Blood pressure responses to testosterone therapy are amplified by hematocrit levels in opioid-induced androgen deficiency: a double-blind, randomized, placebo-controlled trial

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Our study aimed to examine the effect of testosterone replacement therapy (TRT) on blood pressure in opioid-treated men with relative hypogonadism, and whether the effect of TRT on blood pressure was modified by body composition, red blood cell levels, or carotid intima media thickness. Men (over 18 years old) receiving opioid treatment and total testosterone less than 12 nmol were randomly assigned to receive either TRT or placebo. Baseline and 6-month measurements included anthropometric measurements, office blood pressure (OBPM), 24-h ambulatory blood pressure, blood samples, and carotid ultrasound.

The mean systolic OBPM increased by 6.2 mmHg (0.2–12.1) in the TRT group and decreased by 7.0 mmHg (1.0–15.1) in the placebo group, with a mean difference of 13.2 mmHg (3.4–23.1), $P = 0.01$. In the TRT group, a 10 mmHg increase in systolic OBPM was associated with an increase in hematocrit of 0.3% points (0.1–0.5) ($P = 0.01$), whereas no association was observed in the placebo group ($P = 0.266$).

Daytime SBP showed a nonsignificant increase of 5.2 mmHg (-1.7, 12.1) ($P = 0.134$) in the TRT group compared to that in the placebo group. However, the impact of TRT on the increase in daytime ambulatory blood pressure was significantly accentuated by baseline values of BMI, hematocrit, and hemoglobin.

In conclusion, TRT was associated with higher OBPM compared to placebo, and the increase in blood pressure was linked to higher hematocrit during TRT. Our data suggest that men with opioid-induced androgen deficiency, particularly those with obesity or red blood cell levels in the upper normal range, are more susceptible to increased daytime SBP during TRT.

Keywords: blood pressure, male, opium testosterone

Abbreviations: 24hABPM, 24-hour ambulatory blood pressure; BP, blood pressure; cIMT, carotid intima media thickness; CVD, Cardiovascular disease; GCP, good clinical practice; HDL, high-density lipoprotein cholesterol; Hb, hemoglobin; LDL, low-density lipoprotein cholesterol; OBPM, office blood pressure measurement; ODBP, office DBP; OPIAD, opioid-induced androgen deficiency; OSBP, office SBP; SD, standard deviation; TRT, testosterone replacement therapy

BACKGROUND

Opioid analgesic consumption for nonmalignant pain management is globally increasing [1]. Secondary hypogonadism is one of the most well described hormonal side effects of opioid treatment and occurs in men with chronic opioid use due to the suppression of the hypothalamic pituitary gonadal axis, known as opioid-induced androgen deficiency (OPIAD) [2]. Biochemically, OPIAD is characterized by low serum levels of testosterone and low levels of luteinizing hormone [3]. The magnitude of androgen deficiency depends on opioid treatment duration and dosage of opioids [4]. Furthermore, the severity of androgen deficiency in OPIAD appears to be accentuated in patients with comorbidities such as obesity, diabetes mellitus, hypertension, and hyperlipidemia [5]. Cardiovascular disease (CVD) and chronic pain often coexist [6,7] and the prevalence of hypertension in patients attending tertiary pain management clinics is up to 10 times higher compared to the general population [8].

Studies on the effects of testosterone replacement therapy (TRT) on blood pressure (BP) have shown contradictory results. TRT is associated with increased lean body mass and decreased abdominal subcutaneous adipose tissue [9–11], which may have a beneficial impact on BP [12], but TRT also reduces adiponectin levels and elevates red blood cell counts, potentially contributing to increased BP [13–17].

Journal of Hypertension 2023, 42:000–000

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Received 20 September 2023 **Accepted** 3 December 2023

DOI:10.1097/HJH.0000000000003638

The indications for TRT in OPIAD remain a topic of debate. Although observational studies have suggested potential benefits of TRT in terms of reducing all-cause mortality and major adverse cardiovascular events [18], no randomized controlled trials have specifically examined cardiovascular outcomes associated with TRT in OPIAD. Current clinical guidelines emphasize lifestyle interventions and reduction or withdrawal of opioid treatment in individuals with OPIAD, as discontinuation of opioid medications results in normalization of testosterone levels within a few months [19]. However, discontinuation of opioid treatment is not always feasible, necessitating consideration of TRT to alleviate symptoms of androgen deficiency. Clinical guidelines recommend assessment of cardiovascular risk factors prior to initiating TRT and discontinuation of TRT in individuals with consistently elevated hematocrit (Hct) levels [20]. The potential influence of baseline BMI and red blood cell levels on the effects of TRT on BP remains unclear.

Given the potential associations between TRT, BMI, red blood cell levels, and BP, this study aimed to investigate the effects of TRT on BP in opioid-treated men with relative hypogonadism and evaluate whether baseline clinical and laboratory data, such as BMI, Hct, and hemoglobin (Hgb) levels, modify these effects.

