Inverse association between total testosterone concentrations, incident hypertension and blood pressure

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Abstract
Background. Studies on the relationship between testosterone concentrations and blood pressure have yielded inconsistent results. Therefore, this study investigated the prospective association of total testosterone (TT) concentrations with risk of incident hypertension and blood pressure change in 1484 men aged 20–79 years.

Methods. Data from the population-based Study of Health in Pomerania, Germany, were used. Serum TT concentrations, measured by chemiluminescent enzyme immunoassays, were categorised into age-specific quartiles. Generalised Estimating Equation (GEE) models, adjusted for age, waist circumference, physical activity, smoking and alcohol consumption were specified.

Results. During a median follow-up time of 5.0 years, the prevalence of hypertension increased from 50.6% to 57.1%. TT concentrations were significantly lower in men with baseline and incident hypertension. Analyses revealed that men with baseline TT concentrations in the lowest quartile had an increased risk of incident hypertension (odds ratio (OR), 1.19 (95% CI, 1.10–1.28)) compared to men with higher TT concentrations. Furthermore, we found a significant inverse association of TT concentrations and blood pressure, showing that men with baseline TT concentrations in the lowest quartile showed the slightest change in systolic blood pressure (7.6.01 mmHg), diastolic blood pressure (7.2.11 mmHg) and pulse pressure (7.3.98 mmHg). Sensitivity analyses in a subpopulation of men without antihypertensive medication confirmed these findings.

Conclusion. These results show that low male TT concentrations are predictive of hypertension, suggesting TT as a potential biomarker of increased cardiovascular risk.

Keywords: Testosterone, hypertension, blood pressure, men, Study of Health in Pomerania (SHIP)

Introduction
Elevated blood pressure and hypertension are major risk factors for cardiovascular diseases (CVD) [1], including arteriosclerosis, stroke and myocardial infarction [2,3]. Furthermore, hypertension is a major contributor in half of all cardiovascular deaths [4,5], especially among men [6]. A decline in male total testosterone (TT) concentrations with increasing age is well established [7], and low TT concentrations have been associated with a less favourable cardiovascular risk profile, including obesity [8], unfavourable lipid profiles [9] and increased risk of incident metabolic syndrome (MetS) [10].

Previous results from case–control and cross-sectional studies suggesting an inverse association between TT, hypertension and blood pressure have been comprehensively reviewed [11]. In addition, TT concentrations have been found to be inversely associated with pulse pressure (PP) [12,13]. Results from interventional studies have demonstrated beneficial effects of testosterone supplementation on blood pressure [14,15]. Previous prospective studies showed conflicting results, partly confirming the suggested inverse relationship between TT, hypertension and blood pressure [16–19], and partly reporting no association [20,21].

In the Caerphilly [19] and Rancho Bernardo studies [16], an inverse association between TT concentrations and blood pressure was found among middle-aged men. By contrast, a small study of former participants in the Multiple Risk Factor Intervention
Trial (MRFIT) [21] and a nested case–control study [20] found no association between TT and blood pressure. These inconsistencies may relate to differences in study design, study sample, characteristics of the study population or methodologies used.

Therefore, the present study aimed to investigate the prospective association between TT concentrations, hypertension and blood pressure in a large population-based sample of 1484 men aged 20–79 with completed 5-year follow-up.

Methods

Study population

Data from the Study of Health in Pomerania (SHIP), a population-based cohort study in north-eastern Germany, were used. Details of the study design, recruitment and procedures have been published previously [22]. In brief, a two-stage stratified cluster sample of adults aged 20–79 years was drawn from the total population of West Pomerania, comprising 213,057 inhabitants in 1996. The net sample (without migrated or deceased persons) comprised 6265 eligible subjects. Only individuals with German citizenship and main residency in the study area were included. All subjects received a maximum of three written invitations. In cases of non-response, letters were followed by several phone calls or by home visits if contact by phone was not possible. Finally, after written informed consent was obtained from each participant, 4308 participants were examined (response rate, 68.7%) in two examination centres (Greifswald and Stralsund) between 1997 and 2001. The study protocol is consistent with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald. From 2117 male baseline participants, 1589 were re-examined after 5 years between 2002 and 2006. Complete blood pressure readings were available in 1583 men. We excluded 82 men with missing TT data. Furthermore, 17 men were excluded for taking sex steroids (anatomic-therapeutic-chemical (ATC) code G03, n = 3), testosterone 5α-reductase inhibitors (ATC code G04CB, n = 9) or sex steroid antagonists (ATC code L02B, n = 5) at either or both of the two examinations. The final study population comprised 1484 men.

