reported by 11 out of 13 studies [5,8,12,14–20,22] and pooled analysis revealed that treatment with testosterone was associated with a decrease in DBP (WMD = −1.04 [−2.42, 0.34] p = 0.25; I2 = 23.2%) whereas a slight increase in SBP was seen after treatment with testosterone compared to placebo (WMD = 0.42 [−5.82, 6.66] p = 0.55; I2 = 0%). In addition to the above results, our study also considered body fat, waist circumference, and BMI index. 3 out of 13 studies [15,18,19] provided body fat, and a pooling of these studies demonstrated that therapy with testosterone was linked with a reduction in body fat (WMD = −0.75 [−1.17, −0.34] p = 0.30; I2 = 6.4%). In addition, the waist circumference was reported by 10 out of 13 studies [5,8,12–16,18,21,22] that reported that testosterone therapy was related to a higher reduction in waist circumference following treatment (WMD = −0.90 [−2.36, 0.56] p = 0.03;

A



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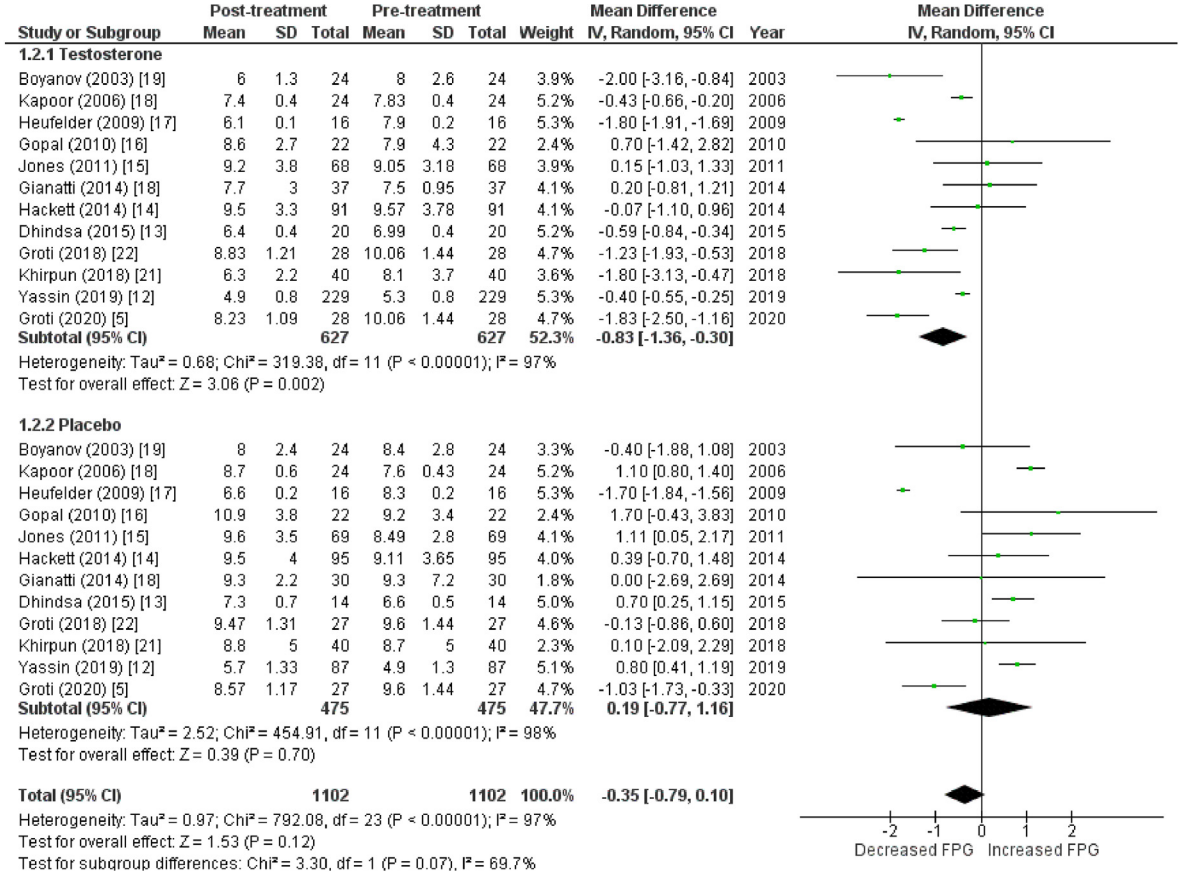
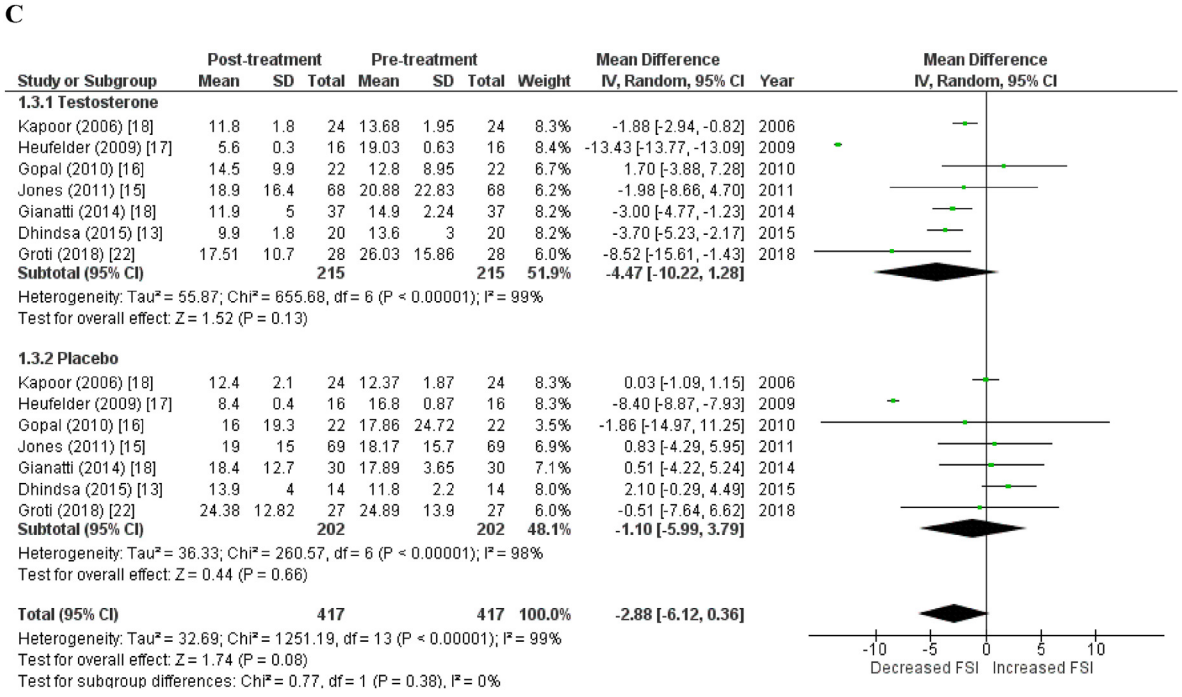


Fig. 2. Effects on Glucometabolism; A = HOMA-IR (Homeostatic model assessment for insulin resistance), B= FSG (Fasting serum glucose), C= FSI (Fasting serum insulin), D = HbA1C (Glycated hemoglobin), WMD = weighted mean difference, CI = confidence interval.

