**THE INFLUENCE OF TESTOSTERONE ON BLOOD PRESSURE AND RISK FACTORS FOR CARDIOVASCULAR DISEASE IN A BLACK SOUTH AFRICAN POPULATION**

**Objectives**: Traditionally high testosterone levels have been thought to have a detrimental effect on lipid profiles. Recently, reports have shown that testosterone has a beneficial effect on lipid profiles. On the other hand, androgens may increase blood pressure via the renin-angiotensin system. The aim of this study was to determine whether the level of testosterone is increased in hypertensive subjects or if other cardiovascular risk factors are altered with increased levels of testosterone in the Black population of South Africa.

**Methods**: For this study, 536 male and 666 female Black subjects were included. The subjects were divided into hypertensive and normotensive groups and high and low testosterone groups. Resting blood pressure was recorded with a finger arterial pressure device. Blood sampling and biochemical analyses were done by using standardized methods.

**Results**: The levels of testosterone in the hypertensive males and females were significantly higher compared to the normotensives. In the male high testosterone group, the level of triglyceride was significantly lower, while the high-density lipoprotein cholesterol level was significantly higher. In the female high testosterone group, systolic blood pressure, cortisol level, and renin activity were significantly higher.

**Conclusion**: In the males, we found beneficial effects of testosterone, which may explain the reported lower incidence of atheroma. However, the testosterone level is also higher with hypertension. The elevated levels of systolic blood pressure and renin activity that were found in the female group with high testosterone levels may be an indication of the role of the renin-angiotensin system in this regard.

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**Key Words**: Blood Pressure, Lipid Profile, Renin-Angiotensin System, Testosterone

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**INTRODUCTION**

Hypertension is a health concern in the Black population of South Africa, and epidemiologic studies are needed in Africa to determine risk factors for the development of hypertension. Reports from the literature show beneficial and detrimental effects of testosterone on blood pressure and other risk factors for cardiovascular disease, like lipid profiles. Low androgen levels in men are associated with low levels of high-density lipoprotein (HDL) cholesterol, elevated triglycerides (TG), and high levels of low-density lipoprotein (LDL) cholesterol. Traditionally, high testosterone levels are thought to have a detrimental effect on lipid profiles. Reports also exist that show that testosterone has a beneficial effect on total and LDL cholesterol without changing HDL cholesterol and TG.

In some studies, higher plasma levels of HDL cholesterol and lower TG plasma levels were reported with high testosterone levels. However, some reports show a decrease in plasma levels of HDL cholesterol with higher levels of testosterone. Therefore, results are contradictory regarding the influence of testosterone on the lipid profile. Most previous studies were experimental studies in which exogenous androgens were applied.

A lower-than-normal testosterone level in humans is associated with atherosclerotic disease, coronary disease, and myocardial infarction. In animals, high levels of testosterone are associated with atheroma and endothelial dysfunction.

Blood pressure is also influenced when the delicate balance between vasoconstriction and vasodilatation is disturbed by testosterone. Testosterone may act as a direct vasodilator through influence on the vascular wall endocrine/paracrine factors, but other studies reported decreased endothelium-dependent dilatation with androgen replacement therapy. Elevated blood pressure may be the outcome of a disturbed lipid profile (high HDL and low HDL cholesterol levels).

Blood pressure may also be increased by androgens via the renin-angiotensin system. Androgens may stimulate the renin-angiotensin system, which leads to increased levels of angiotensin II, which will cause vasoconstriction and concomitant increase in blood pressure. In addition, blood pressure and the risk of coronary disease may also be increased via the influence of testosterone on cortisol production.

The outcome of androgen effects on the vasculature is changes in blood pressure. In a previous study, we found an increase in testosterone levels with increasing levels of westernization in the Black population, especially in the males, as well as a positive correlation between blood pressure and westernization. Therefore, the aim of this study was to determine whether the level of testosterone is increased in Black hypertensive subjects. A second aim was to determine whether differences exist in the lipid parameters or endocrine factors between high- and low-testosterone subjects that...
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may contribute to an increase in blood pressure.

