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Effects of testosterone therapy on BMI, blood pressure, and laboratory profile of transgender men: a systematic review

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SUMMARY

Testosterone is the main hormonal agent used for cross-sex hormone therapy in female-to-male transgender persons. Our aim was to systematically review the literature concerning the effects of testosterone on body mass index (BMI), blood pressure, hematocrit, hemoglobin, lipid profile, and liver enzymes in transgender men. PUBMED and EMBASE were searched for studies published until March 2017. Studies were included if they reported interventions with any dose of testosterone and comparison of variables before and during treatment. Of 455 potentially eligible articles, 13 were reviewed. Study duration ranged from 6 to 60 months, sample size ranged from 12 to 97 patients, and the most common treatment was parenteral testosterone undecanoate 1000 mg/12 weeks. Slight but significant increases in BMI were reported (from 1.3 to 11.4%). Three out of seven studies assessing the impact of different testosterone formulations on blood pressure detected modest increases or clinically irrelevant changes in this variable. In another study, however, two patients developed hypertension, which was resolved after cessation of testosterone therapy. Decreases in HDL-cholesterol and increases in LDL-cholesterol were consistently observed. Eight studies observed a relationship between testosterone and increased hemoglobin (range: 4.9–12.5%) and hematocrit (range: 4.4–17.6%), but discontinuation of androgen therapy was not necessary. In one study, two patients developed erythrocytosis (hematocrit >52%) after 9 and 12 months of treatment. One study analyzing testosterone formulations observed smaller increases in hemoglobin and hematocrit with testosterone gel. Six studies assessing liver function showed slight or no changes. Overall, the quality of evidence was low, given the lack of randomized clinical/controlled trials and the small sample sizes. In conclusion, exogenous testosterone administration to transgender men was associated with modest increases in BMI, hemoglobin/hematocrit, and LDL-cholesterol, and with decreases in HDL-cholesterol. Long-term studies are needed to assess the long-term risks of testosterone therapy, particularly as they relate to cardiometabolic risks such as diabetes, dyslipidemia and the metabolic syndrome.

INTRODUCTION

Gender dysphoria is characterized by a persistent desire to live and be accepted as a member of the opposite sex (World Health Organization, 1992; American Psychiatric Association, 2000, 2013). People who experience gender dysphoria require cross-sex hormones to induce secondary sexual characteristics of the desired sex. In this context, female to male transgender persons (transgender men) may desire treatment with androgen hormones to induce virilization (Moore *et al.*, 2003; Gooren, 2005).

Testosterone is the main hormonal agent used for cross-sex hormone therapy in transgender men. Injectable testosterone esters have been traditionally used, administered in doses of 100–250 mg every 7–21 days (Pelusi *et al.*, 2014). A long-acting testosterone undecanoate formulation which maintains more stable levels of testosterone is also available (Pelusi *et al.*, 2014). In addition, transdermal testosterone formulations, administered as gel or patches, are another option for transgender men, which is available in many countries.

Few studies so far have evaluated the effects of testosterone therapy in transgender men. Some suggest that testosterone administration is safe and associated with low risk of adverse effects (Hembree *et al.*, 2009; Coleman *et al.*, 2012). Other

studies, however, have reported hypertension, increased erythropoiesis, decreased high density lipoprotein (HDL), increased low-density lipoprotein (LDL), elevation of liver enzymes, obesity, and acne, among others, associated with this treatment in transgender individuals (Van Kesteren *et al.*, 1997; Michel *et al.*, 2001; Levy *et al.*, 2003; Moore *et al.*, 2003).

Therefore, the aim of the present systematic review was to summarize the available information regarding the effects of testosterone administration on clinical and metabolic variables of transgender men, especially body mass index (BMI), blood pressure, and hematologic and metabolic profiles.

MATERIALS AND METHODS

Search strategy and study selection

This systematic review was performed in accordance with PRISMA guidelines (Stroup *et al.*, 2000; Liberati *et al.*, 2009). Medline (PUBMED) and EMBASE databases were searched for articles published until March/2017. There were no other limits except for the end date.

The following search strategy was developed for PUBMED and modified as needed for EMBASE: 'transsexualism' or 'transgender person' or 'person, transgender' or 'persons, transgender' or 'transgenders' or 'transgender' or 'transgendered persons' or 'person, transgendered' or 'persons, transgendered' or 'transgendered person' or 'transsexual persons' or 'person, transsexual' or 'persons, transsexual' or 'transsexual person' and 'testosterone' or 'cross sex hormone therapy.'

The selection criteria for the studies were as follows: focus on transgender men, intervention with any dose of testosterone, and comparison of clinical and metabolic variables before and during/after treatment. The main outcomes of interest were BMI, blood pressure, hematocrit, hemoglobin, lipid profile, and liver enzymes.

