

Supplementary Table S1: Detailed search strategy

Database	Search strategy	Results
PubMed	((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	300
Google Scholar	((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	284
Embase	((((Testosterone)) OR (Androgen)) OR (androgenic hormone)) AND (((Type 2 diabetes) OR (insulin independent diabetes)) OR (adult-onset diabetes))) AND (treatment)) AND (male hypogonadism)	75

Supplementary Table 2: Characteristics of RCTs

Characteristic	Dhindsa (2015) [13]	Gianatti (2014) [8]	Hackett (2014) [14]	Jones (2011) [15]	Gopal (2010) [16]	Heulfelder (2009) [17]	Kapoor (2006) [18]	Boyonav (2003) [19]	Hackett (2018) [20]	Khirpun (2018) [21]	Groti (2018) [22]	Groti (2020) [5]	Wittert (2021) [23]
Study name	Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men with Type 2 Diabetes	Effect of Testosterone Treatment on Glucose Metabolism in Men with Type 2 Diabetes: A Randomized Controlled Trial	Testosterone Replacement Therapy Improves Metabolic Parameters in Hypogonadal Men with Type 2 Diabetes but Not in Men with Coexisting Depression: The BLAST Study	Testosterone Replacement in Hypogonadal Men with Type 2 Diabetes and/or Metabolic Syndrome (the TIMES2 Study)	Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus	Fifty-two—Week Treatment with Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycaemic Control in Men with Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone	Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes	Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors	Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors	Influence of testosterone substitution on glycaemic control and endothelial markers in men with newly diagnosed functional hypogonadism and type 2 diabetes mellitus: a randomized controlled trial	The impact of testosterone replacement therapy on glycaemic control, vascular function, and components of the metabolic syndrome in obese hypogonadal men with type 2 diabetes	Testosterone treatment longer than 1 year shows more effects on functional hypogonadism and related metabolic, vascular, and obesity parameters (results of the 2-year clinical trial)	Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial
Patients, n	94	88	211	220	22	32	27	48	857	80	55	55	1007
Enrolment	2010	2009	2008	2006	2006	2005	2002	1998	2007	2012	2014	2014	2013

Initiation Enrolment completion Year of completion Population	2014	2013	2012	2007	2009	2008	2006	2002	2009	2017	2018	2018	2017
Year of completion Population	2014	2014	2014	2011	2010	2009	2006	2003	2018	2018	2018	2020	2021
Population	Male subjects with type 2 diabetes between the ages of 30 and 65 years, HbA1c #8% (64 mmol/mol), and stable diabetes regimen for 3 months	Study subjects were recruited from specialist diabetes clinics, primary care, and the general community	Patients were recruited from routine diabetes assessment	Male subjects with diabetes and hypogonadism.	Patients with T2DM in the 25- to 50-year age-group who were diagnosed with hypogonadism were included in the study.	Male patients with type 2 diabetes and hypogonadism	men aged over 30 years with type 2 diabetes and with hypogonadism.	middle-aged men with both type 2 diabetes mellitus and mild androgen deficiency.	Male subjects with diabetes and hypogonadism.	men newly diagnosed with T2DM according to the criteria of the American Diabetes Association and referring to HbA1c levels as leading parameter (HbA1c levels had to be measured two times within 4 weeks above 6.5%)	Obese males with hypogonadism and diabetes	Obese males with hypogonadism and diabetes	men newly diagnosed with T2DM according to the criteria of the American Diabetes Association and referring to HbA1c levels as leading parameter (HbA1c levels had to be measured two times within 4 weeks above 6.5%)
Trial type	randomized, parallel, placebo-controlled, double-blind, prospective, single-centre trial	randomized, double-blind, placebo-controlled trial	double-blind, placebo-controlled intervention study	prospective, randomized, double-blind, placebo-controlled, multicentre study	double-blind, placebo-controlled, crossover study	randomized, double-blind, placebo-controlled trial	double-blind placebo-controlled crossover study	open-label, randomized, no-treatment controlled study	double-blind placebo-controlled study	double-blind placebo-controlled study	double-blind randomized placebo-controlled study	double-blind randomized placebo-controlled study	randomised, double-blind, placebo-controlled

