

<b>Inclusion criteria</b>	<b>Isidori et al., 2005 (81)</b>		<b>Bolona et al., 2007 (82)</b>		<b>Corona et al., 2014 (83)</b>		<b>Elliot et al., 2016 (84)</b>	
Number of trials included	17		17		29		17	
Number of patients analyzed	657		862		1,930		3,165	
Hypogonadism definition (TT)	10 nmol/L		10.4 nmol/L		12 nmol/L		12 nmol/L	
	<b>Outcomes according to TT levels</b>		<b>Outcomes according to TT levels</b>		<b>Outcomes according to TT levels</b>		<b>Outcomes according to TT levels</b>	
<b>Sexual parameter analyzed</b>	< 10 nM	≥10 nM	< 10.4 nM	≥10.4 nM	< 12.0 nM	≥12 nM	< 12.0 nM	≥12 nM
Erectile function	<b>1.87[0.31;3.42]</b>	0.19[-0.24;0.63]	0.80[-0.10;1.60]	<b>0.34[0.03;0.65]</b>	<b>1.21[0.65;1.78]</b>	0.22[-0.17;0.61]	<b>0.25[0.10;0.41]</b>	0.22[-0.17;0.61]
Libido	<b>1.60[0.29;2.92]</b>	<b>0.61[0.12;1.09]</b>	<b>1.31[0.40;2.22]</b>	0.41[-0.01;0.83]	<b>0.95[0.41;1.50]</b>	0.25[-0.24;0.74]	<b>0.33[0.16;0.50]</b>	0.25[-0.24;0.74]
Morning erections	<b>1.53[1.00;2.06]</b>	<b>1.10[0.65;1.48]</b>	-	-	<b>0.92[0.36;1.48]</b>	<b>0.74[0.32;1.16]</b>	-	-
Orgasmic function	-	-	-	-	<b>0.74[0.35;1.21]</b>	0.73[-0.73;2.18]	-	-
Sexual satisfaction	<b>1.16[0.04;2.29]</b>	0.26[-0.07;0.58]	-	-	<b>0.86[0.40;1.32]</b>	0.62[-0.06;1.29]	-	-
Erectile function TRT+PDE5i	-	-			0.49[-0.16;1.15]*			
<b>Inclusion criteria</b>	<b>Ponce te al. 2018 (52)</b>		<b>Algeffari et al., 2018 (85)</b>		<b>Zhu et al., 2020 (86)</b>			
Number of trials included	4		6		8			
Number of patients analyzed	1,179		587 on diabetic		913			
Hypogonadism definition (TT)	10 nmol/L		Only overall population		10.0 nmol/L			
	<b>Outcomes according to TT levels</b>		<b>Overall population</b>		<b>Outcomes according to TT levels</b>			
<b>Sexual parameter analyzed</b>	< 10 nM	≥10 nM			< 10.4 nM	≥10.4 nM		
Erectile function	<b>0.16[0.06;0.27]</b>	-	<b>0.20[0.01;0.40]</b>		-	-		
Libido	<b>0.17[0.01;0.24]</b>	-	<b>0.31[0.08;0.55]</b>		-	-		
Morning erections	-	-	-		-	-		
Orgasmic function	-	-	0.24[-0.13;0.60]		-	-		
Sexual satisfaction	<b>0.16[0.01;0.31]</b>	-	<b>0.09[-0.12;0.29]</b>		-	-		
Erectile function TRT+PDE5i	-	-			<b>0.66[0.30;1.03]</b>	0.42[-0.06;0.90]		

**Supplementary Table 1.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy (TRT) and several sexual parameters. TT= total testosterone. PDE5i= phosphodiesterase type 5 inhibitors; -=not available; \* only overall population. All data are reported as standardized difference in means,