Data extraction and quality control

Two investigators independently screened titles and abstracts of all articles selected in order to evaluate if the studies were eligible for inclusion in the systematic review. The selected articles were read in full for confirmation of eligibility and data extraction. Disagreements were resolved by discussion among all investigators. The following information was extracted from each individual study: name of the first author, publication year, country, number of subjects, duration of the follow-up, intervention, and evaluation time.

RESULTS

Study selection

Figure 1 shows the flowchart of study selection. Initially, 455 potentially eligible articles were identified; 438 were excluded after reading the abstracts and/or titles; and 17 articles were read in full. After this step, three articles were excluded because the variables of interest were not reported, and one because a progestin was added to androgen treatment. Thirteen articles were thus included in the systematic review (Giltay *et al.*, 2004; Berra *et al.*, 2006; Jacobeit *et al.*, 2007, 2009; Mueller *et al.*, 2007, 2010; Chandra *et al.*, 2010; Cupisti *et al.*, 2010; Pelusi *et al.*, 2014; Wierckx *et al.*, 2014; Deutsch *et al.*, 2015; Quirós *et al.*, 2015; Fisher *et al.*, 2016).

Characteristics of included studies

As shown in Table 1, study duration ranged from 6 to 60 months, sample size ranged from 12 to 97 patients, and the most common treatment was parenteral testosterone undecanoate 1000 mg/12 weeks, which was reported in eight of 13 articles (Jacobeit *et al.*, 2007, 2009; Mueller *et al.*, 2007, 2010; Cupisti *et al.*, 2010; Pelusi *et al.*, 2014; Wierckx *et al.*, 2014; Quirós *et al.*, 2015; Fisher *et al.*, 2016). The design of most studies was observational (non-controlled).

Most of the studies followed a protocol in which a second injection of testosterone undecanoate was prescribed 6 weeks after the first administration, with subsequent 1000 mg injections recommended every 12 weeks. However, one study (Quirós *et al.*, 2015) prescribed either intramuscular testosterone undecanoate 1000 mg or 1% transdermal gel, according to patient

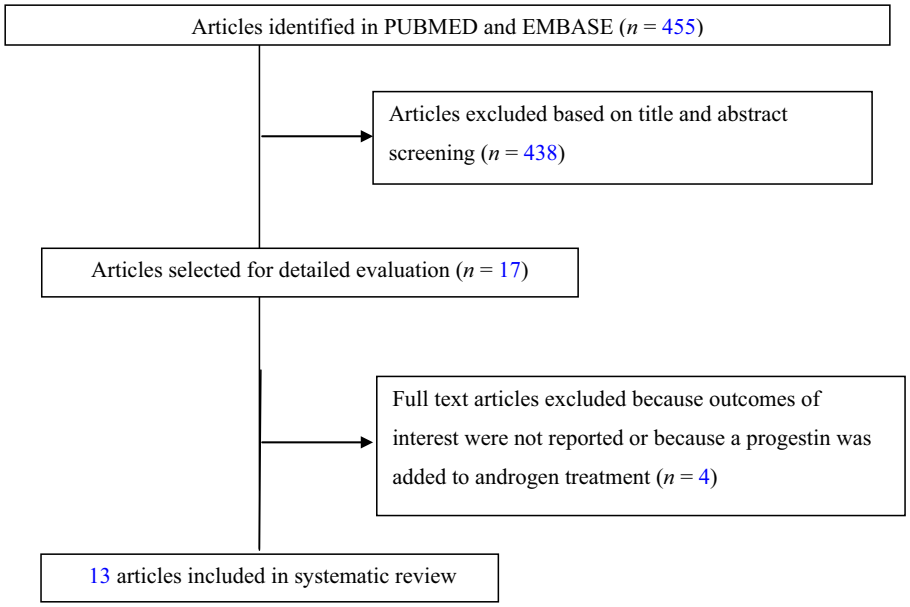

Figure 1 PRISMA flow diagram of the study selection process.

Table 1 Characteristics of the studies included in the systematic review about the effects of testosterone on transgender men

