*Original Article*

# Serum Testosterone Levels and Arterial Blood Pressure in the Elderly

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**The aim of this study was to evaluate the relationship between serum testosterone levels and arterial blood pressure (BP) in the elderly. We studied 356 non-diabetic, non-smoking, non-obese men aged 60 to 80 years and untreated for hypertension. All subjects were evaluated in the morning after an overnight fast. Evaluation included measurements of the following: BP (by mercury sphygmomanometer, Korotkoff I and V), body weight, height and free testosterone (T) plasma levels (by radioimmunoassay). According to the BP values, the subjects were classified as normotensives (NT; $n$=112; SBP/DBP<140/90 mmHg), systolic and diastolic hypertensives (HT; $n$=127; SBP/DBP>140/90 mmHg), and isolated systolic hypertensives (ISH; $n$=117; SBP>140 mmHg and DBP<90 mmHg). T values decreased with increasing age in all 3 groups and was significantly lower in HT (−15%) and ISH men (−21%) than in NT men ($p$<0.05). In each group, the T levels showed a highly significant negative correlation with BMI ($p$<0.001). A significant negative correlation was also found between T levels and SBP in NT ($r$=−0.35, $p$<0.001), ISH ($r$=−0.67, $p$<0.001), and HT ($r$=−0.19, $p$<0.05) men, whereas a negative correlation with DBP was observed only in the NT men ($r$=−0.19, $p$<0.05). Adjusting for the BMI confirmed a significant difference in plasma T levels between ISH and NT men, but not between HT and NT men. Multiple regression analysis employing BP as a dependent variable confirmed a strong relationship between T levels and SBP in all 3 groups, whereas a significant relationship between T levels and DBP was found only in NT men. In conclusion, although further studies are needed to clarify the relationship between plasma T levels and BP, our findings suggest that in elderly men with ISH, the reduced plasma levels of testosterone might contribute to the increased arterial stiffness typical of these subjects. (*Hypertens Res* 2005; 28: 625–630)**

***Key Words*: testosterone, blood pressure, elderly**

## Introduction

High androgen levels are presumed by many to explain the higher incidence of cardiovascular disesase in men than in women, but conflicting evidence has been reported in the literature. On the one hand, it is known that testosterone promotes noradrenaline synthesis and facilitates vasoconstriction (*1*, *2*); the abuse of high doses of anabolic steroids has been linked to sudden cardiac death (*3*); testosterone increases plasma total homocysteine levels, which in turn damages vascular endothelium (*4*); and men with complete androgen suppression showed improved endothelial function compared to controls (*5*). On the other hand, it has been demonstrated that the replacement of natural androgens inhibits atheroma formation in castrated male animals (*6*). Moreover, lower levels of androgens have been found in men with coronary artery disease than in normal controls (*7*), and acute intravenous administration of testosterone has been demonstrated to exert a marked anti-ischemic effect in men with coronary artery disease (*8*, *9*). There is also increasing evidence in the literature that low levels of androgens are associated with adverse

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**Table 1. Main Characteristics of the Study Population**

| | NT ($n$=112) | HT ($n$=127) | ISH ($n$=117) |
|---|---|---|---|
| Age (years) | 69.71±5.29 | 70.21±5.55 | 69.09±5.48 |
| BMI (kg/m$^2$) | 25.72±1.20 | 26.10±1.07 | 26.13±1.18 |
| SBP (mmHg) | 128.21±6.93 | 167.00±14.48 | 168.4±19.32 |
| DBP (mmHg) | 78.80±4.50 | 103.98±6.86 | 78.03±5.87 |
| FT (mmol/l) | 13.10±6.10 | 11.14±4.43 | 10.26±5.42 |

Mean values±SD of age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) and plasma free testosterone (FT) in normotensive (NT), systolic/diastolic hypertensive (HT) and isolated systolic hypertensive (ISH) subjects are displayed.

cardiovascular risk factors, including an atherogenic lipid profile (*10*), obesity (*11*), insulin resistance (*12*, *13*), and raised fibrinogen levels (*14*) in humans.