I2 = 79.2%). BMI index was included in 11 out of 13 researches [5,8,13–16,18–22], and our analysis revealed that Testosterone therapy was related to a higher reduction after follow-up than placebo (WMD = −0.16 [−0.45, 0.14] p = 0.58; I2 = 0%).

3.7. The effects on AMS and IIEF scores (Fig. 5)

Only 3 of 13 studies [12,14,15] reported AMS and IIEF scores, and their pooled analysis revealed that treatment with testosterone was related with a significant increase in IIEF scores (WMD = 2.59



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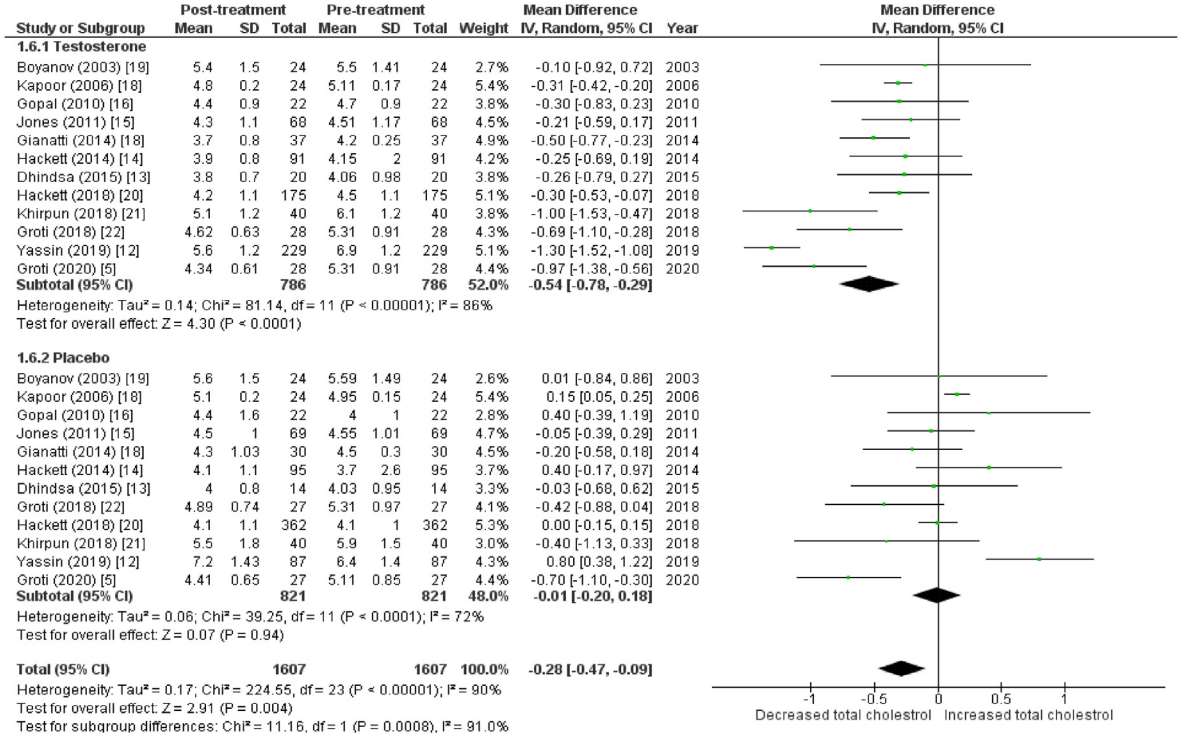

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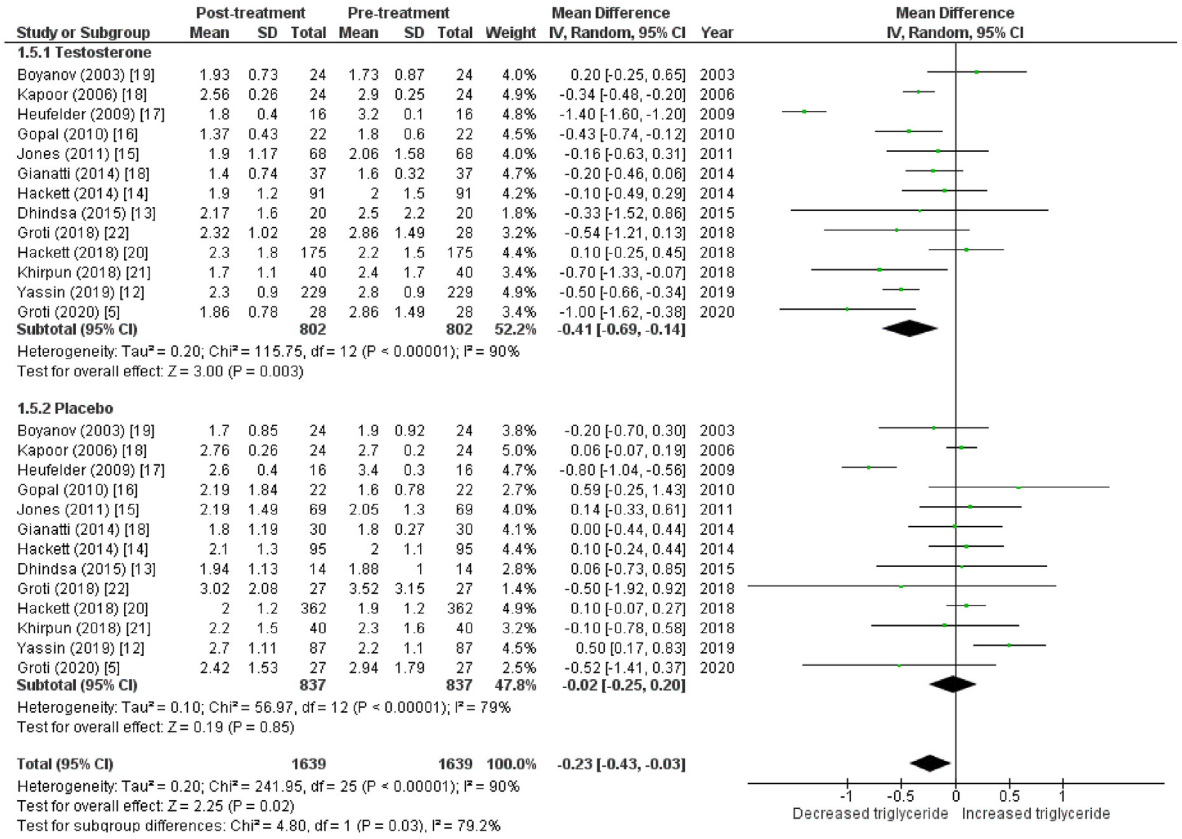

Fig. 3. Effects on lipid parameters; A = Total serum cholesterol, B = triglycerides, C= HDL (high density lipoprotein), D = LDL (LDL cholesterol), WMD = weighted mean difference, CI = confidence interval.