<b>Inclusion criteria</b>	<b>Isidori et al., 2005 (94)</b>	<b>Tracz et al., 2006 (95)</b>	<b>Junjie et al., 2019 (96)</b>	<b>Zhang et al., 2020 (97)</b>
Number of trials included	8	8	7	10
Number of patients analyzed	329	365	800	1,236
Hypogonadism definition (TT)	Only overall population	Only overall population	Only overall population	Only overall population
	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>
<b>Bone parameter analyzed</b>				
Lumbar spine	<b>0.03[0.00;0.07]</b>	<b>0.62[0.32;0.92]*</b>	0.03[-0.02;0.08]	0.00[-0.01;0.02]
Femoral neck	0.02[-0.02;0.05]	0.17[-0.11;0.45]	0.00[-0.02;0.03]	0.00[-0.02;0.02]
Trochanter	0.01[-0.02;0.07]	-	<b>0.04[0.04;0.04]</b>	-
Ward triangle	0.02[-0.02;0.06]	-	0.02[-0.02;0.06]	-
Total hip	-	-	<b>0.03[0.03;0.03]</b>	0.01[-0.01;0.03]
Whole body	-	-	0.00[-0.03;0.03]	0.00[-0.02;0.01]
Bone resorption markers	<b>-0.51[-0.84;-0.18]</b>	-	0.37[-2.68;3.43]	-
Bone formation markers	-0.14[-0.37;0.08]		0.30[-0.63;1.24]	-
<b>Inclusion criteria</b>	<b>Corona al., 2021 (98)</b>			
Number of trials included	24			
Number of patients analyzed	2,793			
Hypogonadism definition (TT)	12 nmol/L			
	<b>Outcomes according to TT levels</b>			
<b>Bone parameter analyzed</b>	< 12 nM	≥12 nM		
Lumbar spine	<b>0.03[0.01;0.06]</b>	<b>0.05[0.01;1.00]</b>		
Femoral neck	<b>0.02[0.001;0.04]</b>	0.01[-0.01;0.03]		
	<b>Overall population</b>			
Trochanter	0.02[-0.01;0.04]			
Ward triangle	0.01[-0.02;0.04]			
Total hip	0.01[-0.01;0.03]			
Whole body	-0.005[-0.010;0.0001]			
Bone resorption markers	-0.07[-0.34;0.20]			
Bone formation markers	-0.14[-0.27;0.13]			

**Supplementary Table 2.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several bone parameters. TT= total testosterone; - = not available.\* only intramuscular preparations

<b>Inclusion criteria</b>	<b>Zarrouf et al., 2009 (113)</b>		<b>Amanatkar et al., 2014 (114)</b>		<b>Walther et al., 2018 (115)</b>	
Number of trials included	7		16		27	
Number of patients analyzed	355		944		2,070	
Hypogonadism definition (TT)	Mixed definitions		Mixed definitions		Mixed definitions	
<b>Outcomes according to T levels</b>	Hypogonadal	Eugonadal	Hypogonadal	Eugonadal	Hypogonadal	Eugonadal
HAM-D response	<b>0.35[0.20;0.60]</b>	<b>0.35[0.25;1.21]</b>	-	-	-	-
Mixed questionnaires *	-		<b>0.09[0.21;0.57]</b>	0.16[-0.48;0.15]	<b>0.48[0.19;0.76]</b>	0.21[-0.23;0.64]
<b>Outcomes according to symptoms severity</b>			Mixed	Severe	Subclinical	Severe
Mixed questionnaires*	-		<b>0.18[0.45;1.16]</b>	<b>0.20[0.02;0.80]</b>	<b>0.60[0.11;1.11]</b>	0.39[-0.07;0.84]

**Supplementary Table 3.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and depressive symptoms. TT= total testosterone; -= not available.\* Standardized means. HAM-D=The Hamilton Depression Rating Scale

<b>Inclusion criteria</b>	<b>Buskbjerg et al., 2019 (121)</b>	<b>Tan et al., 2019 (122)</b>	<b>Corona et al., 2020 (117)</b>
Number of trials included	23	14	17
Number of patients analyzed	1,638	1,406	1,438
Hypogonadism definition (TT)	11 nmol/L	Only overall population	Only overall population
<b>Outcomes overall population</b>			
Overall cognitive domain	0.09[-0.02;0.19]	<b>0.11[0.00;0.21]</b>	-
Attention/working memory	0.16[-0.07;0.33]	0.16[-0.03;0.35]	0.15[-0.23;0.52]
Executive function	0.02[-0.07;0.12]	<b>0.14[0.03;0.26]</b>	-0.08[-0.19;0.03]
Verbal fluency	0.07[-0.11;0.24]	-	0.10[-0.13;0.33]
Verbal memory (immediate recall)	0.08[-0.06;0.22]	0.10[-0.01;0.21]	0.05[-0.06;0.17]
Verbal memory (delayed recall)	-	-	0.03[-0.08;0.15]
Visual memory	<b>-0.80[-1.30;-0.30]</b>	0.14[-0.05;0.32]	0.12[-0.04;0.27]
Visuomotor ability	0.15[-0.14;0.43]	0.15[-0.02;0.31]	-0.14[-0.67;0.38]
Visuospatial ability	0.00[-0.11;0.12]	0.05[-0.07;0.18]	0.01[-0.13;0.15]
<b>Overall cognitive domain according to gonadal status</b>			
Eugonadism	<b>0.17[0.00;0.33]</b>	-	-
Hypogonadism	0.02[-0.13;0.17]	-	-