Inclusion Criteria	Male subjects with type 2 diabetes between the ages of 30 and 65 years, HbA1c #8% (64 mmol/mol), and stable diabetes regimen for 3 months were recruited between December 2010 and January 2014	Men aged 35–70 years of age were eligible to participate in this trial if they had a history of T2D, and the total testosterone (TT) level (averaged from two fasting morning specimens) was #12.0 nmol/L (346 ng/dL).	Inclusion criteria for the BLAST intervention study were men aged 18–80 with type 2 diabetes and willing to give written informed consent. Eligibility included an initial finding of either a total testosterone between 8.1 and 12 nmol/L or FT 0.181–0.25 nmol/L (mild group), or total testosterone of 8.0 nmol/L or less or 0.18 nmol/L FT or less (severe group) according to the current 2006 ISSAM EAU guidelines, and with symptoms of	Men aged 40 years were eligible to enter the study if they had confirmed hypogonadism (early morning [0800h] total testosterone [TT] #11 nmol/L or free testosterone #255 pmol/L on two occasions \$1 week apart), with at least two symptoms of hypogonadism (14) and/or MetS	Patients with T2DM in the 25- to 50-year age-group who were diagnosed with hypogonadism were included in the study. Hypogonadism was defined as a calculated free testosterone level less than 64.8 pg/mL (0.225 nmol/L) on at least 2 occasions in the presence of symptoms of hypogonadism.	males with the MetS and newly diagnosed T2D (fasting plasma glucose .7.0 at baseline and/or .11.1 after a 2-hour, 75-g oral glucose tolerance test, and an elevated level of HbA1c)	Type 2 diabetic men with HbA1c up to 9.5% showing no significant symptoms of hyperglycemia. Hypogonadism was defined as total testosterone nmol/l (on two separate occasions) and symptoms of hypogonadism (positive ADAM score)	subjects had to be aged between 45 and 65 years, be married or living in a stable relationship with a female sexual partner for at least 6 months, have a waist–hip ratio (WHR) of at least 0.9, have symptoms of andropause or erectile dysfunction, and have serum testosterone	Men aged 18 to 80 years with an initial finding of either a TT (on 2 separate occasions) ≤12 nmol/L or FT≤0.18 nmol/L with symptoms of HG defined by the Ageing Male Symptom score.	Men with newly diagnosed diabetes potential functional hypogonadism according to the diagnostic criteria of the EAU guideline on male hypogonadism as of 2015 (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)	men aged > 35 years body mass index > 30 kg/m2 confirmed hypogonadism type 2 diabetes mellitus treated with non-insulin therapy	. Men aged 50–74 years, with a waist circumference of 95 cm or higher, a serum testosterone concentration of 14.0 nmol/L or lower but without pathological hypogonadism, and impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose 7.8–11.0 mmol/L) or newly diagnosed type 2 diabetes (provided OGTT 2-h glucose ≤15.0 mmol/L)
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		sleep apnea, estimated glomerular filtration rate , 30 mL/min, cardiac insufficiency (New York Heart Association score .2), active malignancy, unstable psychiatric disease, weight .135 kg (the weight limit for the dual-energy X-ray absorptiometry [DXA] scanner), current use of glucagonlike peptide-1 agonist therapy or very low-calorie diet, or an	BPH, and malignancy had been recently excluded, patients were eligible	elevated age-specific prostate-specific antigen (PSA).	range; patients with an American Urological Association questionnaire (used for symptoms of prostatism) score >22; and those with uncontrolled blood glucose levels—hemoglobin A1c (A1C) >10%			evidence of prostate enlargement or abnormalities.			> 4.0 lg/l) severe heart failure acute coronary event or procedure during the six months leading up to the study chronic obstructive lung disease hypothyroidism severe obstructive sleep apnea (OSA) active infection rheumatoid arthritis		
Treatments	250 mg testosterone cypionate (Watson	Intramuscular testosterone undecanoate 1,000 mg or a	Subjects were randomized to receive	Subjects were randomized (1:1) to	Testosterone cypionate (Cernos),	Patients were randomized to either supervised diet	Sustanon 200 mg (testosterone propionate	oral testosterone undecanoate	long-acting testosterone undecanoate	T-Gel at a dose of 50 mg per day	testosterone undecanoate	testosterone undecanoate 1000	intramuscular injection of testosterone