[−3.22, 8.39] p = 0.04; I2 = 75.6%) but a decrease in AMS (WMD = −6.45 [−16.25, 3.35] p = 0.10; I2 = 62.3%)

3.8. Mortality (Fig. 6)

The data on mortality was reported by only two studies [14,20] and their pooling revealed that testosterone therapy was associated

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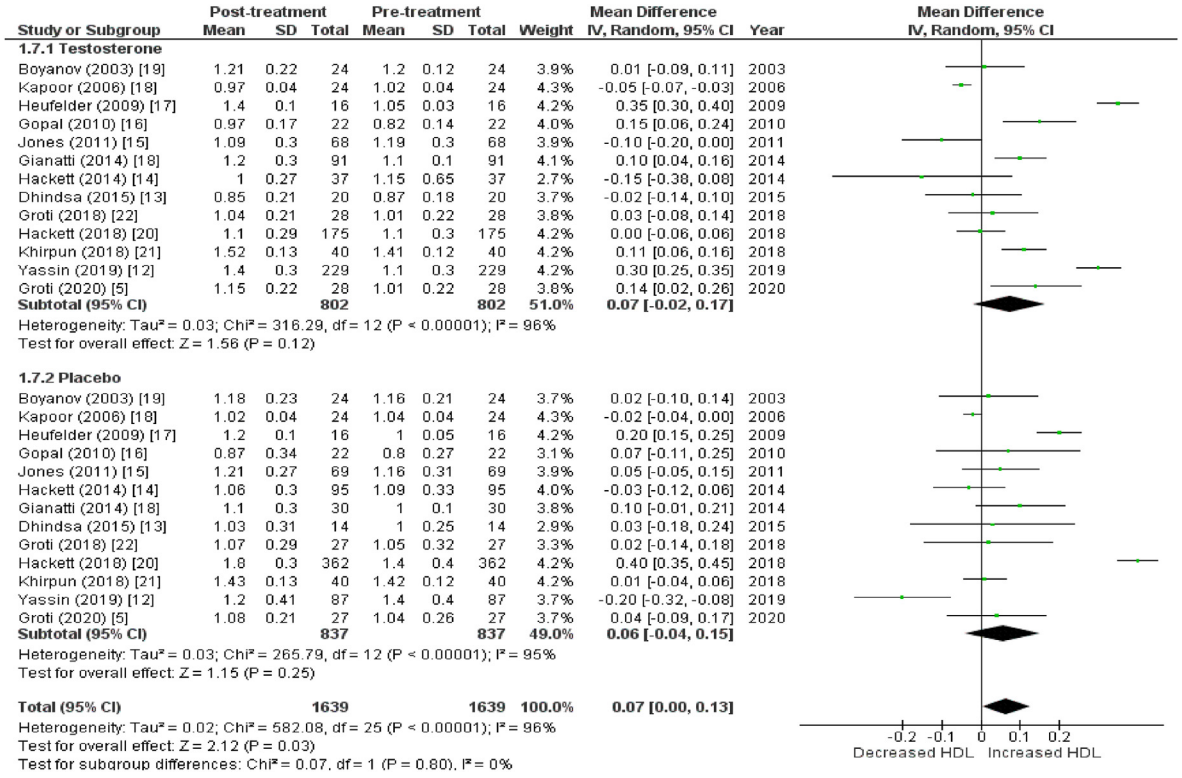

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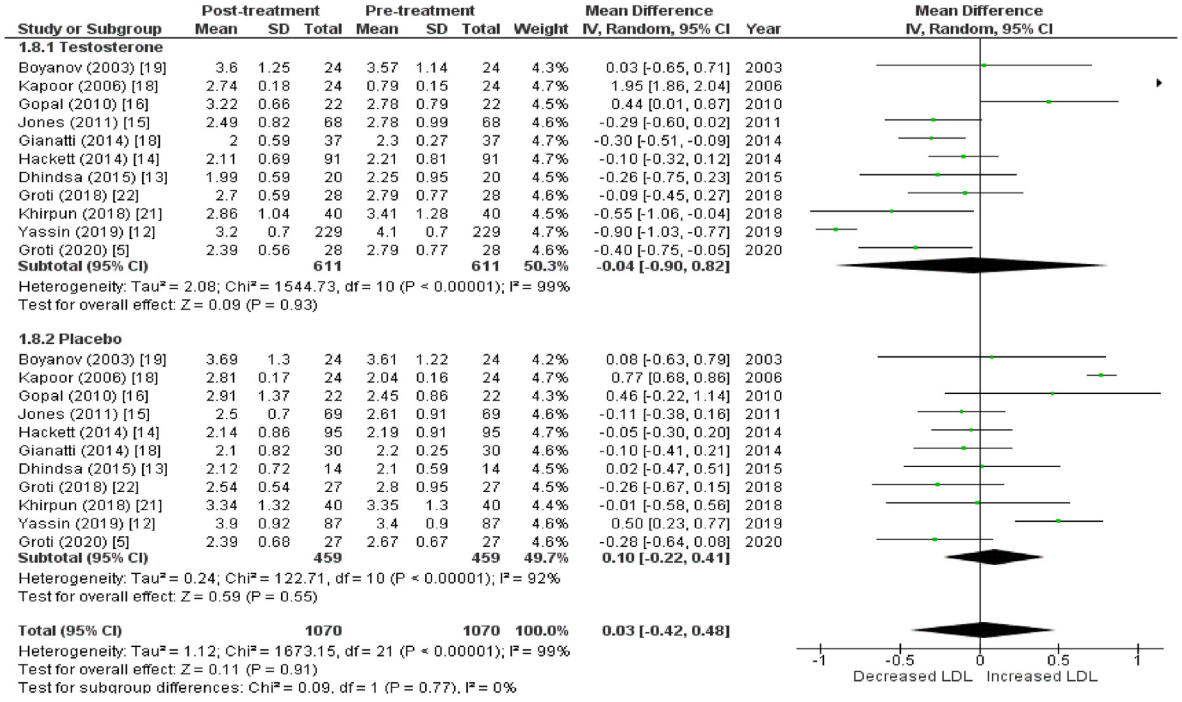