MATERIALS AND METHODS

Study design

The full trial protocol has been described previously [21] (https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-004729-42/DK). In brief, men aged at least 18 years who were treated with opioids for at least 3 months at an opioid dosage corresponding to at least 50 mg morphine/day were eligible for inclusion if the total testosterone level was less than 12 nmol/l without elevated luteinizing hormone and prolactin levels. A cut-off value of total testosterone less than 12 nmol/l was applied to allow for comparison with similar previous studies [22]. The primary aim and principal outcome of this study was to assess the efficacy of TRT in men with OPIAD with a specific focus on its influence on body composition. In addition, 24-h ambulatory BP measurement (24hABPM) was predefined as a secondary outcome, parallel to changes in body composition, and was analyzed in this manuscript. Randomization numbers were assigned to the participants in the order of enrollment in the study. The randomization list, medicine labeling, and randomization and code-break envelopes were generated by the pharmacy at Odense University Hospital to ensure double-blinding. Participants were randomly assigned to receive injections containing 1000 mg of testosterone undecanoate (Nebido) ($n = 20$) or placebo ($n = 21$). Of the 41 randomized participants, full data from five individuals were not available for analysis in this study. Two participants withdrew consent, three participants did not have valid 24hABPM, and one participant died during the study. The analysis was performed based on two groups: TRT [$n = 18$ /($n = 15$ with 24 h ABPM)] and placebo ($n = 20$) (Fig. 1). Injections were administered at the time of randomization and repeated at 6 and 18 weeks. The study investigators and participants were blinded to the treatment allocation. Participants were examined before and 24 weeks after the intervention. Assessments included BP

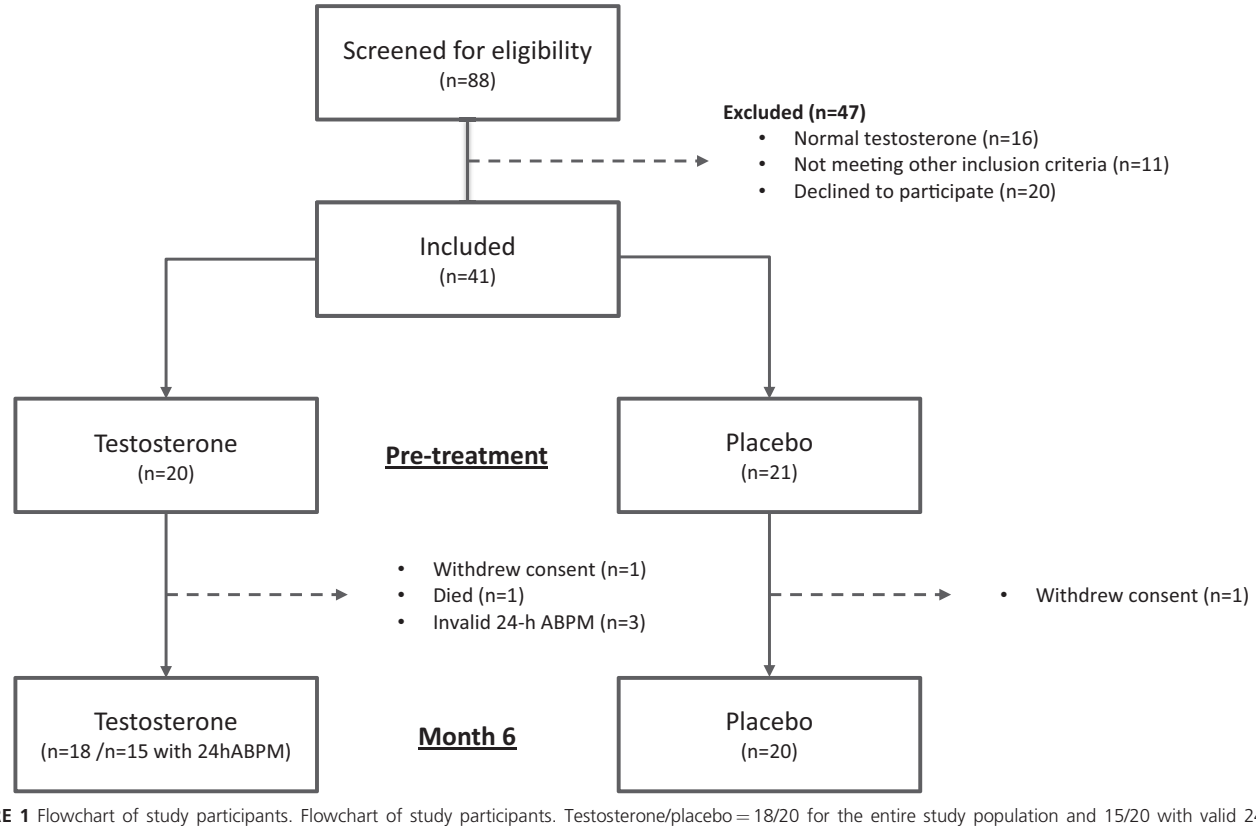

FIGURE 1 Flowchart of study participants. Flowchart of study participants. Testosterone/placebo = 18/20 for the entire study population and 15/20 with valid 24hABPM. 24hABPM, 24-h blood pressure measurement.

measurements, carotid ultrasound, clinical examinations, and fasting blood samples.

All the participants provided written informed consent. This study was approved by The Regional Scientific Ethical Committees for Southern Denmark (S-20150004) and Danish Health and Medicines Agency (EudraCT:2014-004729-42). Monitoring was performed according to good clinical practice (GCP) by the GCP unit at Odense University Hospital, and all procedures were carried out in accordance with the revised (2013) Helsinki Declaration. This trial has been registered at www.clinicaltrials.gov (NCT02433730).