Measures

Socio-demographic and behavioural characteristics, as well as information about antihypertensive drug use, were assessed by computer-assisted personal interviews. Men who participated in physical training for at least 1 h a week were classified as being physically active. Mean daily alcohol consumption was calculated using beverage-specific pure ethanol volume proportions [23]. Smoking habits were assessed by dividing men into categories of current, former and never-smokers. Waist circumference (WC) was measured to the nearest 0.1 cm using an inelastic tape midway between the lower rib margin and the iliac crest in the horizontal plane, with the subject standing comfortably with weight distributed evenly on both feet. After a resting period of at least 5 min, systolic (SBP) and diastolic blood pressure (DBP) were measured three times on the right arm of seated subjects by use of an oscillometric digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan). The interval between the readings was 3 min. The mean of the second and third measurements was calculated and used for the present analyses. Hypertension was defined as SBP or DBP of ≥140 mmHg or ≥90 mmHg, respectively, or of antihypertensive medication (ATC codes C02, C03, C04, C07, C08, C09) [24,25]. PP was defined as the difference between mean systolic and diastolic pressures.

Non-fasting blood samples were taken from the cubital vein in the supine position and were prepared for immediate analysis or stored at −80 °C for further analysis. TT concentrations were measured from frozen serum aliquots using competitive chemiluminescent enzyme immunoassays on an Immulite 2500 analyser (Siemens Healthcare Medical Diagnostics, Bad Nauheim, Germany) [26]. All assays were performed according to the manufacturers’ recommendations by skilled technical personnel. Baseline TT measurements were carried out from December 2005 to January 2006. An aliquot of two alternating levels of a third party commercial control material (Bio-Rad Lyphochek Immunoassay Plus Control, lot 40151 and lot 40152; Bio-Rad, Munich, Germany) was included in each series in single determination. The inter-assay coefficient of variation was 13.2% with a systematic deviation of +2.3% at the 3.2 nmol/l level, and 8.9% with a systematic deviation of +0.24% at the 22.5 nmol/l level. Follow-up TT measurements were carried out from April 2008 to May 2009. An aliquot of three levels of the manufacturer’s control material (Immunoassay Control, ref. CON6, lot 021, Siemens Healthcare Medical Diagnostics, Bad Nauheim, Germany) was included within each series in single determination. The inter-assay coefficient of variation was 14.3% with a systematic deviation of −8.8% at the 4.1 nmol/l level, 10.5% with a systematic deviation of −4.4% at the 12.1 nmol/l level and 13.6 with a systematic deviation of −8.5% at the 29.4 nmol/l level.

Statistical analysis

Categorical data are given as percentages, continuous data are given as mean (SD). To assess the association of baseline TT concentrations and risk of incident hypertension and changes in blood pressure variables, the generalised estimating equation (GEE) methodology with an exchangeable
correlation matrix and robust standard errors was used [27]. Categorical (hypertension) and continuous (SBP, DBP and PP) outcomes and the predictor variable (TT) were modelled with appropriate binomial or Gaussian distribution and logit or identity link functions, respectively. To analyse the risk of incident hypertension, the sample was limited to men without prevalent hypertension at baseline. Covariates adjusted for in the analyses included age, WC, physical activity, smoking and alcohol consumption. TT concentrations were categorised into the age-specific (by decades) quartiles of its distribution. To adjust for possible bias introduced by drop out, inverse probability weighting was used. We also considered adjustment for differences in the length of follow-up time by including the log of the length of follow-up in each of the longitudinal regression models. To assess the potential impact of antihypertensive medication, we conducted sensitivity analyses in a subpopulation without any medication. In addition, we stratified the study sample by blood sampling time (<11 a.m. vs. ≥11 a.m.) to assess the effect of diurnal variation on the estimates. P values <0.05 were considered statistically significant. All analyses were performed with Stata 10.0 (Stata Corp., College Station, TX).