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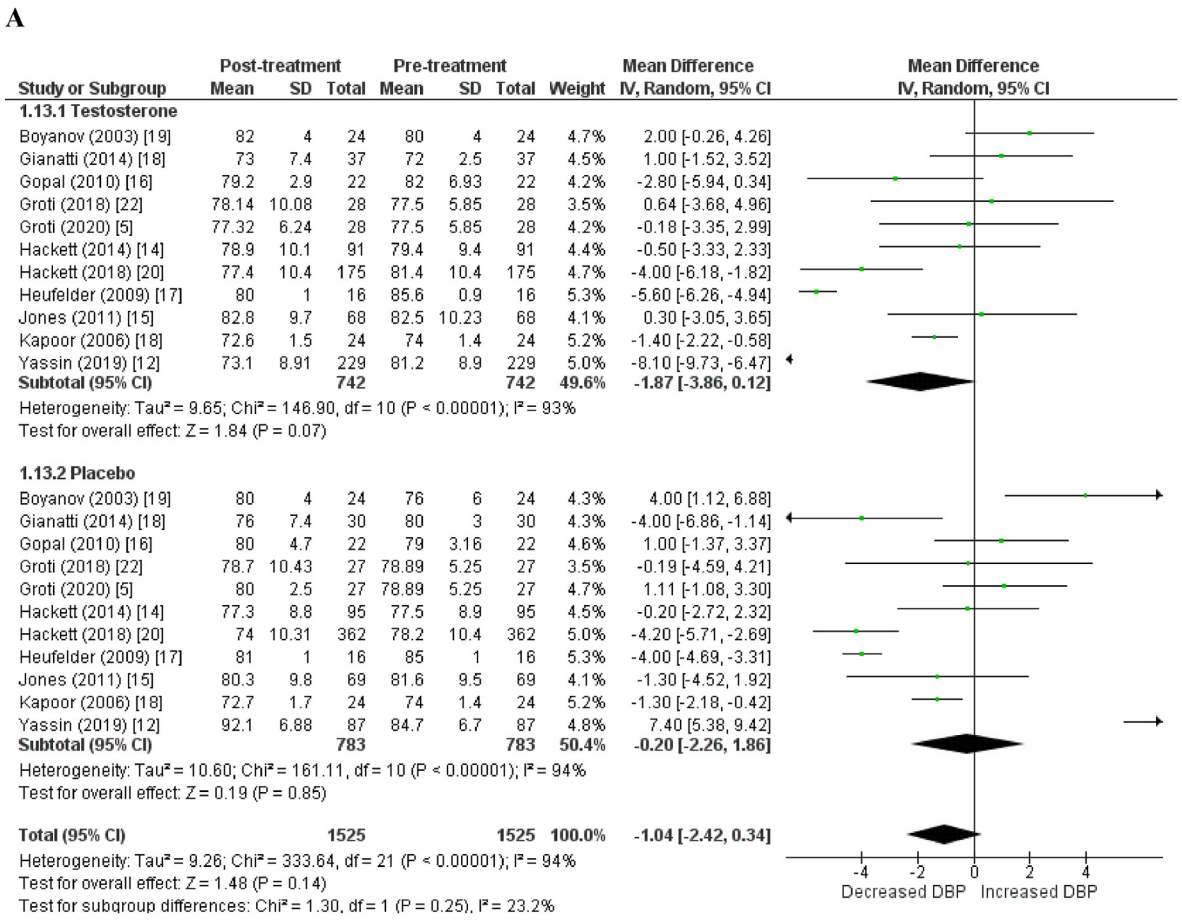

Fig. 4. Effects on blood pressure, body fat percentages and BMI indexes; A = DBP (Diastolic blood pressure), B= SBP (Systolic blood pressure), C= Body fat, D = Waist circumference, E = BM1.

with a significant decrease in mortality risk compared to placebo (RR = 0.21 [0.10, 0.46] p = 0.0001; I2 = 0%)

3.9. The effects on hormonal levels (Fig. 7)

To evaluate the influence of testosterone on the level of hormones following variables were taken into consideration: total testosterone, free testosterone, SHBG and PSA. 7 publications [5,12,13,18,19,21,22] had included total testosterone levels, and the pooled analysis showed that testosterone therapy is related to a significant rise in total testosterone levels (WMD = 5.08 [2.90, 7.26] p = 0.0002; I2 = 92.9%). Excluding the studies one-by-one from the pooled analysis did not reduce the in-study heterogeneity.

Free testosterone levels were evaluated in 3 papers [13,14,21], and their pooling indicated a substantially larger increase in the patients who got testosterone therapy than placebo (WMD = 81.21 [23.87, 138.54] p = 0.07; I2 = 70%). SHBG level was included in 4 studies [13,17,21,22] and pooling revealed a higher drop in SHBG level was associated with treatment with testosterone (WMD = −3.24 [−6.33, −0.14] p = 0.80; I2 = 0%). PSA levels were evaluated in 6 studies [8,13–15,17,21], and their analysis found no clinically significant difference in the PSA levels after therapy among the two groups (WMD = 0.06 [−0.02, 0.13] p = 0.47; I2 = 0%)

4. Discussion

Numerous studies have demonstrated the association between T2DM and hypogonadism. Hypogonadism is more prevalent in T2DM patients than in the general population, which may be due to the activation of the insulin signalling pathway [6]. This comprehensive systematic review and meta-analysis of 13 studies comprising of 1596 patients compared outcomes of testosterone supplemental therapy group versus control arm group in hypogonadal males with type 2 diabetes mellitus (T2DM). According to guidelines of Society of Endocrinology, testosterone treatment is required to reverse or prevent the symptoms and long-term effects of male hypogonadism because it induces or completes secondary sexual development; improves sex drive, libido, and sexual function; improves mood and well-being; improves muscle mass and strength; restores or maintains masculine characteristics, such as facial and body hair; and maintains bone strength and prevents osteoporosis and anaemia [24]. Considering the glycometabolic effects, testosterone therapy group patients had reduction in HOMA-IR levels, FSG, FSI and HBA1C as shown by previous studies [5,6,8,13,14,16,17,21–23]. While the insulin-sensitizing effect of testosterone has been observed in type 2 diabetics, studies in non-obese men or those with low normal testosterone concentrations sometimes fail to show an impact on insulin sensitivity. Recent research on testosterone replacement in hypogonadal patients with type 2 diabetes has shown promising results [25]. A study

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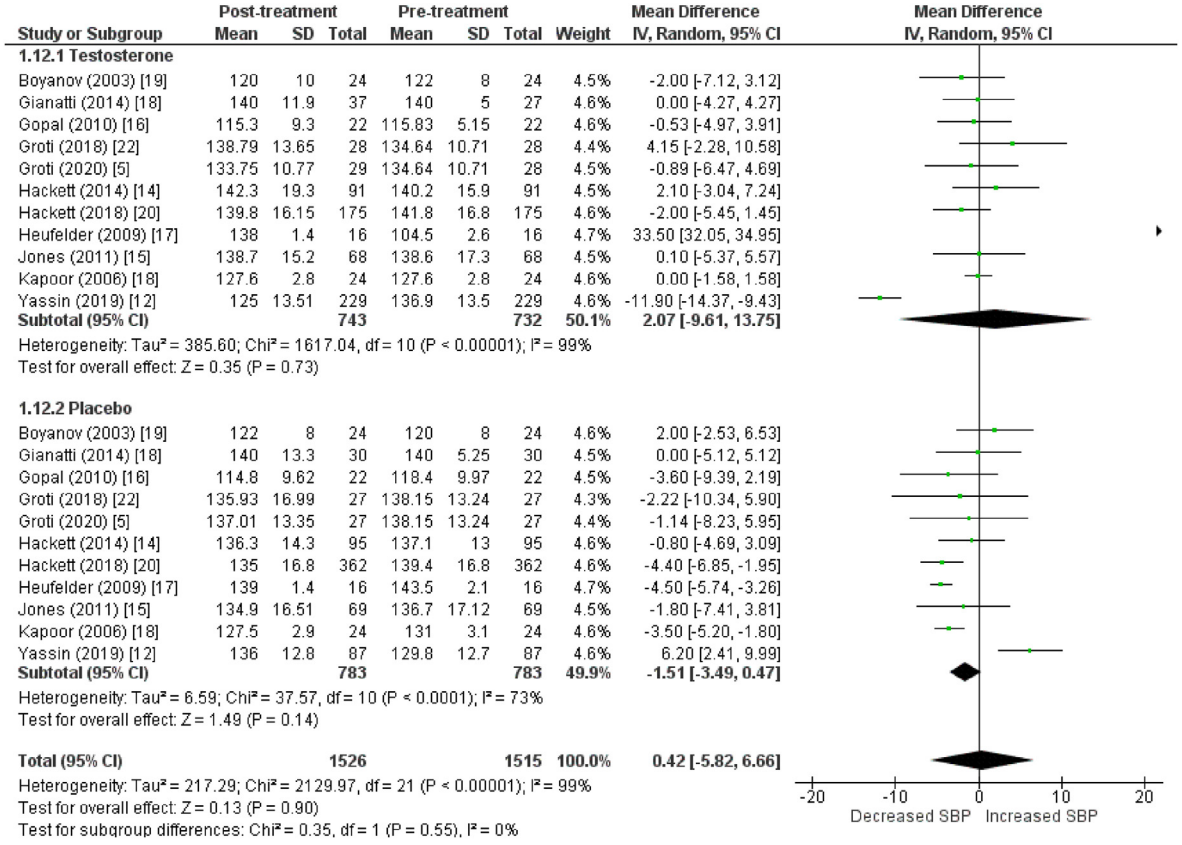