STUDY OUTCOME MEASURES

Blood pressure

Office blood pressure measurement

Office SBP (OSBP) and office DBP (ODBP) were obtained as routine clinical BP measurements using a calibrated semi-automated device with the physician present.

Twenty-four hour ambulatory blood pressure measurement

The 24hABPM was measured using an oscillometric cuff-based technique (Mobil-O-Graph NG, I.E.M., Stolberg, Germany). Daytime BP and heart rate (HR) recordings were made every 15 min between 0700 and 2300 h, and nighttime recordings were recorded every 30 min between 2300 and 0700 h. Daytime and nighttime weighted mean SBP and DBP were computed, considering the varying time intervals between consecutive measurements [23].

Carotid ultrasound

Carotid ultrasound was performed using B-mode imaging (Model IE33, Koninklijke Philips Electronics N.V, Eindhoven, The Netherlands) with a linear array transducer (L11-3) at a frequency of up to 11 MHz. Longitudinal images were obtained from the left and right common carotid arteries at three different angels (90°, 120°, and 150°). Ten millimeters of the common carotid artery just below the carotid bulb was used for analysis [24]. Far wall carotid intima-media thickness (cIMT) was calculated using automated software (Carotid analyzer 5; Medical Imaging Applications LLC, Coralville, Iowa, USA) over at least three and up to five cardiac cycles. The average values combined for the left and right carotid sides were reported for the far-wall IMT.

Body composition measures

Clinical examination included height, weight, and waist circumference.

Biochemical analyses

Testosterone levels were measured in the morning in the fasting state using liquid chromatography-tandem mass spectrometry. For testosterone measurements, the intra-assay coefficient of variation was 10% for total testosterone more than 0.2 nmol/l and 30% in the range between 0.1 and 0.2 nmol/l. Sex hormone-binding globulin (SHBG) was measured using the autoDELFIA assay, and bioavailable testosterone (BioT) was calculated according to the formula of Vermeulen [25], http://www.issam.ch/freetesto.htm. During the calculations, we assumed that the albumin concentration in the participants was 4.3 g/l. The normal range and 95% confidence interval for BioT was 7.3 nmol/l (7.0–7.5 nmol/l) [15]. Total cholesterol, high-density lipoprotein cholesterol (HDL), and triglycerides were analyzed using enzymatic colorimetric reactions (Modular P, Roche), and low-density lipoprotein cholesterol (LDL) was calculated using the Friedewald equation. For fasting lipid parameters, reference intervals were as follows: total cholesterol: 3.6–6.8 mmol/l, LDL: 1.8–4.5 mmol/l, HDL: 0.76–1.68 mmol/l, and TG: 0.47–2.31 mmol/l.

STATISTICS

Baseline characteristics are presented as mean ± standard deviation (SD). The effect of TRT at 6 months of intervention was evaluated by comparing the change from baseline between the TRT and placebo groups using Student's *t*-test for normally distributed variables and the two-sample Wilcoxon rank-sum (Mann–Whitney) test for nonnormally distributed variables.

Subgroup analysis was performed using linear regression models with the change from baseline as the dependent variable and the interaction term (including main effects) between the randomization group (TRT versus placebo) as a factor variable and baseline variables (i.e., BMI, Hct, Hgb, and cIMT) as continuous variables. Antihypertensive treatment was included as a factor in interaction analysis. To visualize the interaction, we constructed a forest plot displaying differences in change from baseline (placebo versus TRT) with baseline values above and below their median values.

Linear regression was used to evaluate which variables were associated with changes in BP.

RESULTS

Study population

The baseline data of the participants included in this study are presented in Table 1. The two groups (TRT, $n = 18$; placebo, $n = 20$) were comparable at baseline for all clinical and biochemical variables. The types of antihypertensive medication used by the study population are shown in Supplemental Table 1, http://links.lww.com/HJH/C360.

Testosterone replacement therapy versus placebo treatment

OSBP increased 6.2 mmHg in the TRT group and decreased 7.0 mmHg in the placebo group resulting in a net mean difference of 13.2 mmHg [3.4–23.1] ($P = 0.01$). In the TRT group, ODBP increased 0.6 mmHg compared to a decrease of 3.9 mmHg in the placebo group, resulting in a between group difference of 4.5 mmHg [-0.8 to 9.8] ($P = 0.09$) (Table 1). The difference in the change in daytime SBP from baseline to follow-up was 5.2 mmHg [-1.7, 12.1] ($P = 0.134$) between the TRT and placebo groups. BMI increased insignificantly during TRT compared to placebo with a mean difference in change from baseline of 0.9 kg/m^2 [-0.2, 2.0] ($P = 0.075$). TRT was associated with