Results
The median follow-up time was 5.0 years (15,284 person-years). Mean baseline SBP and DBP were at high-normal levels (142.2 mmHg and 86.4 mmHg, respectively) in these 1484 men with mean age 50.7 years. Comparing the characteristics of the study cohort by prevalent baseline hypertension and incident follow-up hypertension, we found significantly lower TT concentrations in hypertensive men than in non-hypertensive men at both baseline and follow-up examinations (Table I). While mean levels of SBP, DBP and PP were significantly higher in hypertensive men at baseline, follow-up SBP and DBP were similar or even lower for men with incident hypertension compared to those without (Table I). This finding is consistent with the increased use of antihypertensive medication, which rose from 30.3% at baseline to 43.3% at follow-up. Furthermore, men with prevalent baseline hypertension were significantly older, physically less active and had a higher WC than men without prevalent baseline hypertension (Table I).

GEE analyses revealed that men with baseline TT concentrations in the lowest quartile had an increased risk of incident hypertension (OR, 1.19 (95% CI, 1.10–1.28)) compared to men with TT concentrations in the highest quartile. This finding was independent of age, WC, physical activity, smoking and alcohol consumption (Table II). Furthermore, we found a significant inverse association between TT and SBP, DBP and PP change (Table II).

In age-adjusted models, men with low baseline TT concentrations showed the smallest decrease in blood pressure over the study period (−5.52, −2.10, −3.43 mmHg in SBP, DBP and PP, respectively, for the lowest quartile), compared to men with TT concentrations in the highest quartile. Men with higher baseline TT concentrations showed a stronger decrease in blood pressure (−6.33, −3.08, −3.25 mmHg decrease in SBP, DBP and PP, respectively, for the second quartile; −8.30, −3.80, −4.50 mmHg decrease in SBP, DBP and PP, respectively, for the third quartile). Additional adjustment for WC, physical activity, smoking and alcohol consumption increased the overall estimates only slightly (Table II). The revealed inverse association is depicted by negatively sloped linear fit lines for mean concentrations of baseline and follow-up TT over blood pressure (Figure 1).

Subgroup analyses in 789 men without antihypertensive medication yielded slightly decreased estimates, with statistical significance maintained.

Table I. Characteristics of cohort of 1484 men.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No prevalent hypertension</th>
<th>Prevalent hypertension</th>
<th>No incident hypertension</th>
<th>Incident hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=733)</td>
<td>(N=751)</td>
<td>(N=627)</td>
<td>(N=106)</td>
</tr>
<tr>
<td>Age, years</td>
<td>45.6 (15.2)</td>
<td>55.4 (13.9)*</td>
<td>47.8 (14.2)</td>
<td>65.6 (10.9)*</td>
</tr>
<tr>
<td>Total testosterone (nmol/l)</td>
<td>17.4 (5.7)</td>
<td>15.7 (5.6)*</td>
<td>18.7 (6.4)</td>
<td>16.2 (5.9)*</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.5 (11.1)</td>
<td>98.9 (11.0)*</td>
<td>91.0 (10.4)</td>
<td>101.5 (10.9)*</td>
</tr>
<tr>
<td>Physically active (%)</td>
<td>47.1</td>
<td>37.7*</td>
<td>28.2</td>
<td>21.7*</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>37.4</td>
<td>25.2*</td>
<td>36.9</td>
<td>13.2*</td>
</tr>
<tr>
<td>Alcohol consumption (g/day)</td>
<td>19.5 (22.5)</td>
<td>20.7 (24.3)</td>
<td>16.1 (18.7)</td>
<td>10.1 (13.3)*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>134.6 (16.3)</td>
<td>149.4 (18.4)*</td>
<td>124.9 (9.3)</td>
<td>124.7 (12.1)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>83.4 (10.2)</td>
<td>89.4 (11.5)*</td>
<td>78.9 (6.6)</td>
<td>74.9 (8.9)*</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>51.3 (11.0)</td>
<td>60.0 (14.2)*</td>
<td>46.1 (7.4)</td>
<td>49.8 (11.0)*</td>
</tr>
</tbody>
</table>

Values shown are expressed as mean (SD) or percentage. Total testosterone concentrations may be converted to ng/dl by multiplying these values by 28.82.