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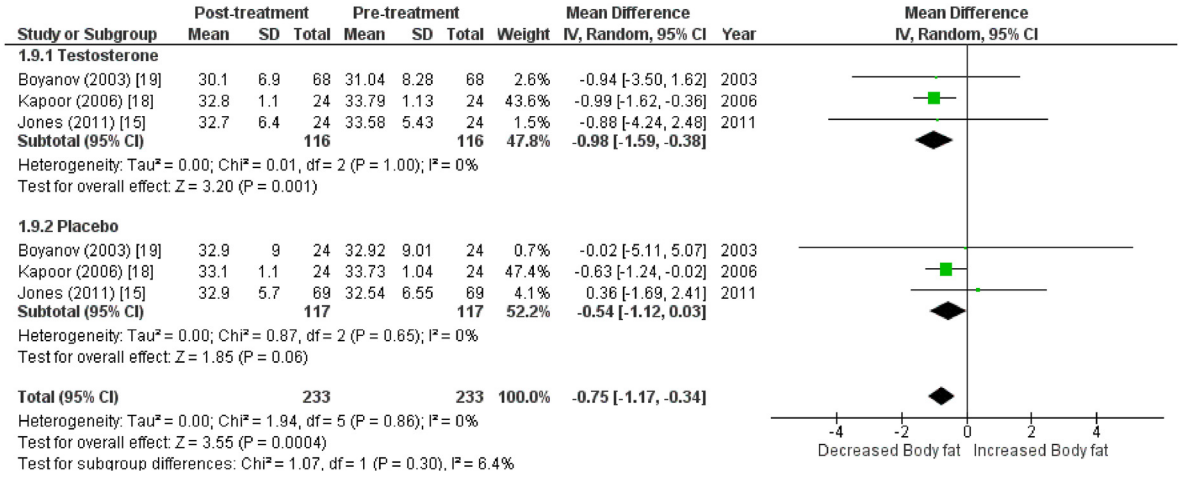

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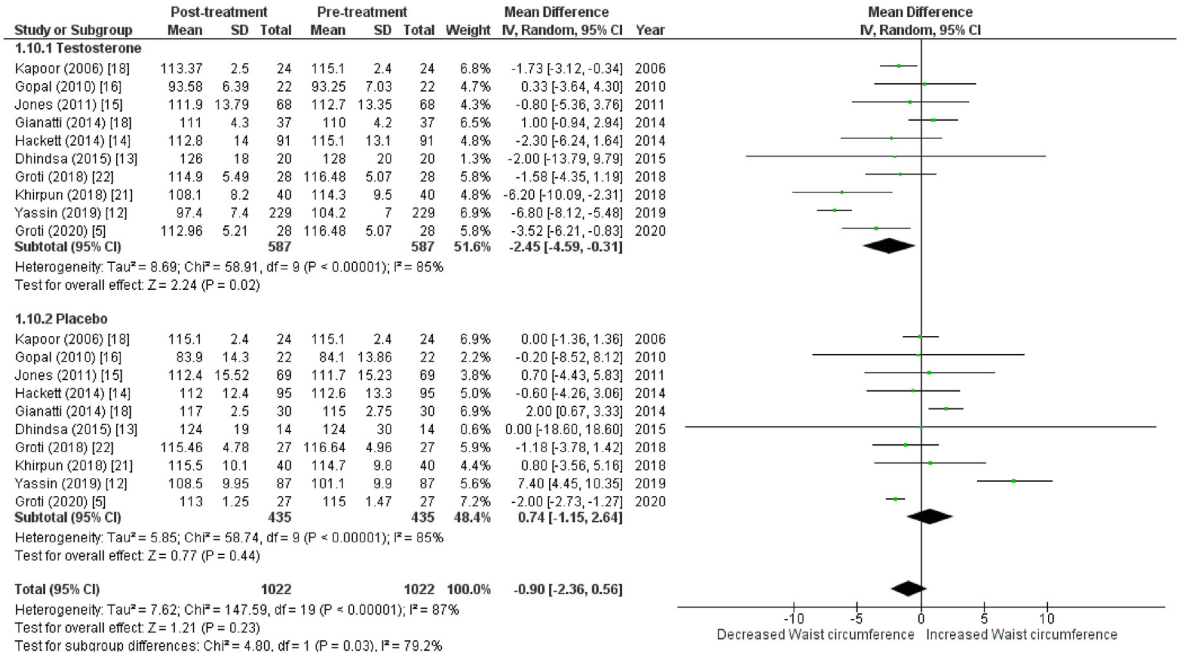
compared 178 men who received long-acting testosterone undecanoate to 178 men with subnormal testosterone who were not treated. The mean follow-up was eight years, and the maximum was 11. The mean age in the testosterone group was 62 and in the untreated group was 64. The use of testosterone reduced HbA1c, fasting plasma glucose, and HOMA-IR. 90% of patients achieved a HbA1c of <7%, 83% achieved <6.5%, and 46% achieved <5.7%. In addition, 34% participants had total remission of diabetes with no anti-diabetes drugs. No diabetes recurrence was seen in the remission group after 2.5 years. Conversely, untreated men with diabetes and hypogonadism had steadily rising glycemia and HbA1c, along with rising HOMA-IR [25]. However, more interventional studies are required to fully comprehend the relationship between circulating sex hormones and carbohydrate metabolism.