Study	Country	*n*	Treatment duration (months)	Mean age (years)	Treatment	Variables assessed
Giltay *et al.* (2004)	Netherlands	81	7	36.7 (21–61)[a]	-Testosterone esters (250 mg/2 weeks) -Oral testosterone undecanoate (160–240 mg/day)	BMI, blood pressure, lipid profile
Berra *et al.* (2006)	Italy	16	6	30.4 ± 3.4	Testosterone enanthate (100 mg) + testosterone propionate (25 mg/10 days)	BMI, blood pressure, lipid profile
Jacobeit *et al.* (2007)	Netherlands	12	12	33.0 ± 6.0	Testosterone undecanoate (1000 mg/12 weeks)	Lipid profile, hematocrit/ hemoglobin
Mueller *et al.* (2007)	Germany	35	12	29.6 ± 8.9	Testosterone undecanoate (1000 mg/12 weeks)	BMI, blood pressure, lipid profile, liver function, hematocrit and hemoglobin
Jacobeit *et al.* (2009)	Netherlands	17	36	34.0 ± 7.0	Testosterone undecanoate (1000 mg/12 weeks)	Lipid profile, liver function, hematocrit and hemoglobin
Mueller *et al.* (2010)	Germany	45	24	30.4 ± 9.1	Testosterone undecanoate (1000 mg/12 weeks)	BMI, blood pressure, lipid profile, liver function, hematocrit and hemoglobin
Cupisti *et al.* (2010)	Netherlands	29	12	29.9 (18–40)[a]	Testosterone undecanoate (1000 mg/12 weeks)	BMI
Chandra *et al.* (2010)	United States	12	12	29.0 ± 9.0	Testosterone cypionate or testosterone enanthate (50–125 mg/2 weeks)	BMI, blood pressure, lipid profile, liver function, hematocrit
Pelusi *et al.* (2014)	Italy	45	12	28.2 (25.6–30.9)[a] −29.4 (26.6–32.1)[a] −30.9 (27.9–33.9)[a]	-Testosterone undecanoate (1000 mg/12 weeks) -Testosterone gel (5 mg/day) -Testosterone enanthate (100 mg/10 days)	BMI, lipid profile, liver function, hematocrit and hemoglobin
Wierckx *et al.* (2014)	Belgium (Ghent) Norway (Oslo)	27 26	12	27.3 ± 8.5 21.7 ± 5.1	Testosterone undecanoate (1000 mg/12 weeks)	BMI, blood pressure, lipid profile, liver function, hematocrit
Quirós *et al.* (2015)	Spain	97	24	28.6 ± 8.6	-Testosterone gel (5 g/day) -Testosterone undecanoate (1000 mg/12 weeks)	BMI, blood pressure, lipid profile, hemoglobin
Deutsch *et al.* (2015)	United States	31	6	27.0 ± 6.9	-Testosterone gel (5 g/day) -Testosterone cypionate (50 mg/week) -Testosterone patch (4 mg/day)	BMI, blood pressure, lipid profile
Fisher *et al.* (2016)	Italy	26	24	33.9 ± 9.2[b]	-Testosterone undecanoate (1000 mg/12 weeks) -Testosterone enanthate[c] -Transdermal testosterone[c]	BMI

BMI, body mass index. [a]Median and interquartile interval. [b]Age of all sample (transgender men and women). [c]Dose not informed.

preference and depending on the patient's clinical condition. Other testosterone formulations were also prescribed: testosterone patch (4 mg/day) (Deutsch *et al.*, 2015), testosterone gel (1%, 5 g/day) (Deutsch *et al.*, 2015; Quirós *et al.*, 2015), testosterone cypionate (Chandra *et al.*, 2010; Deutsch *et al.*, 2015); testosterone enanthate (100 mg) associated with testosterone propionate (25 mg/10 days) (Berra *et al.*, 2006; Fisher *et al.*, 2016); testosterone esters (250 mg/2 weeks); and oral testosterone undecanoate (160–240 mg/day) (Giltay *et al.*, 2004) (Table 1). Except for one study (Quirós *et al.*, 2015), all others included only patients without previous treatment. In the study by Quirós *et al.* (2015), 13.4% of the patients had already used some hormone therapy.

Qualitative data synthesis

Most participants in the studies were around 30 years of age (Table 1). Ten studies included participants living in Europe, and two included participants living in the United States. Baseline prevalence of obesity and hypertension varied among the studies, as can be inferred from baseline BMI and blood pressure values (Tables 2 and 3).

The prevalence of smoking was high in the five studies that reported this cardiovascular risk factor: 37% (Mueller *et al.*, 2007), 30% (Chandra *et al.*, 2010), 51% (Pelusi *et al.*, 2014), 20% (Wierckx *et al.*, 2014), and 60% (Quirós *et al.*, 2015). Slight but significant increases in BMI were observed in most studies, ranging from 1.3 to 11.4%, during testosterone treatment (Table 2). In three studies using bioimpedance (Berra *et al.*, 2006) or dual-energy X ray absorptiometry (DXA) (Pelusi *et al.*, 2014; Wierckx *et al.*, 2014) to assess body composition, an increase in lean mass and reduction in fat mass were also detected during androgen treatment. One study observed a lean mass gain of up to 14.6% after only 6 months of androgen therapy (Berra *et al.*, 2006). Among the studies that evaluated body composition by DXA, lean mass gain ranged from 8.5% (Pelusi *et al.*, 2014) to 12.3% (Wierckx *et al.*, 2014) within 12 months of follow-up. Three other studies reported no changes in BMI during testosterone therapy (Chandra *et al.*, 2010; Cupisti *et al.*, 2010; Mueller *et al.*, 2010), but one had a sample limited to only 12 patients (Chandra *et al.*, 2010). While Mueller *et al.* (2010) found no changes in BMI, a significant increase in 4.7% in lean mass was detected.