METHODS

Study Design

The THUSA study (Transition and Health during Urbanization of South Africans) was a cross-sectional comparative survey. A model designed in consultation with the statistical consultation services of the North-West University Potchefstroom campus was used to recruit subjects. A community-based sample of 1202 apparently healthy African subjects between the ages of 20 and 60 years was recruited from 37 randomly selected sites, representing all the health districts in the North West Province as well as all the different levels of urbanization. Included in the study were 536 males and 666 females. The health status of the subjects was evaluated by a health questionnaire and a clinical evaluation by a qualified nurse. Exclusion criteria were pregnancy, lactation, alcoholism and treatment for chronic diseases, for example, hypertension, diabetes mellitus, mental diseases, tuberculosis, or other serious diseases. Subjects who did not meet the inclusion criteria were screened for hypertension and diabetes mellitus and referred for treatment where necessary.

All biochemical and cardiovascular parameters were not necessarily assessed for all subjects because of financial limitations (endocrine measurements), difficulties with sampling enough blood, or other technical difficulties. Local organizers assisted in the recruitment of subjects. A field laboratory was established in each center to process blood samples. The ethics committee of the university approved the study, and all the subjects gave informed consent.

Data Collection

Data were collected between 9:00 a.m. and 1:00 p.m. Subjects were introduced to the experimental set-up, and blood was taken during the first part of the data collection period (before 11:00); the number of subjects was adequate to limit the effect of circadian hormonal rhythms. Blood samples were drawn from the vena cephalica or medial cubital vein of fasting subjects, and plasma and serum were prepared according to standard methods. Blood samples were centrifuged in a cooled centrifuge at 3000 rpm for 10 minutes and kept on ice until plasma and serum were divided into aliquots. In the field, aliquots were immediately frozen with a mixture of salt and ice and placed in a standard freezer (−18°C to −22°C). Back in the laboratory, samples were stored at −84°C until analyzed.

All analyses were done in the same laboratory. The testosterone analyses were done with the testosterone 125I RIA kit (INCSTAR, Stillwater, Minn, USA) according to manufacturer’s instructions. The intra-assay coefficient of variation was between 6% and 9%. The assay sensitivity was 0.059 ng/mL with the 2-standard deviation (SD) method. The cortisol analyses were done by making use of the cortisol 125I RIA kit (INCSTAR) according to manufacturer’s instructions. The intra-assay coefficient of variation was between 6.5% and 8%. The calculated sensitivity was 0.21 μg/dL. The plasma renin activity was analyzed with the plasma renin activity 125I RIA kit (INCSTAR) according to manufacturer’s instructions. The intra-assay coefficient of variation was between 5% and 10%. The calculated sensitivity was 0.018 ng/tube.

Levels of serum lipids were determined by standard methods for: total cholesterol (TC); high-density lipoprotein cholesterol (HDLC); low density lipoprotein cholesterol (LDLC); and triglycerides (TG).

Subsequently, each subject was connected to a Finapres (finger-arterial pressure) apparatus (FMS, Amsterdam, The Netherlands), and blood pressure was recorded continuously. After at least a 10-minute rest, resting blood pressure values were obtained. Blood pressure was regarded as resting when the systolic blood pressure (SBP) did not change by >10 mm Hg during the last minute of this period; otherwise the resting period was extended with a maximum of two minutes. This procedure was followed because we needed to obtain reliable resting values. The resting blood pressure was then recorded continuously for one minute.

The data were stored on magnetic tape by means of a Kyowa RTP-50A four-channel data recorder and digitized for further analysis by means of the Fast Modelflow software program. In this way the, the SBP, diastolic blood pressure (DBP), and “Windkessel” compliance of the arterial system (Cw) were obtained.

Statistical Analysis

All processed data were transferred to Microsoft Excel XP and analyzed with STATISTICA. A covariance analysis (corrected for age) was performed, and P values ≤ .05 were regarded as significant, except where stated otherwise. Partial correlation coefficients were used to show associations between testosterone and some variables while adjusting for age.

For each sex, subjects were divided into normotensive and hypertensive groups, where blood pressure ≥140/90 mm Hg was regarded as hypertensive (European Society of Hypertension – European Society of Cardiology). The male and female groups were also divided into low and high testosterone level groups, based on the mean testosterone level and independent of whether
they were normotensive or hypertensive. The mean serum testosterone levels used for this group subdivision were for the male low and high testosterone groups of 3.43 ± .08 ng/mL and 7.52 ± .18 ng/mL, respectively. The mean serum testosterone levels for the female low and high testosterone groups were .08 ± .004 ng/mL and .90 ± .19 ng/mL, respectively.