TABLE 1. Characteristics at baseline and at 6 months intervention

	Testosterone		Placebo			
	Baseline	6 months	Baseline	6 months	Delta	*P*
n (%)	18 (47)		20 (53)			
General characteristics						
Age, years, mean (sd)	53 (7)		53 (11)			
Prior CVD, *n* (%)	3 (17)		4 (20)			
Participants in antihypertensive treatment, *n* (%)	9 (50)		10 (50)			
BMI (kg/m^2), mean (sd)	31.5 (3.7)	32.5 (4.3)	32.0 (4.1)	32.2 (4.0)	0.9	0.075
Laboratory data						
Hba1c (mmol/mol), mean (sd)	36.2 (5.1)	37.5 (6.2)	39.6 (11.5)	41.0 (12.7)	-0.6	0.549
Free testosterone (nmol/l), mean (sd)	0.12 (0.04)	0.43 (0.17)	0.14 (0.02)	0.13 (0.05)	0.32	<0.001
Total testosterone (nmol/l), mean (sd)	7.10 (2.45)	21.03 (9.51)	7.37 (3.04)	7.03 (2.38)	14.3	<0.001
Hemoglobin, mmol/l, mean (sd)	8.8 (0.8)	9.7 (1.0)	8.7 (0.5)	8.7 (0.5)	0.9	<0.001
Hematocrit, %, mean (sd)	0.43 (0.03)	0.47 (0.04)	0.42 (0.03)	0.42 (0.02)	0.04	<0.001
Office blood pressure measurement						
SBP, mmHg (sd)	135 (15)	141 (14)	142 (14)	135 (13)	13.2	0.001
DBP, mmHg (sd)	83 (7)	84 (8)	86 (9)	82 (9)	4.5	0.093
24-h ambulatory blood pressure measurement						
n (%)	15 (43)		20 (57)			
SBP daytime, mmHg, mean (sd)	125 (9)	129 (13)	128 (9)	128 (10)	5.2	0.134
DBP daytime, mmHg, mean (sd)	81 (6)	81 (8)	81 (7)	80 (10)	1.4	0.551
HR daytime, BPM, mean (sd)	72 (10)	76 (10)	75 (12)	76 (12)	2.4	0.410
SBP nighttime, mmHg, mean (sd)	119 (10)	123 (11)	119 (9)	122 (10)	1.5	0.672
DBP nighttime, mmHg, mean (sd)	74 (8)	75 (5)	74 (7)	74 (7)	1.2	0.589
HR nighttime, BPM, mean (sd)	64 (10)	67 (9)	67 (9)	69 (10)	1.2	0.712
Carotid ultrasound						
cIMT, mm, mean (sd)	0.66 (0.10)	0.68 (0.14)	0.71 (0.15)	0.72 (0.13)	-0.01	0.731

Delta values indicate the difference in change from baseline to 6 months between the TRT and placebo group with corresponding *P* values. A positive value denotes a relative increase for participants in the TRT compared to placebo.
cIMT, carotid intima media thickness; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; HR, heart rate.

higher testosterone levels (total and free testosterone), higher red blood cell counts (Table 1), and unchanged levels of lipids (T-cholesterol, LDL, triglycerides, and HDL) (not shown). TRT did not affect cIMT compared to placebo.

Subgroup analysis

The effect of TRT on OBPM was not affected by baseline values of BMI, Hct, Hgb, or cIMT (not shown). The effect of TRT on daytime SBP was positively modified by baseline BMI, Hct, and Hgb values (all $P < 0.019$) (Fig. 2). In participants with baseline BMI above the study median (30.7 m^2/kg), daytime SBP increased from baseline with 17.6 mmHg [10.6, 24.6] ($P = 0.002$) in the TRT group and 0.4 mmHg [-5.5, 4.7] ($P = 0.864$) in the placebo group. In participants with baseline Hct levels above the study median (43%), daytime SBP increased 8.4 mmHg [-1.9, 18.8] ($P = 0.09$) in the TRT group and decreased -2.3 mmHg [-11.3, 6.8] ($P = 0.564$) in the placebo group. Similarly, in participants with baseline Hgb more than 8.7 mmol/l daytime, SBP change was 11.2 mmHg [0.6–21.7] ($P = 0.041$) in the TRT group and -2.9 mmHg [-4.1, 9.9] ($P = 0.367$) in the placebo group. Baseline cIMT also increased the strength of the association between TRT and changes in SBP, almost reaching statistical significance (P for interaction = 0.09). Similar results were observed for the daytime (DBP) measurements (Fig. 3). For BP measured at night, only cIMT showed a significant interaction with the association between TRT and BP (Supplemental Figure 1 and 2, http://links.lww.com/HJH/C360).

Variables associated with an increase in SBP

Table 2 displays the association between the delta values of the selected variables and changes in OSBP and daytime SBP. ΔBMI, ΔHgb, and ΔHct were associated with an increase in daytime SBP in all the participants. When regression analysis was repeated in groups stratified for placebo or TRT, statistical significance was lost for all the variables. ΔHgb and ΔHct were associated with increased OSBP in the TRT group only, and a 10 mmHg increase in OSBP was associated with an increase in Hct of 0.3% points [0.1–0.5] ($P = 0.01$) and an increase in Hgb of 0.8 mmol/l [0.0–1.6] ($P = 0.05$). The associations between Δ SBP, ΔHct, and ΔHgb are shown in Fig. 4.

DISCUSSION

The present randomized, placebo-controlled study yielded three main findings. First, TRT was found to be associated with an increase in OSBP but did not have a significant impact on 24hABPM. Second, the effect of TRT on 24hABPM was influenced by baseline levels of Hgb, Hct, and BMI. Finally, the TRT-related increase in BP was correlated with increments in Hct and Hgb levels during TRT.