Seven studies (Giltay *et al.*, 2004; Mueller *et al.*, 2007, 2010; Chandra *et al.*, 2010; Wierckx *et al.*, 2014; Deutsch *et al.*, 2015; Quirós *et al.*, 2015) assessed the impact of various testosterone formulations on blood pressure levels in transgender men. One of these studies (Mueller *et al.*, 2007) observed a slight increase in systolic and diastolic blood pressure during testosterone treatment; two studies found a modest increase only in systolic blood pressure (Mueller *et al.*, 2010 and Wierckx *et al.*, 2014) while two did not observe significant changes (Deutsch *et al.*, 2015 and Quirós *et al.*, 2015) and one reported a decrease in systolic and

Table 2 Effects of testosterone administration on BMI, lipid profile and liver enzymes in transgender men

Study	BMI	Lipid profile	Liver enzymes (U/I)
Giltay *et al.* (2004)	22.89 ± 4.53 and 24.46 ± 3.85; ↑6.8%, $p < 0.001$	TC (mmol/L): 4.57 ± 0.87 and 4.53 ± 1.12; ↓0.8%, p = NS HDL (mmol/L):1.41 ± 0.43 and 1.14 ± 0.29; ↓19.1%, $p < 0.001$ LDL (mmol/L): 2.72 ± 0.86 and 3.03 ± 1.14; ↑11.3%, $p = 0.002$ TGL(mmol/L): 0.70 (0.55–1.20) and 0.80 (0.60–1.05); ↑14.2%, p = NS	NA
Berra *et al.* (2006)	21.8 ± 2.9 and 22.8 ± 25.6; ↑4.5%, $p < 0.001$	TC (mmol/L): 4.5 ± 0.8 and 4.7 ± 0.7; ↑4.4%, p = NS HDL (mmol/L):1.7 ± 0.4 and 1.5 ± 0.4; ↓11.7%, $p < 0.005$ LDL (mmol/L):2.5 ± 0.8 and 2.8 ± 0.8; ↑12%, p = NS TGL (mmol/L): 0.6 ± 0.1 and 0.7 ± 0.1, ↑16.6%, p = NS	NA
Jacobeit *et al.* (2007)	NA	TC (mg/dL); 215.8 ± 58.5 and 196.7 ± 39.6; ↓8.8%, $p < 0.05$ HDL (mg/dL): 51.7 ± 10.8 and 52.2 ± 11.6; ↑0.9%, p = NS LDL (mg/dL): 140.5 ± 47.0 and 118.3 ± 30.7; ↓15.8%, <0.05	NA
Mueller *et al.* (2007)	23.94 ± 4.86 and 24.29 ± 4.64; ↑1.4%, $p = 0.03$	TC (mg/dL): 187.26 ± 45.65 and 191.00 ± 42.09; ↑1.9%, p = NS HDL (mg/dL): 59.00 ± 10.88 and 48.29 ± 9.77; ↓18.1%, $p < 0.0001$ LDL (mg/dL):126.60 ± 35.27 and 133.49 ± 36.87; ↑5.4%, p = NS TGL (mg/dL): 122.14 ± 54.67 and 152.43 ± 51.24; ↑24.7%, $p = 0.02$	AST: 18.9 ± 6.3 and 21.7 ± 6.8; ↑14.9%, $p = 0.05$ ALT:20.3 ± 9.9 and 24.5 ± 9.4; ↑20.4%, $p = 0.05$ GGT:15.8 ± 11.0 and 20.7 ± 12.2; ↑30.8%, $p = 0.05$
Jacobeit *et al.* (2009)	NA	TC (mg/dL): 218 ± 47 and 188 ± 42; ↓13.7%, $p < 0.05$ HDL (mg/dL): 50 ± 11 and 51 ± 10; ↑2%, p = NS LDL (mg/dL): 139 ± 48 and 119 ± 46; ↓14.3%, $p < 0.05$ TGL (mg/dL): 88 ± 14 and 87 ± 15; ↓1.1%, p = NS	AST:24 ± 9 and 23 ± 9; ↓4.1%, p = NS ALT:22 ± 7 and 22 ± 7; 0%, p = NS
Mueller *et al.* (2010)	24.1 ± 4.5 and 24.2 ± 3.8; ↑0.4%, p = NS	TC (mg/dL):185.8 ± 33.4 and 185.8 ± 34.0; 0%, p = NS HDL (mg/dL): 61.8 ± 16.3 and 47.3 ± 13, ↓23.4%; $p < 0.0001$ LDL (mg/dL): 131.2 ± 32.4 and 141.4 ± 29.0; ↑7.7%, $p = 0.05$ TGL (mg/dL): 120.5 ± 64.0 and 148.3 ± 43.2; ↑23%, $p < 0.01$	AST: 19.6 ± 6.4 and 21.3 ± 4.5; ↑8.6%, p = NS ALT: 19.9 ± 9.6 and 22.9 ± 4.6; ↑15%, $p < 0.01$ GGT:16.4 ± 12.7 and 25.2 ± 11.0; ↑53.5%; $p < 0.0001$