**RESULTS**

In this study, 25% of the male group and 16% of the female group were hypertensive. The level of testosterone in the male hypertensive group was significantly higher (18.5%) than in the male normotensive group (F[1,375]=7.00, P=.008). The testosterone level in the hypertensive female group was almost double than in the normotensive female group (F[1,327]=2.82, P=.09) (Table 1).

High-density lipoprotein (HDL) cholesterol was also significantly higher in the hypertensive group for both male (HDL F[1, 520]=5.68, P=.02) and female subjects (HDL F[1, 651]=6.32, P=.01) as well as the TG level (F[1, 639]=4.81, P=.03) in the female group. Low-density lipoprotein (LDL) cholesterol did not differ significantly between the hypertensive and normotensive groups for both sexes. The arterial compliance was significantly lower (F[1, 533]=195.3, P<.001) in the hypertensive male group (Table 1).

In the male high-testosterone group, the level of TG (F[1,384]=4.94, P=.027) was significantly lower, while the HDL cholesterol level (F[1,398]=7.75, P=.006) was significantly higher than in the male low-testosterone group. A small positive correlation was found for men between the testosterone levels and HDL cholesterol (r=.20, P<.001).

In the female high-testosterone group, SBP (F[1,327]=4.35, P=.04), cortisol (F[1,343]=3.59, P=.05), and renin activity levels (F[1,302]=5.31, P=.02) were significantly higher than in the female low-testosterone group (Table 2, Figure 1).

**DISCUSSION**

We found that the testosterone levels in both men and women were higher in the hypertensive group than in the normotensive group. No significant difference in blood pressure was encountered in the male high-testosterone group compared to the low-testosterone group. This result can be explained by the fact that the mean testosterone value was used arbitrarily to divide the group in low and high testosterone groups and it is likely that normotensive subjects were included in the high-testosterone group, which would mask the effect of testosterone on blood pressure in the males. In addition to the higher testosterone levels, HDL cholesterol was significantly higher in the hypertensive groups. Further, we found significantly higher HDL cholesterol and lower triglyceride values in the male high-testosterone group compared to the low-testosterone group and also a positive correlation between testosterone and HDL cholesterol. No significant differences were found in women’s lipid

Table 1. Differences between the normotensive and hypertensive groups for male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td></td>
<td>NT (95% CI)</td>
<td>HT (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n=420</td>
<td>n=116</td>
</tr>
<tr>
<td>Systolic blood pressure mm Hg</td>
<td>112* (110–113)</td>
<td>142* (139–145)</td>
</tr>
<tr>
<td></td>
<td>n=420</td>
<td>n=116</td>
</tr>
<tr>
<td>Diastolic blood pressure mm Hg</td>
<td>71* (70–72)</td>
<td>95* (93–97)</td>
</tr>
<tr>
<td></td>
<td>n=301</td>
<td>n=77</td>
</tr>
<tr>
<td>Testosterone ng/mL</td>
<td>5.02* (4.7–5.3)</td>
<td>5.96* (5.3–6.6)</td>
</tr>
<tr>
<td></td>
<td>n=271</td>
<td>n=77</td>
</tr>
<tr>
<td>Cortisol μg/dL</td>
<td>1.84 (1.6–2.1)</td>
<td>2.14 (1.6–2.7)</td>
</tr>
<tr>
<td></td>
<td>n=271</td>
<td>n=77</td>
</tr>
<tr>
<td>HDL cholesterol mmol/L</td>
<td>14.8 (14.1–15.50)</td>
<td>15.1 (13.7–16.4)</td>
</tr>
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<td></td>
<td>n=315</td>
<td>n=79</td>
</tr>
<tr>
<td>LDL cholesterol mmol/L</td>
<td>1.16* (1.12–1.20)</td>
<td>1.27* (1.19–1.35)</td>
</tr>
<tr>
<td></td>
<td>n=411</td>
<td>n=112</td>
</tr>
<tr>
<td>Triglyceride mmol/L</td>
<td>2.37 (2.27–2.46)</td>
<td>2.37 (2.18–2.56)</td>
</tr>
<tr>
<td></td>
<td>n=402</td>
<td>n=104</td>
</tr>
<tr>
<td>Arterial compliance mL/mm Hg</td>
<td>1.72* (1.68–1.75)</td>
<td>1.28* (1.22–1.33)</td>
</tr>
<tr>
<td></td>
<td>n=419</td>
<td>n=115</td>
</tr>
<tr>
<td></td>
<td>n=402</td>
<td>n=107</td>
</tr>
</tbody>
</table>

* Differs significantly (P<.05) for the same sex and parameter.
† P<.05.