Pharmaceuticals, New Jersey; 200 mg/mL) or placebo (1.25 cc saline) intramuscularly in the buttock.	visually identical placebo injection (both in oily base) was injected into the upper outer quadrant of the buttock at 0, 6, 18, and 30 weeks	either TU 1,000 mg at week 0, week 6, week 18, administered by the practice nurse or GP over 5 minutes into the right or left upper outer buttock, or matching placebo	receive either 3 g metered-dose 2% testosterone gel (60 mg testosterone, Tostran [also known as Fortigel, Tostrex, Itnogen, Foresta; ProStrakan, Galashiels, Scotland, U.K.]) or placebo gel once daily	200 mg, a depot preparation of testosterone administered by deep intramuscular injection. Placebo was given as 0.9% isotonic saline	and exercise (D&E) alone in combination with testosterone gel (50 mg once daily; Testo gel; Bayer Schering Pharma AG, Berlin, Germany)	30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL, Organon Laboratories, Cambridge, UK), a depot preparation.	(TU; AndriolÒ, Organon, Oss, The Netherlands) for 3 months, at a daily oral dosage of 120 mg, divided into 80 mg at breakfast and 40 mg at dinner (during the meals).	1000 mg intramuscular injections two years; according to the protocol every 10 weeks. Placebo arm patients were receiving placebo throughout the first year of this study and testosterone undecanoate 1000 mg intramuscular injections during second year.	one undecanoate (1000 mg) or placebo at baseline, 6 weeks, and then every 3 months for 2 years.
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Primary Outcomes	The impact of HH on insulin resistance, inflammation, and body composition in men with type 2 diabetes	The primary outcome measure was the change across groups and time from baseline in the homeostasis model index of insulin resistance (HOMA-IR).	The primary outcome measure was the difference between treatment groups in time from baseline in the homeostasis model index of insulin resistance (HOMA-IR) assessment.	The primary end point was the difference between treatment groups in homeostasis model index of IR, fasting blood glucose level, and A1C value.	changes in the homeostasis model index of IR, fasting blood glucose level, and A1C value.	The primary end point was the difference between treatment groups in homeostasis model index of IR, fasting blood glucose level, and A1C value.	Changes in the homeostasis model index of insulin resistance, fasting blood glucose and glycated haemoglobin.	changes in the homeostasis model index of IR, fasting blood glucose level, and A1C value.	The primary outcome measure was the change across groups and time from baseline in the homeostasis model index of insulin resistance (HOMA-IR).	The primary outcome measure was the change across groups and time from baseline in the homeostasis model index of insulin resistance (HOMA-IR).	Effects of testosterone replacement therapy on glycaemic control - fasting plasma glucose (FPG) mmol/l, HbA1c, HOMA-IR, vascular function - change in flow mediated dilatation (FMD) %.	Effects of testosterone replacement therapy on glycaemic control - fasting plasma glucose (FPG) mmol/l, HbA1c, HOMA-IR, vascular morphology - change in intima-media thickness (IMT)	type 2 diabetes (2-h OGTT glucose ≥ 11.1 mmol/L) and mean change from baseline in 2-h OGTT glucose, assessed by intention to treat.
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Secondary outcome	-	The secondary outcome measure was the change across group and time in glycaemic control as measured by HbA1c. Other outcome measures were considered as explanatory variables.	The secondary outcome measure was the change across group and time in glycaemic control as measured by HbA1c. Other outcome measures were considered as explanatory variables.	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, BMI, waist circumference, and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	changes in fasting lipids, anthropometric factors including BMI, waist circumference, and WHR, blood pressure, and androgen deficiency symptoms	Secondary end points were changes from baseline in fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Changes in fasting lipids, blood pressure and anthropometric factors including BMI, waist circumference, waist/hip ratio, BMI and % body fat	changes in fasting lipids, anthropometric factors including BMI, waist circumference, blood pressure, and androgen deficiency symptoms	Secondary end points were changes from baseline in fasting insulin, FPG, lipid parameters, body composition, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Secondary end points were changes from baseline in HbA1c, fasting insulin, FPG, lipid parameters, BMI, waist circumference, AMS and IIEF scores, AEs, and other safety parameters. HOMA of b-cell function (HOMA-B) was determined post hoc	Effects of testosterone replacement therapy on non-alcoholic fatty liver disease (NAFLD), bone mineral density (BMD), total testosterone (TT), prostate specific antigen and haematocrit	Effects of testosterone replacement therapy on non-alcoholic fatty liver disease (NAFLD), bone mineral density (BMD), total testosterone (TT), prostate specific antigen and haematocrit	monitoring of haematocrit and prostate-specific antigen, and analysed prespecified serious adverse events
Follow up	24 weeks	40 weeks	52 weeks	12 months	7 months	52 weeks	7 months	3 months	3.4 years	9 months	1 year	2 years	2 years