Cupisti *et al.* (2010)	23.5 (21.6–26.0) and 24.2 (22.0–26.5); ↑2.9%; $p = 0.001$	NA	NA
Chandra *et al.* (2010)	27.5 ± 5.2 and 27.6 ± 3.9; ↑0.3%, p = NS	TC(mg/dL):184 ± 26 and 181 ± 34; ↓1.6%, p = NS HDL (mg/dL): 52 ± 11 and 40 ± 7; ↓23%; $p < 0.001$ LDL (mg/dL):113 ± 22 and 121 ± 29; ↑7.0%, p = NS TGL (mg/dL);92 ± 72 and 94 ± 41;↑2.1%, p = NS	AST: 21 ± 5 and 25 ± 7; ↑19%; p = NS ALT: 19 ± 7 and 24 ± 10; ↑26.3%; $p < 0.01$
Pelusi *et al.* (2014)	22.1 (19.5–24.6) and 22.4 (20.0–24.8); ↑1.3% a 23.9 (21.2–26.6) and 24.3 (21.8–26.9); ↑1.6% b	TC(mg/dL): 161.5 (145.8–177.1) and 172.6(152.5–192.7); ↑6.8%a 161.3 (145.6–176.9) and 155.7(135.6–175.8); ↓3.4% b 174.4 (158.7–190.1) and 178.6 (158.7–198.7); ↑2.4% c p = NS HDL (mg/dL): 62.9 (52.9–70.8) and 58.9(50.167.7); ↓6.3%a 67.8 (60.2–75.4) and 58.0(49.6–66.4); ↓14.4%b 70.2 (62.6–77.8) and 58.3 (49.9–66.6); ↓16.9% c $p < 0.0005$ LDL (mg/dL): 83.3 (67.3–99.3) and 98.9(79.8–118.2); ↑18.7%a 82.0 (66.8–97.3) and 84.9(66.6–103.1); ↑3.5%b 92.6 (77.4–107.8) and 107.0 (88.7–125.3); ↑15.5% c $p = 0.001$	AST: 16.9 (13.7–20.1) and 19.4 (16.5–22.3); ↑14.7% a 20.2 (16.9–23.4) and 18.8 (15.9–21.7); ↓6.9% b 16.6 (13.7–19.5) and 18.4 (15.7–21.1); ↑10.8% c p = NS
	22.3 (19.9–24.6) and 23.6 (21.4–25.8); ↑5.8% c; $p < 0.0005$	TGL (mg/dL):72.5 (54.0–90.9) and 68.7(41.3–96.2); ↓5.2% a 60.8 (40.4–81.2) and 71.1(40.8–101.5) b 57.4 (38.1–76.7) and 62.6 (33.8–91.4); ↑9.0% c p = NS	ALT:12.8 (9.5–16.1) and 17.4 (11.9–22.8); ↑35.9% a 15.2 (11.9–18.5) and 15.0 (9.6–20.4); ↓1.3% b 14.5 (11.5–17.6) and 15.3 (10.3–20.3) c ↑5.5% c p = NS
Wierckx *et al.* (2014)	24.8 ± 5.3 and 25.6 ± 4.4; ↑3.2%; $p = 0.01$	TC (mg/dL): 171.9 ± 28.1 and 178.2 ± 30.6; ↑3.6%, $p = 0.04$ HDL (mg/dL): 56.3 ± 12.7 and 47.8 ± 10.7; ↓15%; $p < 0.001$ LDL (mg/dL): 98.4 ± 26.3 and 116.1 ± 28.9; ↑17.9%; $p = 0.006$ TGL(mg/dL): 69.0 (51.7–89.5) and 81.1 (65.3–124.6); ↑17.5%; $p < 0.001$	AST: 20.0 (17–23) and 24 (18–29.5); ↑20%; $p = 0.01$ ALT: 16.0 (11.5–20) and 20 (15–25); ↑25%; $p = 0.02$
Quirós *et al.* (2015)	25.0 ± 4.7 and 26.0 ± 3.8; ↑4%; p = 003	TC (mg/dL):166.0 ± 35.1 and 175.6 ± 38.2; ↑5.7%; $p = 0.001$ HDL (mg/dL): 52.2 ± 12.2 and 45.4 ± 13.8; ↓13%; $p = 0.001$ LDL (mg/dL): 103.8 ± 28.7 and 112.8 ± 30.3; ↑8.6%; $p = 0.013$ TGL (mg/dL): 70.6 ± 30.7 and 102.3 ± 68.5; ↑44.9%; $p < 0.001$	NA
Deutsch *et al.* (2015)	29.1 ± 11.2 and 30.0 ± 11.4; ↑3%; $p = 0.024$	TC (mg/dL): 177 ± 38 and 178 ± 42; ↑0.5%; p = NS HDL (mg/dL): 58 ± 22 and 56 ± 29; ↓3.4%; $p = 0.006$ LDL (mg/dL): 93 ± 33 and 97 ± 38; ↑4.3%; p = NS TGL (mg/dL): 75 ± 56 and 73 ± 69; ↓2.6%; p = NS	NA
Fisher *et al.* (2016)	24.9 ± 0.5 and 27.7 ± 4.0; ↑11.4% $p < 0.01$	NA	NA