*p < 0.05 for tested differences between both men with and without prevalent hypertension at baseline as well as between men with and without incident hypertension at follow-up, based on the χ² test or the analysis of variance (T test).
**Table II.** Association of baseline total testosterone concentrations (in quartiles) with change in blood pressure variables from GEE analyses.

<table>
<thead>
<tr>
<th></th>
<th>Hypertension, OR (95% CI)</th>
<th>Systolic blood pressure, (mmHg) (95% CI)</th>
<th>Diastolic blood pressure, (mmHg) (95% CI)</th>
<th>Pulse pressure, (mmHg) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (N=1484)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1, (Q 4) Ref.</td>
<td>Q1: 1.17 (1.10; 1.24)*</td>
<td>-5.52 (-7.55; -3.49)*</td>
<td>-2.10 (-3.25; -0.94)*</td>
<td>-3.43 (-4.78; -2.07)*</td>
</tr>
<tr>
<td></td>
<td>Q2: 1.11 (1.06; 1.17)*</td>
<td>-6.33 (-8.37; -4.29)*</td>
<td>-3.08 (-4.24; -1.92)*</td>
<td>-3.25 (-4.64; -1.86)*</td>
</tr>
<tr>
<td></td>
<td>Q3: 1.11 (1.06; 1.17)*</td>
<td>-8.30 (-10.05; -6.53)*</td>
<td>-3.80 (-4.88; -2.72)*</td>
<td>-4.50 (-5.72; -3.28)*</td>
</tr>
<tr>
<td></td>
<td>Q4: 1.17 (1.10; 1.24)*</td>
<td>-6.01 (-8.32; -3.69)*</td>
<td>-2.11 (-3.44; -0.78)*</td>
<td>-3.98 (-5.51; -2.43)*</td>
</tr>
<tr>
<td>Model 2, (Q 4) Ref.</td>
<td>Q1: 1.11 (1.05; 1.17)*</td>
<td>-6.60 (-8.93; -4.27)*</td>
<td>-3.24 (-4.55; -1.92)*</td>
<td>-3.43 (-4.98; -1.87)*</td>
</tr>
<tr>
<td></td>
<td>Q2: 1.13 (1.07; 1.20)*</td>
<td>-8.37 (-10.33; -6.41)*</td>
<td>-4.00 (-5.19; -2.81)*</td>
<td>-4.37 (-5.74; -3.03)*</td>
</tr>
<tr>
<td>Subpopulation of men without antihypertensive medication (N=789)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>Q1: 1.01 (0.97; 1.05)</td>
<td>-3.88 (-5.99; -1.78)*</td>
<td>-0.73 (-1.90; 0.45)</td>
<td>-3.14 (-4.74; -1.54)*</td>
</tr>
<tr>
<td></td>
<td>Q2: 0.99 (0.98; 1.02)</td>
<td>-4.78 (-6.78; -2.79)*</td>
<td>-2.26 (-3.47; -1.05)*</td>
<td>-2.52 (-3.93; -1.11)*</td>
</tr>
<tr>
<td></td>
<td>Q3: 0.99 (0.98; 1.03)</td>
<td>-7.58 (-9.43; -5.73)*</td>
<td>-3.02 (-4.11; -1.92)*</td>
<td>-4.52 (-5.85; -3.20)*</td>
</tr>
<tr>
<td>Model 2</td>
<td>Q1: 1.00 (0.99; 1.01)</td>
<td>-4.09 (-6.53; -1.64)*</td>
<td>-0.70 (-2.05; 0.65)</td>
<td>-3.38 (-5.23; -1.53)*</td>
</tr>
<tr>
<td></td>
<td>Q2: 1.00 (0.99; 1.01)</td>
<td>-5.37 (-7.56; -3.18)*</td>
<td>-2.53 (-3.87; -1.18)*</td>
<td>-2.81 (-4.32; -1.30)*</td>
</tr>
<tr>
<td></td>
<td>Q3: 1.00 (0.99; 1.01)</td>
<td>-7.34 (-9.34; -5.34)*</td>
<td>-3.12 (-4.32; -1.92)*</td>
<td>-4.17 (-5.62; -2.73)*</td>
</tr>
<tr>
<td>Stratified by blood sampling time (&lt;11 a.m. vs. ≥11 a.m.) (Model 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11 a.m. (N=778)</td>
<td>Q1: 1.19 (1.09; 1.30)*</td>
<td>-3.59 (-7.02; -0.17)*</td>
<td>-1.52 (-3.54; 0.50)</td>
<td>-2.04 (-4.48; 0.39)</td>
</tr>
<tr>
<td></td>
<td>Q2: 1.12 (1.04; 1.20)*</td>
<td>-7.07 (-10.33; -3.80)*</td>
<td>-2.15 (-4.24; -0.05)*</td>
<td>-4.92 (-6.88; -2.96)*</td>
</tr>
<tr>
<td></td>
<td>Q3: 1.10 (1.02; 1.19)*</td>
<td>-7.85 (-10.99; -4.72)*</td>
<td>-2.65 (-4.50; -0.80)*</td>
<td>-5.27 (-7.49; -3.04)*</td>
</tr>
<tr>
<td>≥11 a.m. (N=706)</td>
<td>Q1: 1.22 (1.09; 1.36)*</td>
<td>-8.03 (-11.58; -4.48)*</td>
<td>-2.96 (-5.02; -0.89)*</td>
<td>-5.05 (-7.65; -2.44)*</td>
</tr>
<tr>
<td></td>
<td>Q2: 1.08 (0.99; 1.16)</td>
<td>-6.08 (-10.13; -2.02)*</td>
<td>-4.50 (-6.67; -2.32)*</td>
<td>-1.85 (-4.73; 1.01)</td>
</tr>
<tr>
<td></td>
<td>Q3: 1.16 (1.05; 1.27)*</td>
<td>-9.61 (-13.10; -6.11)*</td>
<td>-5.33 (-7.46; -3.20)*</td>
<td>-4.36 (-6.81; -1.91)*</td>
</tr>
</tbody>
</table>