Effect of testosterone replacement therapy on blood pressure

Our study demonstrated a significant TRT-associated increase in OSBP (13.2 mmHg compared to placebo. We found an increase in daytime SBP of 5.2 mmHg compared

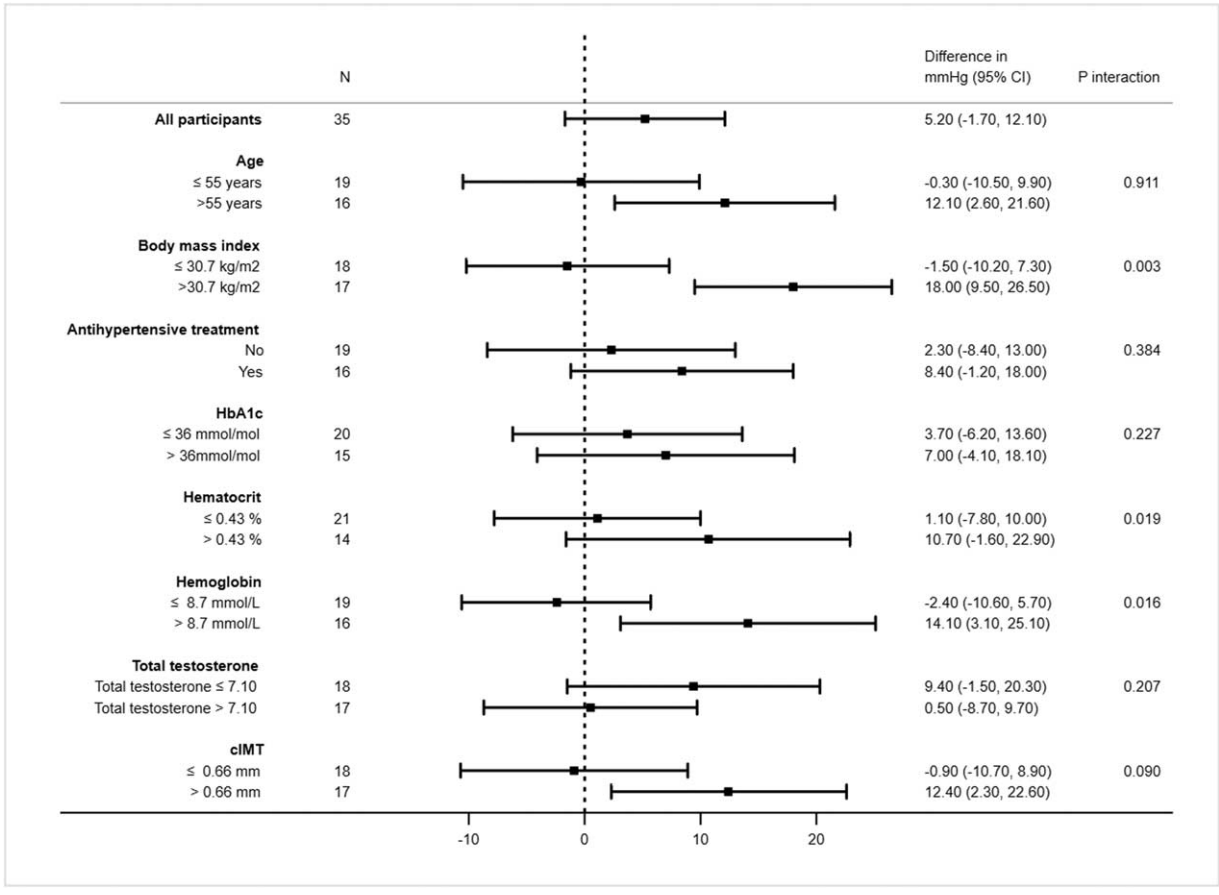

FIGURE 2 Subgroup analysis of daytime SBP response to testosterone replacement therapy (TRT) vs. placebo, stratified by median values of baseline characteristics.

to placebo; however, this was not significant. In cross-sectional studies, endogenous testosterone levels were inversely related to office BP and 24hABPM levels in men [26–29]. The largest observational study examining the effect of TRT (IPASS) found after injectable testosterone therapy a beneficial effect on BP with a small reduction of SBP and DBP of 2.1 and 1.1 mmHg, respectively [30]. Although most TRT studies have not reported an increase in BP during testosterone treatment, recent studies examining the effect of oral TRT on 24hABPM report an increase in SBP in the range of 3–5 mmHg [31–34], which is similar to the findings of our study. A recent large randomized study conducted among men with increased cardiovascular risk and total testosterone levels less than 10.4 nmol/l investigated the effects of TRT with a follow-up period of 33 months [35]. Although there was no difference in the occurrence of major adverse cardiovascular events between the groups, the study reported a small yet significantly higher BP in the TRT group than in the placebo group. Furthermore, the occurrence of kidney disease and atrial fibrillation, both of which are strongly associated with hypertension, was higher among the participants in the TRT group. These findings suggest a potential cautionary signal as the effects of TRT may not manifest as major cardiovascular events within a relatively short follow-up period.