Data are expressed as before and during treatment and %change. BMI, body mass index; TC, total cholesterol; TGL, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not available; NS, not significant.

Table 3 Effects of testosterone administration on blood pressure, hemoglobin and hematocrit in transgender men

Study	Blood pressure (mmHg)	HB	HT
Giltay *et al.* (2004)	SBP: 126.62 ± 13.14 and 122.02 ± 10.75; ↓3.6%; $p = 0.005$ DBP: 79.80 ± 8.00 and 77.72 ± 6.81; ↓2.6%; $p = 0.032$	NA	NA
Berra *et al.* (2006)	NA	NA	NA
Jacobeit *et al.* (2007)	NA	13.8 ± 1.22 and 15.1 ± 0.68, ↑9.4%, $p < 0.05$	41.0 ± 3.6 and 44.3 ± 1.4, ↑8%, $p < 0.05$
Mueller *et al.* (2007)	SBP:129.43 ± 13.38 and 133.71 ± 11.33;↑3.3%; $p = 0.04$ DBP: 81.14 ± 8.14 and 84.00 ± 5.25; ↑3.5%; $p = 0.02$	13.17 ± 1.35 and 14.83 ± 1.15; ↑12.6%; $p < 0.0001$	41.50 ± 3.33 and 46.25 ± 3.35, ↑11.4%, $p < 0.0001$
Jacobeit *et al.* (2009)	NA	13.6 ± 1.2 and 16.0 ± 1.5; ↑17.6%; $p < 0.05$	41.0 ± 4.0 and 46.0 ± 4.0; ↑12.1%; $p < 0.05$
Mueller *et al.* (2010)	SBP: 129.3 ± 12.0 and 135.1 ± 10.3: ↑4.4%; $p = 0.01$ DBP: 81.0 ± 8.1 and 83.8 ± 9.1; ↑3.4%; $p = 0.21$	13.2 ± 1.5 and 14.6 ± 0.7; ↑10.6%; $p < 0.0001$	41.2 ± 3.2 and 44.7 ± 3.7; ↑8.4%; $p < 0.0001$
Cupisti *et al.* (2010)	NA	NA	NA
Chandra *et al.* (2010)	MBP: 87 ± 14 and 91 ± 16; ↑4.5%; p = NS	NA	40 ± 2 and 45 ± 5; ↑12.5%; $p < 0.001$
Pelusi *et al.* (2014)	NA	13.3 (12.7–13.8) and 14.6 (13.8–15.4); ↑9.7% a 13.5 (12.9–14.0) and 14.1 (13.2–14.9); ↑4.4% b 12.6 (12.0–13.2) and 14.3 (13.5–15.2); ↑13.4% c; $p < 0.0005$	39.1 (37.7–40.5) and 43.4 (41.5–45.3);↑10.9% a 40.6 (39.1–42.2) and 42.6 (40.5–44.6); ↑4.9 b 38.4 (36.8–39.9) and 43.1 (40.9–45.2); ↑12.2% c; $p < 0.0005$
Wierckx *et al.* (2014)	SBP: 111.5 ± 12.6 and 115.6 ± 11.7; ↑3.6%; $p = 0.05$ DBP: 70.2 ± 10.5 and 72.5 ± 9.2; ↑3.2%; p = NS	NA	40.8 ± 2.9 and 45.8 ± 3.0; ↑12.2%; $p < 0.001$
Quirós *et al.* (2015)	SBP: 118.2 ± 9.1 and 120.4 ± 13.0; ↑1.8%; p = NS DBP: 75.2 ± 8.9 and 76.7 ± 9.4; ↑1.9%; p = NS	13.5 ± 12.1 and 15.3 ± 18.0; ↑13.3%; $p < 0.001$	NA
Deutsch *et al.* (2015)	SBP:120 ± 23 and 123 ± 14; ↑2.5%; p = NS DBP: 72 ± 16 and 70 ± 16; ↓2.7%; p = NS	NA	NA

HB, hemoglobin; HT, hematocrit; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean arterial blood pressure; NA, not available; NS, not significant.

diastolic blood pressure levels (Giltay *et al.*, 2004). In one study, blood pressure was expressed as mean arterial pressure, and no changes were observed (Chandra *et al.*, 2010) (Table 3).