**Supplementary Table 4.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several cognition parameters; -= not available. All data are reported as standardized means

<b>Inclusion criteria</b>	<b>Isidori et al., 2005 (94)</b>	<b>Ottenbacher et al., 2006 (127)</b>	<b>Skinner et al., 2018 (128)</b>	<b>Parahiba et al., 2020 (129)</b>
Number of trials included	10	11	31	11
Number of patients analyzed	386	474	5,095	773
Hypogonadism definition (TT)	10.4 nmol/l	Not reported	Not reported	Not reported
<b>Outcomes</b>	<b>Outcomes overall population</b>	<b>Outcomes overall population</b>	<b>Outcomes overall population</b>	<b>Outcomes overall population</b>
Knee extension (dominant)	0.27[-0.02;0.56]*	-	-	2.40[-21.58;26.37]60°/sec
Leg extension (dominant)	0.38[-0.03;0.79]*	-	-	<b>144.10[44.21;244.00]</b> kgf
Knee flexion (dominant)	0.61[-0.39;1.60]*	-	-	-
Handgrip	0.25[-0.02;0.52]*	-	-	<b>1.58[0.17;3.00]</b> overall (kgf) 0.43[-2.05;2.90]low risk of bias (kgf)
Strength				
Upper extremity	-	<b>0.47[0.12;0.84]*</b>	<b>1.13[0.78;1.47]*</b>	-
Lower extremity	-	<b>0.63[0.03;1.28]*</b>	<b>0.78[0.45;1.08]*</b>	-
Whole body	-	-	<b>1.12[0.67;1.14]*</b>	-
Physical Performance Test	-	-	-	1.40[-0.69;3.61]

**Supplementary Table 5.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several mobility and strength parameters. TT= total testosterone; -=not available; kgf= kilogram-force.\*Standardized difference in means