Interplay between testosterone, erythrocytosis, and blood pressure

In this study, we found a significant positive interaction between baseline levels of red blood cell measurements and the association between TRT and daytime SBP, and that the degree of increase in both OSBP and daytime SBP was associated with an increase in both Hct and Hgb. In large population studies of healthy individuals, Hgb levels were positively associated with BP levels [16,17]. TRT, especially injectable administration, can lead to erythrocytosis, resulting in increased Hct and Hgb levels [36]. Consistent with our findings, a recent (nonplacebo controlled) study examining the effect of oral TRT on ambulatory BP found that an increase in BP was associated with an increase in Hct levels [31]. They found that men in the top quartile of changes in Hct (range, 6–14%) experienced the largest increase in mean ambulatory SBP of 8.3 mmHg. We found that a 10% change in Hct was associated with an increase in daytime SBP of 7.4 mmHg. This is in line with Poiseuille's law, which states that an increase in viscosity causes an increase in resistance, subsequently leading to increased BP when cardiac output remains constant. To physiologically compensate for a 10% increase in Hct levels, a 20% increase in BP or 5% vasodilation is necessary to maintain adequate perfusion [37].

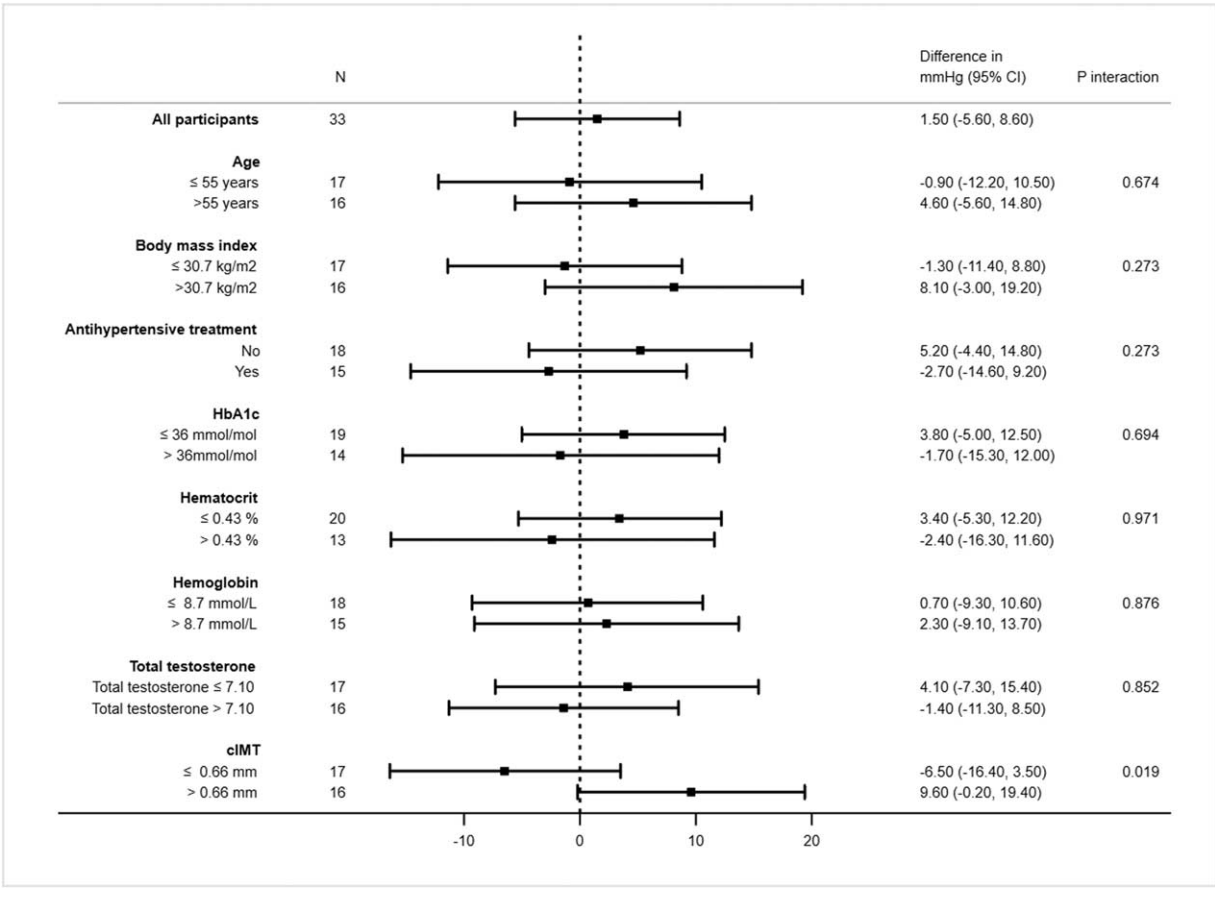

FIGURE 3 Subgroup analysis of daytime DBP response to testosterone replacement therapy (TRT) vs. placebo, stratified by median values of baseline characteristics.

Interplay between testosterone, body composition, and blood pressure

Our study indicates that the effect of TRT on 24hABPM is accentuated by baseline BMI. This finding suggests an interplay between testosterone levels, body composition, and BP.