Data on changes in lipid profile are presented in Table 3. While decreases in HDL-c and increases in LDL-c were consistently observed in most studies, unfavorable changes in total cholesterol and triglycerides were less uniform and varied between studies.

Eight studies assessed hemoglobin and/or hematocrit levels (Table 3), and all observed a relationship between testosterone administration and increased hemoglobin and hematocrit levels. Reference values for males were not exceeded in any of these studies, as inferred from the study results or, in three studies, explicitly reported (Jacobeit *et al.*, 2007; Mueller *et al.*, 2007, 2010); discontinuation of androgen therapy was not required. The increase in hemoglobin ranged from 4.9% (Pelusi *et al.*, 2014) to 12.5% (Chandra *et al.*, 2010), while the increase in hematocrit levels ranged from 4.4% (Pelusi *et al.*, 2014) to 17.6% (Jacobeit *et al.*, 2009). The only study performing a separate analysis of different testosterone formulations observed smaller increases in hemoglobin and hematocrit in patients treated with testosterone gel (Pelusi *et al.*, 2014).

The six studies assessing liver function showed only slight or no changes during testosterone administration (Table 2). The increases did not exceed male reference values.

Adverse effects

Severe adverse effects were not reported by any of the 12 studies. However, in one study (Mueller *et al.*, 2007), two patients developed hypertension. Arterial blood pressure returned to normal after cessation of testosterone therapy. In another study (Wierckx *et al.*, 2014), two patients developed erythrocytosis (hematocrit levels above 52%, the upper limit of the normal adult male range) after 9 and 12 months of treatment. In the same study, two subjects were switched from testosterone undecanoate to short-acting testosterone esters after 9 and 12 months, mainly because of muscle and joint aches.

In one study, hair loss was associated with the duration of androgen administration, and was present in about 50% of subjects after 13 years (Giltay *et al.*, 2004). Hair loss was not associated with BMI, blood pressure or lipid profile during the first 3–4 months of androgen therapy. Acne was observed in approximately 15% of patients in two studies (Mueller *et al.*, 2007, 2010).

DISCUSSION

The present systematic review summarizes the literature on the effects of testosterone therapy on BMI, blood pressure, metabolic profile, hematocrit, hemoglobin, and liver enzymes in transgender men. Although only a few studies are available, there is agreement regarding the relative safety of short term testosterone treatment in transgender men (Gooren *et al.*, 2008;

Irwig, 2016). The studies analyzed describe various periods of exposure to different testosterone formulations and show only modest unfavorable changes in BMI, lipid profile, and hematological variables.

Indeed, until now, only two meta-analyses of data on testosterone treatment of transgender men have been published (Elamin *et al.*, 2010; Klaver *et al.*, 2016): the first of these studies addressed cardiovascular risk events, blood pressure, and lipid profile (Elamin *et al.*, 2010), and the second examined the effects of cross-sex hormone therapy on body composition (Klaver *et al.*, 2016). Elamin *et al.* (2010) found mild changes in lipids and in blood pressure levels. However, because of methodological limitations, the data were inconclusive regarding relevant outcomes such as mortality, stroke, myocardial infarction, or venous thromboembolism.

Sex steroid hormones are important determinants of regional fat deposition (Elbers *et al.*, 1999). In this study, only a very modest increase in BMI was observed in most, but not all, studies. This finding is in line with data from the European Network for Investigation of Gender Incongruence (ENIGI), which did not report changes in BMI after 1 year of parenteral testosterone treatment (Van Caenegem *et al.*, 2015). In turn, a recent meta-analysis about the effects of testosterone on body composition in 354 transgender men found an increase in total body weight and lean body mass, and a decline in body fat (Klaver *et al.*, 2016). These results may reflect the use of different androgen formulations and/or treatment duration, which ranged from 3 to 24 months. Interestingly, in our review, the studies analyzing body composition also reported a significant increase in lean mass, suggesting a link between increased BMI and lean mass gain.

Regarding the effects of testosterone treatment on blood pressure in transgender men, mild, clinically irrelevant, or no changes were found in most studies. However, one study reported two case of hypertension, with return to normal blood pressure values after cessation of testosterone therapy. Other studies beyond the ones included in the present review have reported similar increases (Emi *et al.*, 2008) and decreases (Gooren *et al.*, 2008) in blood pressure during/following testosterone treatment in transgender men. This discrepancy could be explained by differences in ethnicity or treatment duration. In addition, no data are yet available regarding older patients or hypertensive transgender men receiving cross-sex hormone therapy.