In terms of serum lipid profile, four lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) were reported. Ten studies found that total cholesterol levels were lower in the testosterone group after treatment than in the placebo group. While twelve studies reported decrease in triglyceride levels and increases in HDL cholesterol levels simultaneously. However,

no statistically significant difference was found in LDL cholesterol levels in both groups. Considering these changes, improvement in lipid profile should result in cardioprotective effects. However, contrary results have been delineated. Testosterone treatment was reported to increase noncalcified plaque volume and total plaque volume versus placebo, instead of small LDL cholesterol, HDL

D



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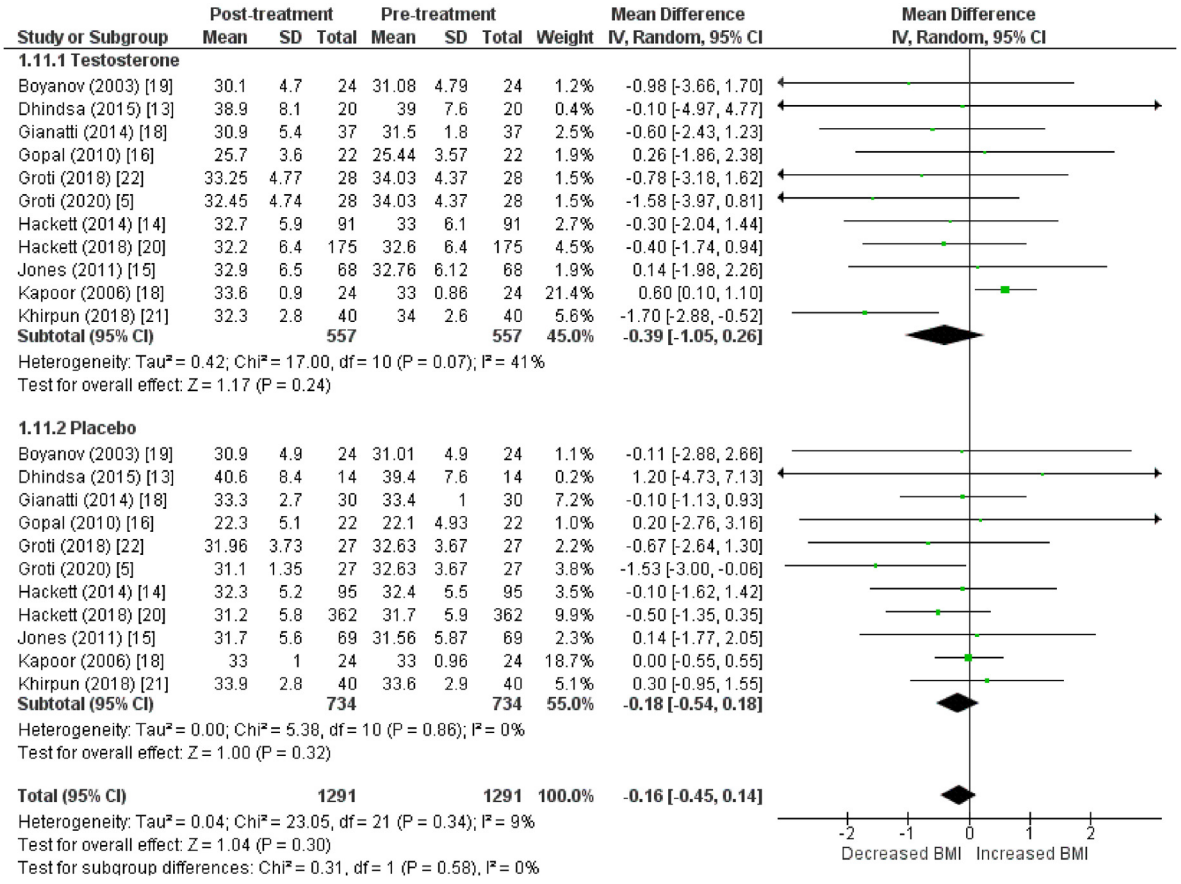

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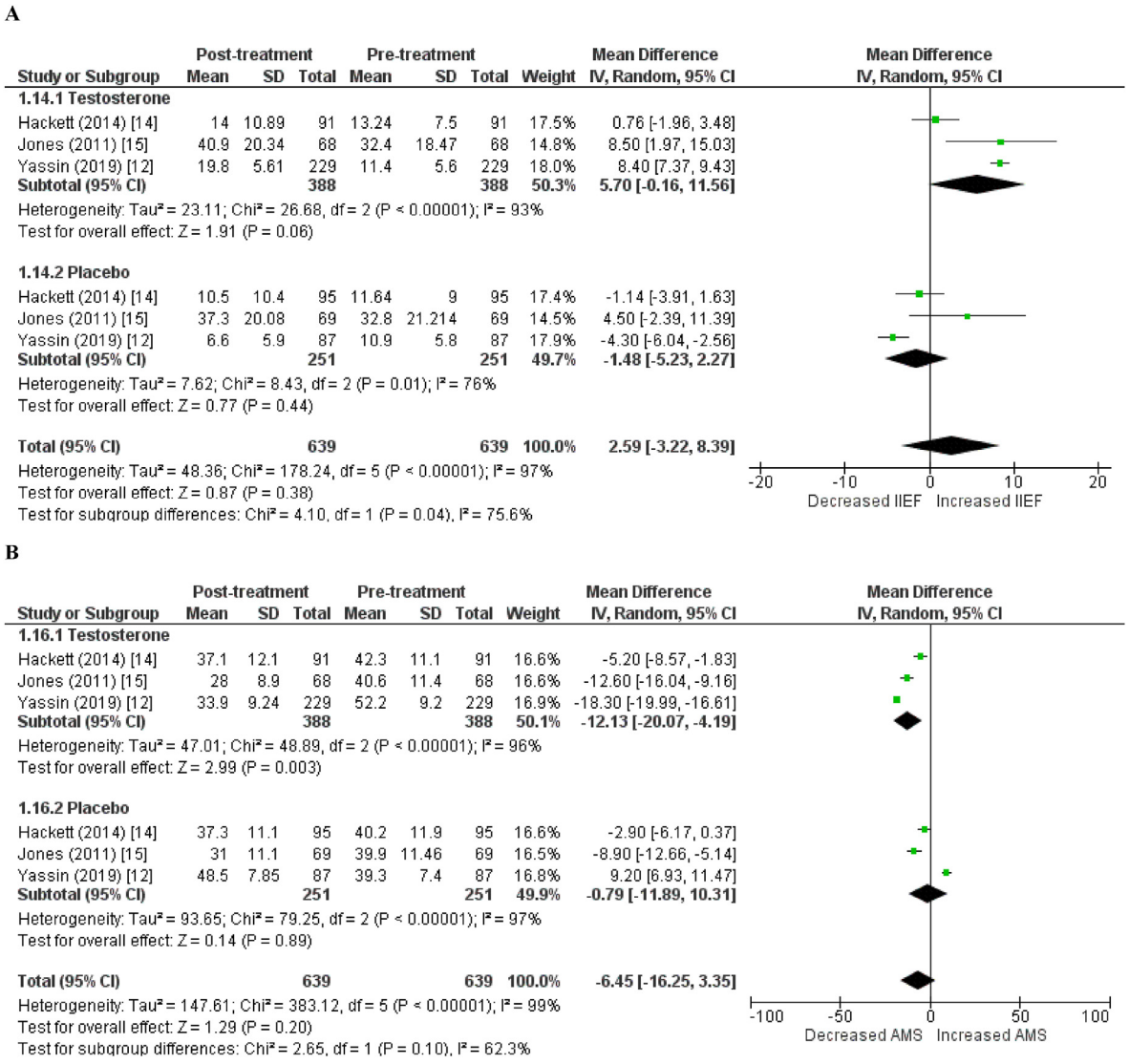


Fig. 5. Effects on AMS and IIEF scores; A = IIEF (International index of erectile function), B = AMS (Aging male score).