<b>Inclusion criteria</b>	<b>Whitsel et al., 2001 (149)</b>	<b>Isidori et al., 2005 (94)</b>		<b>Haddad et al., 2007 (150)</b>		<b>Fernandez-Balsells et al., 2010(151)</b>
Number of trials included	19	25		30		51
Number of patients analyzed	272	1,247		1642		2,679
Hypogonadism definition (TT)	12 nmol/L	10 nmol/L		10.4 nmol/L		Only overall population
	<b>Only hypogonadal population</b>	<b>Outcomes according to T levels</b>		<b>Outcomes according to T levels</b>		<b>Overall population</b>
<b>Body composition</b>	All < 12 nM	< 10 nM	≥10 nM	<10.4 nM	≥10.4 nM	
Fat mass*	-	-1.46[-3.01;0.09]	<b>-1.50[-2.72;-0.28]</b>	-	-	-
Lean mass*	-	1.16[-0.49;2.80]	<b>1.80[0.57;3.03]</b>	-	-	-
Waist (cm)	-	-	-	-	-	-
BMI (kg/m <sup>2</sup> )	-	-	-	-	-	-
<b>Glycometabolic parameters</b>						
Fasting glycemia (mmol/L)	-	-	-	-	-	0.20[-0.02;0.43]
HOMA index	-	-	-	-	-	-
Total cholesterol (mmol/L)	<b>-0.31[-0.57;-0.05]</b>	<b>-0.42[-0.65;-0.19]</b>	-0.14[-0.30;0.03]	-0.22[-0.71;0.27]*	<b>-0.47[-0.77;-0.17]*</b>	-0.04[-0.17;0.09]
LDL cholesterol (mmol/L)	-0.21[-0.54;0.13]	-0.33[-0.80;0.14]	0.02[-0.15;0.18]	0.06[-0.30;0.42]*	-0.25[-0.57;0.08]*	0.01[-0.12;0.13]
HDL cholesterol (mmol/L)	<b>-0.1[-0.16;-0.05]</b>	0.01[-0.05;0.08]	-0.09[-0.17;0.00]	-0.04[-0.39;0.30]*	-0.21[-0.43;0.01]*	-0.01[-0.02;0.00]
Triglycerides (mmol/L)	-0.03[-0.14;0.07]	-	-	-0.27[-0.61;0.08]*	0.15[-0.20;0.50]*	-0.13[-0.03;0.05]
<b>Inclusion criteria</b>	<b>Neto et al., 2015 (152)</b>	<b>Corona et al., 2016 (139)</b>		<b>Guo et al., 2016 (153)</b>		<b>Junjie et al., 2019 (96)</b>
Number of trials included	8	59		16		7
Number of patients analyzed	259 age ≥60 years	5,078		1,921		800
Hypogonadism definition (TT)	-	12 nmol/L		Only overall population		Only overall population
	<b>Overall population</b>	<b>Outcomes according to T levels</b>		<b>Overall population</b>		<b>Overall population</b>
<b>Body composition</b>		< 12 nM	Overall pop			
Fat mass (%)	<b>-1.78[-2.57;-0.99] kg</b>	<b>-0.39[-0.61;-0.17]</b>	<b>-0.32[-0.44;-0.19]</b>	-0.84[-1.74;0.04]		-1.10[-2.34;0.15]
Lean mass*	<b>3.59[2.38;4.81] kg</b>	<b>0.45[0.26;0.63]</b>	<b>0.51[0.37;0.66]</b>	<b>1.22[0.33;2.11]</b>		<b>1.92[0.52;1.20]</b>
Waist (cm)	-	-	-0.66[-2.66;1.35]	-		-
BMI (kg/m <sup>2</sup> )	-	-	0.25[-0.09;0.58]	0.10[-0.62;0.82]		0.32[-0.56;1.20]
<b>Glycometabolic parameters</b>						
Fasting glycemia (mmol/L)	-	<b>-0.37[-0.65;-0.09]</b>	<b>-0.34[-0.51;-0.17]</b>	-		-
HOMA -IR	-	<b>-1.27[-1.84;-0.71]</b>	<b>-0.80[-1.16;-0.45]</b>	-		-0.04[-0.24;0.16]
Total cholesterol mmol/mol	-	<b>-0.35[-0.61;-0.08]</b>	-0.12[-0.25;0.01]	<b>-0.16[-0.29;-0.03]</b>		0.05[-0.14;0.23]
LDL cholesterol	-	-	-	-		<b>-0.07[-0.13;-0.01]</b>
HDL cholesterol	-	-0.03[-0.08;0.01]	-0.03[-0.08;0.01]	-		-0.01[-0.18;0.16]
Triglycerides	-	<b>-0.22[-0.37;-0.08]</b>	-0.08[-0.18;0.01]	-		-

**Supplementary Table 6.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several body composition and glycometabolic parameters. TT= total testosterone; -= not reported.\* SDM; BMI= body mass index; LDL=low density lipoprotein; HDL= high density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance.