In the present review, the effect of the various testosterone formulations seemed to be more unfavorable for HDL- and LDL-cholesterol as compared to the other lipid profile-related variables. Indeed, discrepant results were observed for total cholesterol and triglycerides. A previous systematic review and meta-analysis addressing the effects of different androgen formulations on cardiovascular risk has reported an increase in triglycerides after testosterone treatment of transgender men (Elamin *et al.*, 2010).

In addition, considering that the treatment of hypogonadal men involves testosterone replacement in similar doses to those administered to transgender men, data regarding that population may also be relevant to assess the effects of testosterone treatment on lipid profile in transgender men. In this sense, a recent review and meta-analysis including 16 studies and 1921 hypogonadal individuals to evaluate the efficacy and safety of testosterone therapy found that exogenous testosterone was associated with lower serum concentrations of total cholesterol only after long-term therapy (Guo *et al.*, 2016). In turn, a study with 120 hypogonadal men showed an increase in LDL levels after 8 years of treatment (Permpongkosol *et al.*, 2016). Therefore, further long-term clinical trials are needed to confirm the impact of androgen treatment on LDL-cholesterol in transgender men.

Erythropoiesis is one of the many physiological functions stimulated by androgens. Studies suggest that androgens act indirectly to stimulate erythropoietin and directly to stimulate erythropoiesis in bone marrow (Shahani *et al.*, 2009; Bachman *et al.*, 2014). In a recent meta-analysis about the adverse effects of testosterone treatment in hypogonadal men, Fernandez-Balsells *et al.*, (2010) found a positive association between increased testosterone levels and higher hematocrit and hemoglobin, which is in agreement with our review. In fact, we found a mild increase in hematocrit and hemoglobin in some studies; the final values, however, were still within the physiological male range. While a study of long-term and side effects of cross-sex hormone therapy in transgender people did not observe cardiovascular events or deep venous thrombosis in transgender men (Wierckx *et al.*, 2012), increases in hematocrit and hemoglobin related to sex-hormone therapy may represent a concern in older transgender men, in those who are obese, dyslipidemic and/or hypertensive, and therefore at higher risk of cardiovascular events such as thrombosis. Indeed, the goal of cross-sex hormone treatment for transgender men should be to achieve equal or slightly lower male physiological levels of serum testosterone to maintain adequate androgenization (Hembree *et al.*, 2009; Traish & Gooren, 2010; Meriggiola & Gava, 2015).

Regarding liver enzymes, the studies included in our systematic review again showed inconsistent results; AST and ALT levels remained unchanged in some studies, while others reported increases in these variables after testosterone treatment. It should be noted, however, that the reported increases were not clinically relevant (Mueller *et al.*, 2010). Our data are consistent with the results reported by other studies showing no significant alterations (Meriggiola *et al.*, 2008; Traish & Gooren, 2010). Nevertheless, a retrospective study of morbidity aspects in 293 transgender men found a transient elevation (<6 months) in liver enzymes in 13 patients, and a persistent elevation (more than 6 months) in 20 patients during testosterone treatment (Van Kesteren *et al.*, 1997). Therefore, long-term studies are needed to assess the impact of androgen therapy on liver function. Meanwhile, monitoring liver enzymes might be restricted to transgender men presenting other medical conditions related to risk of potential liver dysfunction, such as obesity, dyslipidemia, insulin resistance associated to type 2 diabetes.

Limitations of the present systematic review are the small number of published articles and the small sample sizes. However, similar analyses are not available in the literature, and since the impact of androgen treatment on transgender men is not fully established, the present findings may serve as basis for future studies.

In conclusion, the present review showed that exogenous testosterone administration to transgender men was associated with modest increases in BMI, hemoglobin/hematocrit, and LDL-cholesterol and decreases in HDL-cholesterol. Less

consistent results were observed for blood pressure values, total cholesterol, triglycerides and liver enzymes. Overall, the studies included in this review had low quality of evidence, mainly because of the absence of clinical randomized trials or controlled studies and to low sample sizes, suggesting that caution is still necessary when prescribing hormone therapy to transgender men, especially those presenting risk factors. Further studies are needed in order to verify the impact of age and cardiometabolic comorbidities on safety, and to investigate if specific formulations are more adequate for transgender men at metabolic or cardiovascular risk.

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DISCLOSURES

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

IV was involved in data collection, analysis/interpretation, drafting of article. TF was involved in data collection, analysis/interpretation, critical revision of article. PZ was involved in data analysis/interpretation, critical revision of article. PMS was involved in concept/design, data analysis/interpretation, drafting of article, critical revision of article. All authors read and approved the final manuscript.

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