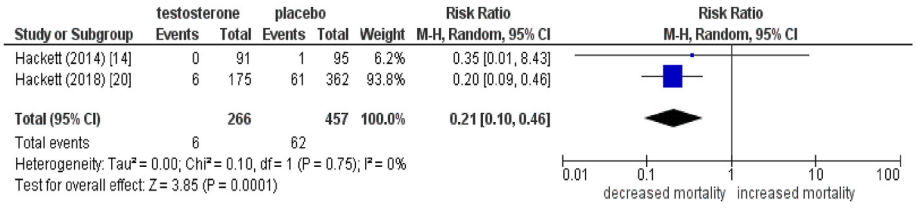


Fig. 6. Mortality.

cholesterol, VLDL cholesterol, and fasting insulin reductions. Men with high cardiovascular risk should be counselled that the cardiovascular safety of testosterone therapy is uncertain [24]. Our meta-analysis decrease in DBP and slight increment in SBP. Nonetheless, a recent study revealed a slight decline in LDL levels and no influence on blood pressure [26]. Eleven studies reported a greater reduction in BMI following treatment, contradicting the proposed studies. Such as, a 2022 study by Michael Kreiberg et al. [27] reported slight increment in BMI indexes after testosterone therapy.

Three studies found a correlation between serum total testosterone levels and AMS scores and IIEF scores. The administration of testosterone led to a significant reduction in AMS scores and an increase in IIEF scores. However, various other studies have found either no association or a weak association between this treatment and both scoring systems. Jae Il Kang et al. [28] found that total serum testosterone had no strong association with the AMS total score or its three subsites ($p > 0.05$). Total serum testosterone demonstrated a weakly significant positive correlation ($r = 0.124$, $p = 0.034$) with IIEF total scores. In another study, A. Sansone et al. [29] discovered that dihydrotestosterone (DHT)

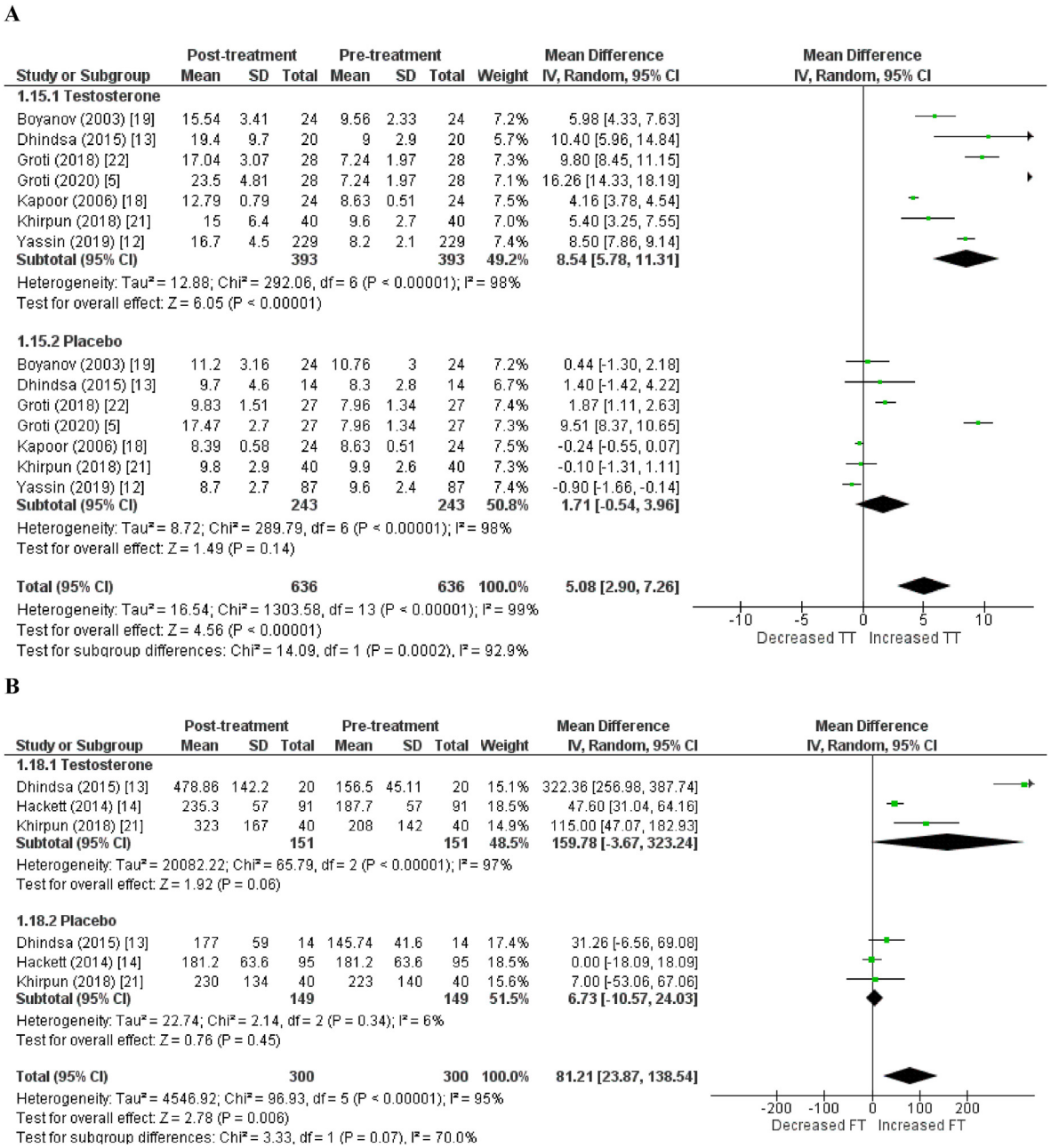
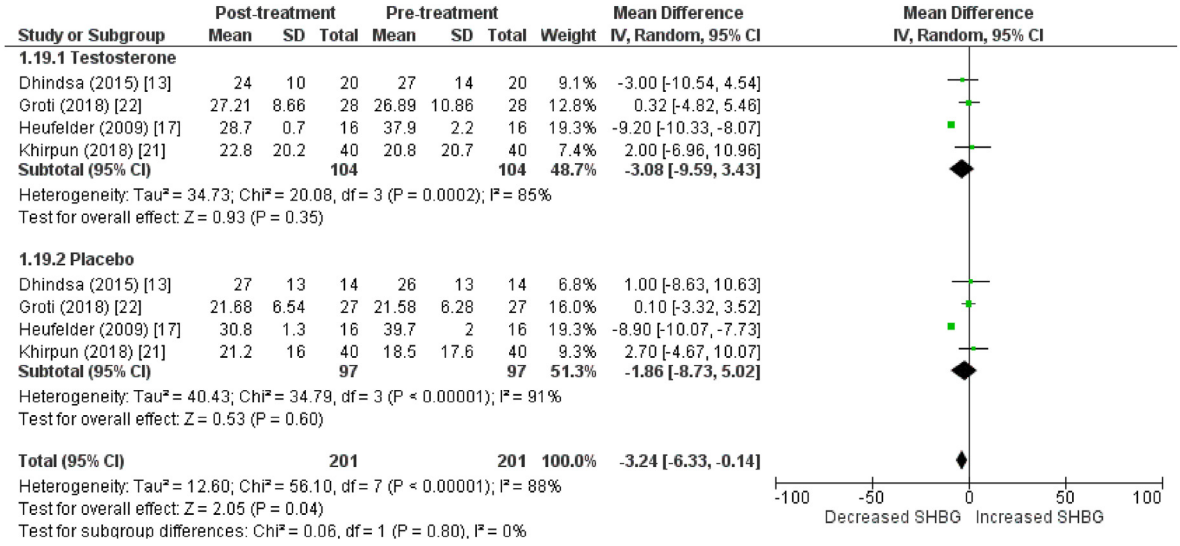