Multiple studies have consistently supported an inverse association between testosterone levels and obesity across different age and ethnic groups [38–41]. Visceral adipose tissue is independently associated with reduced bioavailable and free testosterone [15]. Increased aromatase activity, primarily in visceral adipose tissue, can lead to elevated

TABLE 2. Association between changes in SBP and delta values of selected variables according to testosterone replacement therapy or placebo

	Testosterone				Placebo				Total			
	Beta	95% CI		*P*	Beta	95% CI		*P*	Beta	95% CI		*P*
Δ Daytime SBP												
BMI	2.5	-2.4	7.4	0.29	1.6	-0.6	3.8	0.147	2.2	0.1	4.3	0.04
HbA1c	-1.1	-5.1	2.9	0.56	-1.1	-2.3	0.2	0.090	-1.3	-2.6	0.1	0.06
Total testosterone	-0.1	-0.7	0.6	0.86	-1.6	-2.9	-0.2	0.030	0.1	-0.2	0.4	0.56
Hemoglobin	3.3	-13.8	20.4	0.69	5.3	-1.8	12.4	0.133	5.9	0.5	11.3	0.03
Hematocrit	264	-118	647	0.16	93	-48	234	0.184	135	33	238	0.01
Δ Office SBP												
BMI	0.2	-4.8	5.3	0.92	1.2	-3.8	6.1	0.626	2.1	-1.4	5.6	0.22
HbA1c	-1.5	-4.6	1.5	0.30	0.3	-2.6	3.1	0.852	-0.6	-2.7	1.6	0.59
Total testosterone	-0.1	-0.7	0.5	0.77	-0.5	-3.9	2.8	0.736	0.4	-0.1	0.9	0.12
Hemoglobin	8.0	0.0	16.1	0.05	-8.0	-23.5	7.4	0.290	6.4	-0.7	13.6	0.08
Hematocrit	276	79	472	0.01	-165	-467	137	0.266	147	-8	303	0.06

Beta coefficients for the association between change in SBP and change (delta values) in selected variables from baseline to 6 months.
cIMT, carotid intima media thickness; HbA1c, hemoglobin A1c.

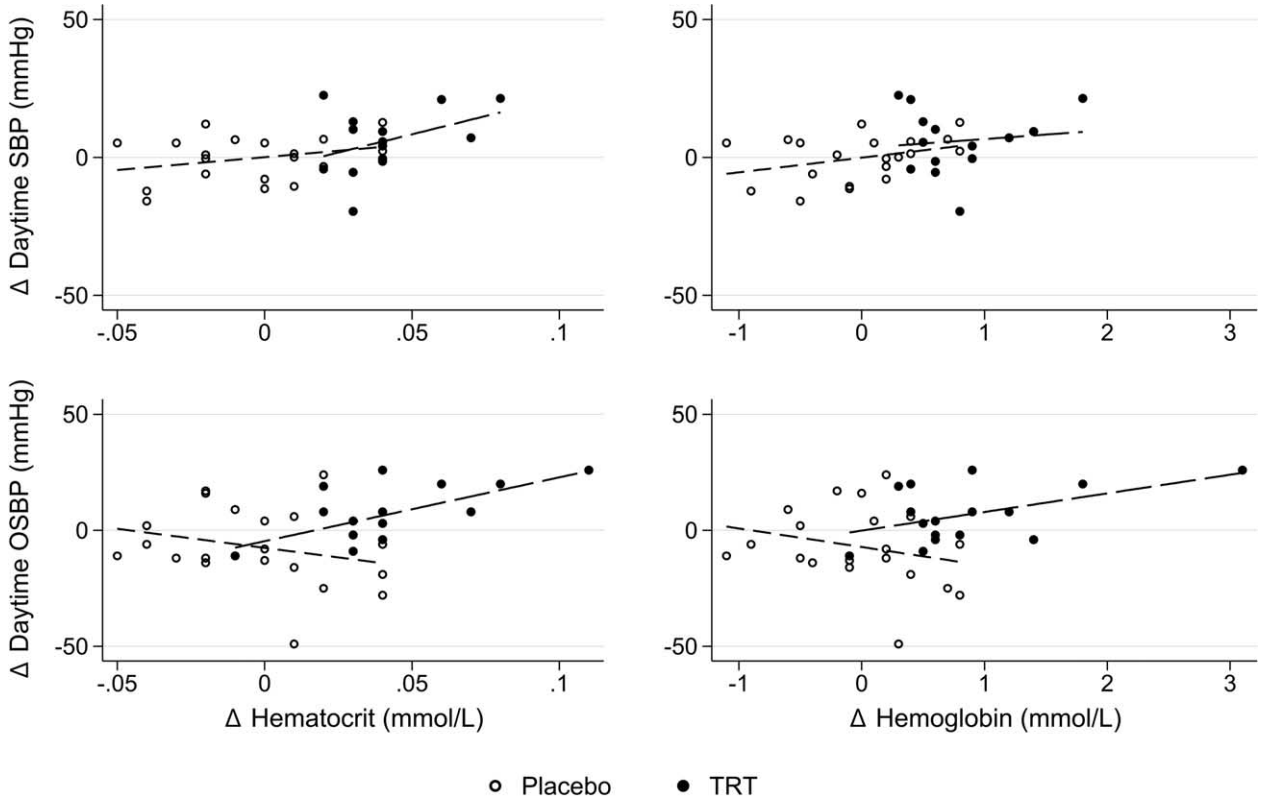

FIGURE 4 Association between Δ SBP and ΔHematocrit / ΔHemoglobin. First row displays the association between Δdaytime SBP (from 24hABPM) and ΔHematocrit or ΔHemoglobin. Second row displays the association between Δ OSBP and ΔHematocrit or ΔHemoglobin. TRT ($n = 18$ for OSBP/($n = 15$ for 24hABPM)) and placebo ($n = 20$). 24hABPM, 24-h ambulatory blood pressure measurement; OSBP, office SBP; TRT, testosterone replacement therapy.