Supplementary Table S3: Characteristics of Observational Studies

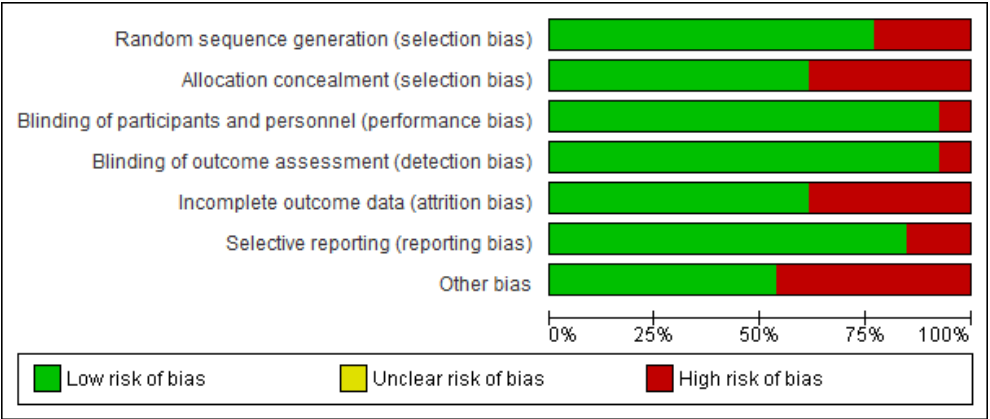
Characteristics	Yassin (2019) ^[12]	Haider (2020) ^[24]
Study name	Testosterone Therapy in Men with Hypogonadism Prevents Progression from Prediabetes to Type 2 Diabetes: Eight-Year Data from a Registry Study	Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study
Patients, n	316	356
Initiation	2011	2008
Completion	2018	2019
Year of publication	2019	2020
Population	Patients in this study were pooled from two ongoing urological registries. Ethical guidelines by the German Medical Association for observational studies in patients receiving standard treatment were followed	Patients with diabetes managed by the same local diabetes centre
Inclusion criteria	Prediabetes, defined as HbA1c 5.7–6.4% (39–46 mmol/mol), and total testosterone levels #12.1 nmol/L (;350 ng/dL) combined with symptoms of hypogonadism.	Patients with T2DM who had total testosterone levels ≤12.1 nmol/L (350 ng/dL) and symptoms of hypogonadism
Exclusion criteria	--	...
Primary Outcome	Anthropometric and metabolic parameters	glucose intolerance, with glycated haemoglobin (HbA1c) and insulin secretion

Supplementary Table S4: New Castle Ottawa scale to assess Publication bias in Observational studies