Fig. 7. Effects on Hormonal levels; A = TT (Total testosterone), B= FT (Free testosterone), C = SBHG (sex hormone binding globulin), D = PSA (Prostate specific antigen).

concentrations in individuals with normal testosterone levels (n = 416, Total T > 12 nmol/L) were powerful determinants of AMS scores employing multivariate strategies. In men with biological hypogonadism (Total testosterone 12 nmol/L), total and free testosterone were correlated with AMS results rather than DHT. This relationship was not observed for IIEF scores. Two studies found a substantial decline in mortality versus placebo. In terms of hormones, the concentrations of total testosterone, free testosterone, SHBG, and PSA were investigated. Total and free testosterone levels increased substantially, whereas SHBG levels declined. However, no correlation was observed between this therapy and PSA levels.

Our meta-analysis has several benefits: (1) Due to the inclusion of five additional studies, the sample size of our meta-analysis is more significant than that of previous meta-analyses, which lends credence to our findings. (2) The publication biases were calculated using various plots and tests, including the funnel plot, Egger's test, and Begg's test, revealing no publication bias. (3) Sensitivity analysis was used to determine how heterogeneous studies affected the pooled estimate. (4) Moreover, we compared our meta-analysis to previous meta-analyses conducted by Jianzhong Zhang et al. Which consisted of eight studies, all of which were RCTs. Our meta-analysis did include one observational study whose publication bias was assessed using the New Castle-Ottawa Scale. (5) Our study included some additional outcomes as a result of new data in the literature; these outcomes included mortality, total testosterone,

C



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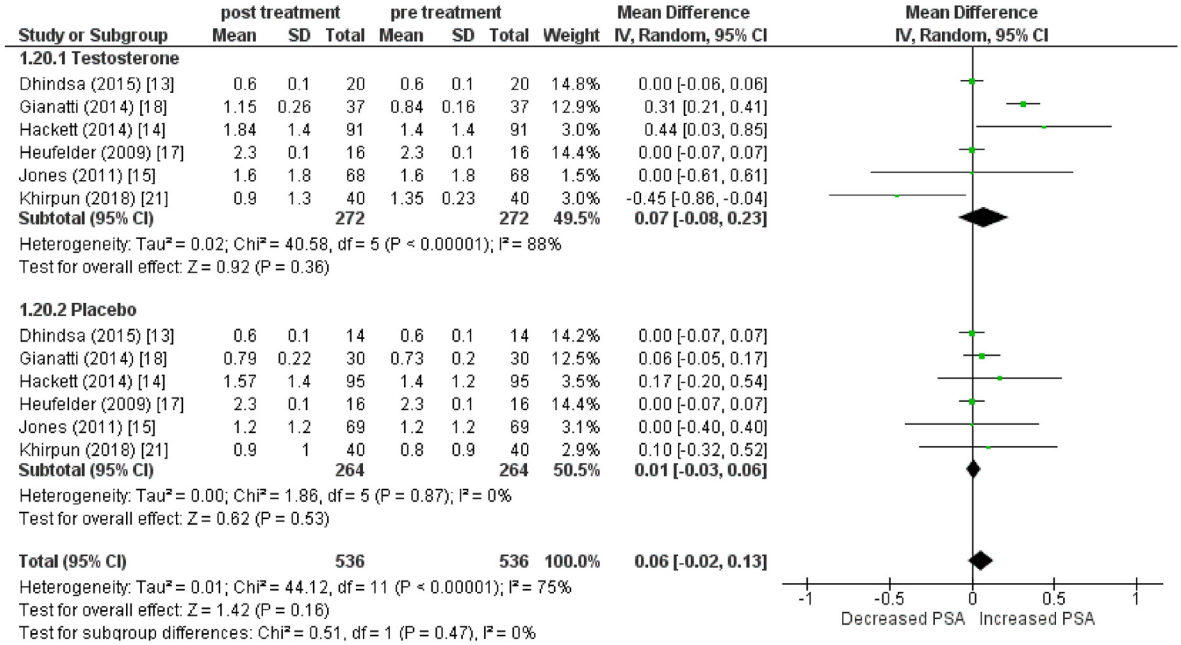

Fig. 7. (*continued*).

free testosterone, SHBG, and PSA.

Even though this analysis produced adequate statistical evidence, some limitations should be highlighted. (1) First, variations in study designs, interventions, patient characteristics such as body mass index, age, sample sizes, and ethnicity, and discrepancies in trial characteristics may have contributed to clinical heterogeneity. (2) Second, the follow-up periods for most studies varied, with some studies reporting longer periods. Long-term follow-ups are more useful when evaluating hormonal diseases like hypogonadism in order to control the body's homeostasis. (3) Numerous studies used different doses of testosterone at different weeks, and the mode of administration of testosterone varied among included studies. Additionally, majority of studies did not include doses of control groups, which could create some uncertainty. (4) Only two or three randomized controlled trials examined body fat, AMS and IIEF scores, free testosterone, and mortality rates. (5) All included RCTs except Groti 2020 [5] had selective reporting bias. More trials were required to investigate the effect of testosterone therapy on sexual function.

5. Conclusion

According to our meta-analysis, testosterone therapy can improve glycemic control, reduce total cholesterol, HDL levels, and triglycerides, as well as decrease BMI and waist circumference in hypogonadal T2DM patients. In these patients, we recommend this therapy in addition to anti-diabetic therapy. In addition, additional standard quality RCTs are required to investigate the additional effects of Testosterone therapy in hypogonadal men with T2DM.

Disclosures

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in the article.

Author's contributions

Satesh Kumar: Protocol development, Data collection, Data analysis, Manuscript writing.**Mahima Khatri:** Protocol development, Data collection, Data analysis, Manuscript writing.**Rahat Ahmed Memon:** Data collection, Data analysis, Manuscript writing.**Jordam Llerena Velastegui:** Data collection, Manuscript writing.**Kristina Zumbana Podaneva:** Manuscript writing.**Daniela Benitez Gutierrez:** Protocol development, Data collection.**Bilawal Nadeem:** Protocol development.**Akhil Raj Anumolu:** Protocol development, Manuscript writing.**Masood Azhar:** Data analysis, Manuscript editing.**Ahmad Zain:** Data analysis, Manuscript editing.

Declaration of competing interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2022.102588.

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