conversion of testosterone to estradiol, resulting in lowered testosterone levels [42]. A recent large observational study reported an interaction between obesity and testosterone levels and BP [43]. They found that endogenous testosterone levels were inversely associated with BP, and this association was attenuated in individuals with high BMI. The authors suggested that serum testosterone levels may have a protective effect on BP that is counteracted by obesity. However, it is challenging to evaluate and delineate the impact of obesity on the testosterone-BP association in cross-sectional studies. It is possible that the association between obesity and BP is accentuated by low testosterone levels, rather than by low testosterone being a causal contributor to increased BP. From this perspective, TRT may not reduce cardiovascular risk and could potentially be harmful in susceptible individuals [44], which is in line with the findings of our study.

Obesity and testosterone may collectively exert their effects on BP through the renin-angiotensin-aldosterone system (RAAS). In obesity, expanded inflamed visceral and perivascular adipose tissue facilitates overactivation of the RAAS [45–48]. TRT may further activate the RAAS, as seen in rat models wherein male rats exhibit higher plasma renin activity than female rats, and castration of male rats reduces plasma renin activity [49]. Clinical studies have also shown that TRT is associated with sodium and water retention, leading to edema, particularly in older individuals [50]. Consequently, the combination of obesity and TRT may potentiate adverse activation of the RAAS, causing fluid retention and an increase in BP.

Discrepancy between the effect of testosterone replacement therapy on office blood pressure and 24-h ambulatory blood pressure

A possible explanation for the larger effect of TRT on OSBP compared to that of 24hABPM could be that TRT increased the participants' alert reaction to the physician's presence during measurements. The neuroadrenergic response to a physician's presence is characterized by generalized vasoconstriction [51,52] with an increase in SBP by 10–20 mmHg when applying a conventional cuff measurement [53,54]. Testosterone is generally considered a vasodilator of resistance arteries (primarily observed at supraphysiological concentrations) [55,56]. However, TRT may also affect vascular response to other vasoactive compounds. One myographical study found that TRT increased the vasoconstrictor response to noradrenaline and reduced the dilating response to acetylcholine in men with hypogonadism [57]. Similarly, other studies have reported that in hypogonodal men, endothelial function is reduced by TRT [58–60]. This could explain why we observed a greater effect of TRT on routine OSBP than that on 24hABPM. We propose that the neuroadrenergic response to physicians' presence may result in a higher OBPM in participants in TRT compared to placebo, which is not reflected to the same extent in the ambulatory setting.

Implications

Although low testosterone levels have been associated with various cardiac risk factors, such as obesity, type 2 diabetes mellitus, and hypertension in cross-sectional studies, this does not necessarily imply that acquired low testosterone levels per se increase CVD risk, and it has not been proven that TRT changes the risk of CVD [61]. In this interventional and placebo-controlled study, we examined the impact of TRT on BP in men with OPIAD for whom the decision to initiate TRT is difficult. Our study highlights the importance of monitoring Hb, Hct, and BP in patients with OPIAD before and during TRT, particularly in obese individuals with red blood cell measurements in the upper-normal range. In men with a substantial increase in Hgb or Hct levels, BP should be monitored closely, including in ambulatory settings.

Strengths and limitations

This is a strength in that the trial was double-blind and placebo-controlled. However, as the primary study outcome was lean body mass, the study could be underpowered to detect minor changes in secondary study outcomes such as 24hABPM. We did not include information about smoking, alcohol consumption, or other lifestyle factors, which could have changed during the study intervention and affected our study results. Several study outcomes were addressed; therefore, the issue of multiple testing arose, and some positive associations may have occurred by chance.

CONCLUSION

The effect of TRT on BP was accentuated by the baseline levels of Hgb, Hct, and BMI. The magnitude of the increase in BP was predominantly associated with an increase in Hct levels. BP should be carefully assessed and monitored when initiating TRT in men with OPIAD, especially in subjects with obesity and red blood cell counts in the upper normal range.

ACKNOWLEDGEMENTS

The authors thank the Novo Nordisk Foundation and Institute of Clinical Research, University of Southern Denmark. Trial data were stored at OPEN, Open Patient Data Explorative Network, Odense University Hospital, Region of Southern Denmark (www.sdu.dk/ki/open).

Bayer provided Nebido and placebo but was otherwise not involved in the study planning or interpretation of results.

Clinical trial registration number: www.clinicaltrials.gov, NCT02433730

Conflicts of interest

Prof. Michael Hecht Olsen discloses that he has received speaker fees from Novo Nordisk A/S, Boehringer & Ingelheim, Astra Zeneca, and Teva. The remaining authors have no disclosures to report.

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