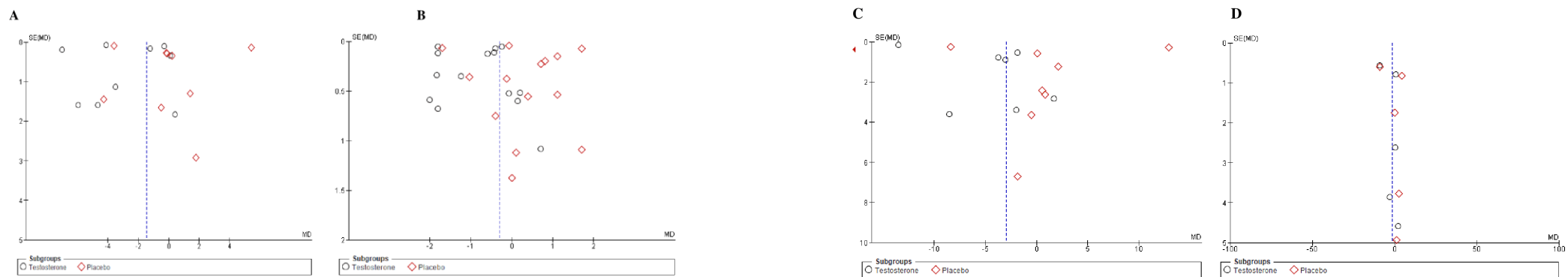
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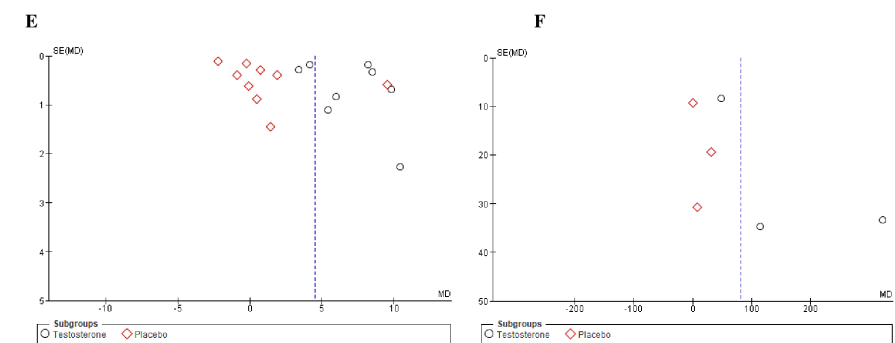
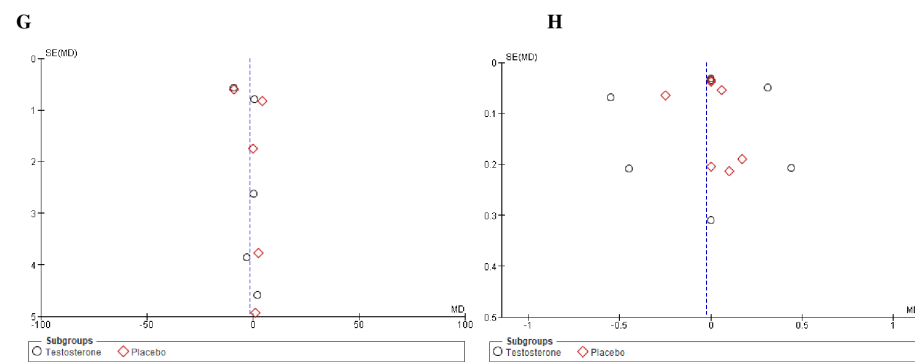
Supplementary Table S4: Cochrane risk of bias tool for assessing publication bias in Randomized controlled trials

	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
Boyanov 2003 [19]	+	+	+	+	-	+	+
Dhindsa 2015 [13]	+	-	+	+	+	+	-
Gianatti 2014 [8]	-	-	+	+	+	+	+
Gopal 2010 [16]	+	-	+	+	+	-	+
Groti 2018 [22]	+	+	+	+	-	+	-
Groti 2020 [5]	+	+	-	+	+	-	+
Hackett 2014 [14]	-	+	+	-	-	+	+
Hackett 2018 [20]	+	+	+	+	-	+	+
Heufelder 2009 [17]	+	+	+	+	-	+	+
Jones 2011 [15]	+	+	+	+	+	+	-
Kapoor 2006 [18]	+	-	+	+	+	+	-
Khirpun 2018 [21]	+	-	+	+	+	+	-
Wittert 2021 [23]	-	+	+	+	+	+	-



Supplementary Figure S1: Funnel Plots of primary outcomes





A: Homeostatic model assessment for insulin resistance (HOMA-IR), B: Fasting plasma glucose (FPG), C: Fasting serum insulin (FSI), D: Glycated hemoglobin (HbA1C), E: Total testosterone (TT), F: Free testosterone (FT), G: Sex hormone binding globulin (SHBG), H: Prostate specific antigen (PSA)