NT=normotensive; HT= hypertensive; 95% CI=95% confidence interval.
profiles between low- and high-testosterone groups. High levels of testosterone may have a beneficial effect on lipid profiles in male Africans, according to findings in the literature that a low testosterone level is associated with atheroma.19,20

However, in females, where normal levels of testosterone are low, renin activity and SBP were significantly increased in the high-testosterone group (Figure 1). This finding may indicate stimulation of the renin-angiotensin system by higher testosterone levels.27 Why renin activity in males did not increase is unclear, but administration of testosterone in women increases renin activity and blood pressure and castration decreases renin activity.27 Renin activity and testosterone levels were higher in the hypertensive groups. Therefore, testosterone may be involved in the increase of blood pressure via the renin-angiotensin system, and the lack of testosterone might protect the vasculature against high blood pressure. However this explanation may be not the only one, and the increased level of cortisol in the female high-testosterone group may also be implicated in the genesis of hypertension (Figure 1).28

Higher testosterone levels were associated with a beneficial effect on the lipid profile. But testosterone may also play a role in the development of hypertension, probably through elevated renin activity and cortisol levels. The lower level of arterial compliance in the male hypertensive group is an indication that the balance of vasodilatation and vasoconstriction is disturbed. Recent studies reported reduced vasodilatation with administration of androgens, and the significantly increased testosterone in the male hypertensive group may be implicated in reduced vascular compliance.25

Table 2. Differences between the high- and low-testosterone groups for male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LT (95% CI)</td>
<td>HT (95% CI)</td>
</tr>
<tr>
<td>HDL cholesterol mmol/L</td>
<td>1.12* (1.06–1.17) n=201</td>
<td>1.23* (1.18–1.29) n=200</td>
</tr>
<tr>
<td>LDL cholesterol mmol/L</td>
<td>2.47 (2.33–2.62) n=199</td>
<td>2.37 (2.23–2.52) n=188</td>
</tr>
<tr>
<td>Triglyceride mmol/L</td>
<td>1.33* (1.21–1.46) n=189</td>
<td>1.13* (1.00–1.26) n=188</td>
</tr>
<tr>
<td>Renin activity ng/mL/hr</td>
<td>1.93 (1.59–2.28) n=180</td>
<td>1.78 (1.43–2.13) n=172</td>
</tr>
<tr>
<td>Cortisol μg/dL</td>
<td>14.82 (14.0–15.6) n=201</td>
<td>14.79 (14.0–15.6) n=199</td>
</tr>
<tr>
<td>Systolic blood pressure mm Hg</td>
<td>118 (115–120) n=189</td>
<td>119 (116–122) n=187</td>
</tr>
<tr>
<td>Diastolic blood pressure mm Hg</td>
<td>75 (73–77) n=189</td>
<td>76 (74–79) n=187</td>
</tr>
</tbody>
</table>

* Differs significantly (P<.05) for the same sex and parameter.

LT=low testosterone level; HT=high testosterone level; 95% CI=95% confidence interval.

Fig 1. Endocrine profile of females with high and low testosterone levels. The mean values for cortisol in μg/dL and renin activity in ng/mL/hr for high and low levels of testosterone. Vertical bars represent standard error of mean.
Our observation that increased testosterone levels might be associated with a favorable lipid profile, as well as the observation that increased testosterone levels are possibly linked with the renin-angiotensin system, are essentially contradictory in terms of the development of hypertension. This finding underlines the possibility that additional (unknown) mechanisms may be involved, whereas testosterone may play a secondary role in the genesis of hypertension.

REFERENCES

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AUTHOR CONTRIBUTIONS
Design concept of study: Huisman, Van Rooyen, N.T. Malan, L. Malan, Kruger
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Manuscript draft: Huisman, A.E. Schutte, Van Rooyen, N.T. Malan, L. Malan, R. Schutte
Statistical expertise: Huisman, A.E. Schutte
Acquisition of funding: N.T. Malan, Kruger
Administrative, technical, or material assistance: Huisman, L. Malan, R. Schutte, Kruger
Supervision: Huisman, A.E. Schutte, Van Rooyen, N.T. Malan, L. Malan