<b>Inclusion criteria</b>	<b>Corona et al., 2011 (154)</b>	<b>Corona et al., 2013 (155)</b>	<b>Cai et al., 2014 (156)</b>	<b>Corona et al., 2016 (5)</b>	<b>Zhang et al., 2018 (158)</b>	<b>Corona et al., 2021 (157)</b>
Number of trials included	4	5	5	8	8	12
Number of patients analyzed	228	263	351	546	596	889
Hypogonadism definition (TT)	11-15 nmol/L	11-15 nmol/L	11-15 nmol/L	11-15 nmol/L	11-15 nmol/L	8-15 nmol/L
	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>
<b>Body composition</b>						
Fat mass*	<b>-2.19[-3.94;-0.42]%</b>	-	-	-	0.33[-0.92;0.26]	<b>-0.45[-0.77;-0.13]</b>
Lean mass*	-	-	-	-		-
Waist (cm)	-	-	-	-		-
BMI (kg/m <sup>2</sup> )	-	-	-	-	0.29[-0.84;1.41]	0.06[-0.62;0.75]
<b>Glycometabolic parameters</b>						
Fasting glycemia (mmol/L)	<b>-1.18[-2.28;-0.08]</b>	<b>-1.09[-1.84;-0.35]</b>	<b>-1.10[-1.88;-0.31]</b>	<b>-0.80[-1.30;-0.30]</b>	<b>-0.98[-1.53;-0.54]</b>	<b>-0.73[-1.13;-0.33]</b>
Fasting insulin (	-	-	<b>-2.73[-3.72;-1.84]-</b>	-	<b>-1.27[-3.99;-0.95]</b>	
HOMA index					<b>-0.79[-1.23;-0.34]-</b>	<b>-1.15[-1.86;-0.44]</b>
HbA1c (%)	<b>-0.76[-0.96;-0.56]</b>	<b>-0.62[-1.00;-0.24]</b>	<b>-0.87[-1.32;-0.42]</b>	<b>-0.43[-0.72;-0.14]</b>	<b>-0.45[-1.73;-0.16]</b>	<b>-0.27[-0.47;-0.08]</b>
Total cholesterol (mmol/L)	-	-	-	-	<b>-0.29[-0.38;-0.19]</b>	-0.26[-0.56;0.04]
LDL cholesterol (mmol/L)	-	-	-	-	-0.06[-0.14;0.02]	-
HDL cholesterol (mmol/L)	-	-	-	-	0.01[-0.08;0.09]	-0.03[-0.04;0.10]
Triglycerides (mmol/L)	<b>-0.67[-0.92;-0.43]</b>	<b>-0.60[-0.83;-0.37]</b>	<b>-0.35[-0.62;-0.07]</b>	<b>-0.31[-0.54;-0.07]</b>	<b>-0.37[-0.59;-0.15]</b>	<b>-0.38[-0.60;-0.17]</b>

**Supplementary Table 7.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several body composition and glycometabolic parameters in patients with type 2 diabetes mellitus. TT= total testosterone; -=not reported.\* SDM; BMI= body mass index; LDL=low density lipoprotein; HDL= high density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance.

<b>Inclusion criteria</b>	<b>Corona et al., 2011 (158)</b>	<b>Corona et al., 2013 (155)</b>	<b>Corona et al., 2021 (157)</b>
Number of trials included	5	6	7
Number of patients analyzed	306	511	526
Hypogonadism definition (TT)	11-15 nmol/L	11-15 nmol/L	8-12 nmol/L
	<b>Overall population</b>	<b>Overall population</b>	<b>Overall population</b>
<b>Body composition</b>			
Fat mass*	-	-	<b>-0.47[-0.93;-0.02]</b>
Lean mass*	-	-	-
Waist (cm)	<b>-5.13[-9.07;-1.18]</b>	<b>-4.09[-7.78;-0.39]</b>	<b>-3.81[-6.92;-0.69]</b>
BMI (kg/m <sup>2</sup> )	-	-	0.02[-1.04;1.08]
<b>Glycometabolic parameters</b>			
Fasting glycemia (mmol/L)	<b>-0.49[-0.83;-0.15]</b>	<b>-0.48[-0.78;-0.19]</b>	<b>-0.40[-0.74;-0.07]</b>
HOMA index	<b>-1.48[-2.16;-0.79]</b>	<b>-1.54[-2.19;-0.50]</b>	<b>-1.38[-2.07;-0.70]</b>
HbA1c (%)	-	-	<b>-0.88[-1.40;-0.35]</b>
Total cholesterol (mmol/L)	-	-	-0.11[-0.26;0.05]
LDL cholesterol (mmol/L)	-	-	-
HDL cholesterol (mmol/L)	<b>0.10[0.00;0.20]</b>	-	0.05[-0.05;0.16]
Triglycerides (mmol/L)	<b>-0.43[-0.73;-0.12]</b>	<b>-0.40[-0.66;-0.14]</b>	<b>-0.32[-0.59;-0.06]</b>

**Supplementary Table 8.** Comparisons of the available meta-analyses evaluating the relationship between testosterone replacement therapy and several body composition and glycometabolic parameters in patients with metabolic syndrome. TT= total testosterone; -=not reported.\* SDM; BMI= body mass index; LDL=low density lipoprotein; HDL= high density lipoprotein; HOMA-IR: homeostasis model assessment-insulin resistance.