Model 1 adjusted for age.
Model 2 adjusted for age, waist circumference, physical activity, smoking and alcohol consumption.
OR, odds ratio; 95% CI, 95% confidence interval.
*p < 0.05.

**Figure 1.** Influence of total testosterone concentrations on systolic blood pressure, diastolic blood pressure and pulse pressure. Scatterplot for the mean of baseline and follow-up values with linear fit line (solid lines), 95% confidence interval (grey) and locally weighted scatterplot smoothing [lowess] (dashed lines). The p-values from bivariate ordinary least-square linear regression models were <0.001 for systolic blood pressure, diastolic blood pressure and pulse pressure.
(Table II). Sensitivity analyses with sample stratified by blood sampling time confirmed the revealed inverse association of TT concentrations with incident hypertension and blood pressure, although the estimates were slightly decreased in men with blood sampled before 11 a.m. and slightly increased in men with blood sampled after 11 a.m. (Table II).

**Discussion**

In the present study, we detected an increased risk of incident hypertension in men with low TT concentrations, independent of major confounders including age, WC, physical activity, smoking and alcohol consumption. Furthermore, we found a prospective inverse association between TT concentrations and changes in SBP, DBP and PP.

Several previous cross-sectional studies investigated the association between low TT concentrations and hypertension. For example, the Tromso study [28], conducted in 1548 men aged 25–84 years, and the Rancho Bernardo study [29], conducted in 1132 men aged 30–79 years, reported lower TT concentrations in men with hypertension (although the latter study [29] used higher threshold levels for the definition of hypertension). Since cross-sectional studies are limited in their ability to assess causality, no direction of the association can be inferred from these studies, distinguishing between the effects of TT concentrations on hypertension versus the effects of hypertension on TT.

Most prospective evidence on the relationship between TT concentrations and blood pressure is based on studies with disease endpoint data [16,19]. A prospective study of 794 men, aged 50–91 years and followed-up for 11.8 years, reported 8% lower TT concentrations in men with hypertension [17]. By contrast, the population-based observational Boston Area Community Health (BACH) survey [30], conducted in 1885 men aged 30–79 years, reported no association of TT and hypertension after adjustment for body mass index.

Previous results from prospective studies examining the association of TT concentrations and blood pressure have been similarly conflicting. In a 5-year follow-up, the Caerphilly study found a negative correlation between testosterone and blood pressure in 2512 middle-aged men [19]. Also, a 12-year follow-up of the Rancho Bernardo study in 1009 men aged 40–79 years found a negative association between TT and blood pressure [16]. By contrast, however, a 13-year follow-up conducted in middle-aged men who were former participants of the MRFIT study [21] and the European Prospective Investigation Into Cancer In Norfolk (EPIC) study found no association between TT and blood pressure [20].

We detected a prospective inverse association between TT concentrations, hypertension and blood pressure in a large population-based sample of 1484 men aged 20–79 years. During the 5-year follow-up, the prevalence of hypertension generally increased among the studied men, whereas overall mean levels of SBP, DBP and PP significantly decreased. This finding is consistent with previous studies [31,32] and reflects the general increase in antihypertensive treatment in our study, from 30.3% at baseline to 43.3% at follow-up. Furthermore, subjects from the SHIP study region were shown to have one of the highest prevalences of hypertension seen among populations within Germany [33]. As some previous studies [34,35] have suggested that antihypertensive medication may lower sex steroid concentrations, we performed sensitivity analyses in a subsample of men without antihypertensive medication. Under these conditions, we still detected an inverse association of TT concentration with blood pressure, although the estimates were less pronounced. The sensitivity analyses we conducted also showed that the risk of incident hypertension appeared to be related to the inclusion of antihypertensive medication in the definition of incident hypertension. This finding emphasises the need to properly consider antihypertensive medication in the definition of hypertension.

The specific mechanisms underlying the association between TT and blood pressure are still a subject of debate [36,37]. Several studies [38,39] have demonstrated the vasodilating effects of testosterone or 5α-dihydrotestosterone on vascular and non-vascular smooth muscle. These effects are probably mediated via inhibition of L-type calcium channels [40,41]. Furthermore, sex steroid receptors have been identified in various cell types, including endothelial and vascular smooth muscle cells [38]. In addition, replacement trials [14,15] reported beneficial effects of TT on blood pressure during treatment. Whether testosterone affects blood pressure directly through its effects on the vascular endothelium, or indirectly through its association with CVD risk factors [42], is currently not well understood [43].

This study has several strengths. These strengths include a representative population-based sample of men from a defined geographic area, assessment of potentially influential medication in the investigated association and the longitudinal study design. But some potential limitations should also be considered. In a large scale population-based study like SHIP, participants were examined at different time points during the day, and blood sampling was done whenever the participants attended. Therefore, TT concentrations are based on a single serum sample, drawn between 8 a.m. and 4 p.m. As TT concentrations show a diurnal variation with a decline in the afternoon [44], we performed sensitivity analyses using stratification of the study sample by blood sampling time (before and after 11 a.m.). Although statistical significance was maintained in these analyses, we did find differences between both groups, which may point to an intra-individual
variance in single point TT measurements. However, there are previous investigations that also employ a single point TT measurement [17,20], and these measurements have usually been considered to reflect fairly reliably the annual mean androgen level in healthy middle-aged and elderly men [45]. Further limitations of our study may arise from the lack of data about free testosterone, sex hormone-binding globulin, estrogen or albumin for calculation of bioavailable testosterone.

Perspectives

Our study provides new insights into the impact of male TT concentrations on hypertension and blood pressure and therefore on men’s health. As the exact mechanisms by which TT concentrations are associated with hypertension and blood pressure are currently unknown [46], we consider TT as a risk marker, rather than a risk factor. Risk markers are not assumed to play a direct causal role, but may be useful to predict risk. Further conclusions concerning causality and pathogenesis may be inferred from long-term, double-blind, randomised and placebo-controlled trials of testosterone replacement in men with well-documented testosterone insufficiency.

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References