As regards the influence of male sex hormones on arterial pressure, it is known that testosterone can affect blood pressure (BP) *via* multiple mechanisms, including direct effects on the heart, the kidney and the vessels, as well as indirect effects mediated by neuro-hormonal factors (*15*, *16*). However, although androgens have been demonstrated to contribute to the development and severity of hypertension in some genetic and nongenetic rat models of hypertension (*1*, *17*) and in some forms of human secondary hypertension, few and contrasting findings have been reported in epidemiological trials regarding the relationship between androgens and essential hypertension; namely, some studies have shown reduced androgen levels in subjects with essential hypertension as compared to normotensive subjects (*18*–*21*), whereas other studies have not demonstrated a significant difference in this respect (*22*, *23*). The disparity among various reports might be due to the following factors: differences in the characteristics of the examined populations; differences in the methodologies used; and the lack of data control for age, body composition (adiposity), smoking habits, drug intake and history of previous sexual dysfunction, all of which may all represent confounding factors. In particular, age and body mass index (BMI) need to be taken into account when evaluating male sex hormone levels, since testosterone are known to decline with increasing age (*24*, *25*) and are inversely related to the BMI (*11*).

Given these issues, no study has yet specifically evaluated male sex hormones and BP values in an elderly population. Hence the present study was undertaken in order to examine the relationship between serum free testosterone levels and arterial BP in elderly subjects with normal BP pressure, in those with elevated systolic and diastolic blood pressure (SBP and DBP), and with isolated systolic hypertension. We evaluated free testosterone levels because there is sufficient evidence suggesting that this fraction more accurately reflects the clinical situation than does the total plasma hormone value (*26*).

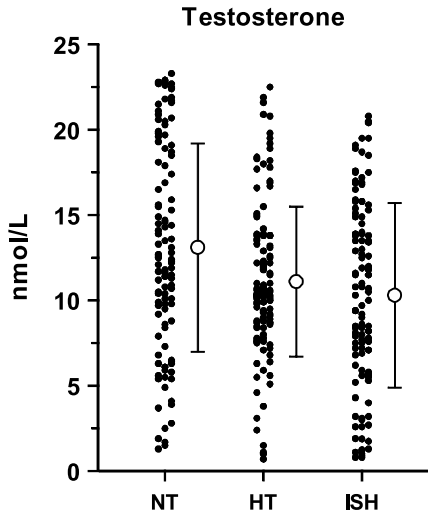


**Fig. 1.** *Individual values, means±SD of plasma free testosterone in normotensive (NT), systolic/diastolic hypertensive (HT) and isolated systolic hypertensive (ISH) men.*

## Methods

We examined 356 non-diabetic, non-smoking men, aged between 60 and 80 years. Patients were excluded if their BMI was >28 kg/m$^2$, if they were taking any antihypertensive drugs or medications known to affect sex hormone levels, or if they had any past history of the following: hypogonadism, medical or surgical treatment for any prostatic disease, and/or evidence of clinically significant cerebrovascular disease. Informed consent was obtained from all participants.

All subjects were evaluated in the morning, between 8:30 AM and 9:30 AM, after an overnight fast. Clinical examination included measures of resting BP, body weight, height and venous blood samples drawn for the determination of plasma testosterone levels. BP was measured by trained physicians using a standard mercury sphygmomanometer (Korotkoff phases I and V) with a cuff size appropriate to individual body habitus. Measurements were taken on the right arm in the seated position, after the subject had rested for 5 min in a quiet room. Three readings were taken at 2-min intervals, and the results were averaged. According to the BP values, the subjects were classified as follows: normotensives (NT; $n$=112), with SBP/DBP values < 140/90 mmHg; systolic and diastolic hypertensives (HT; $n$=127), with SBP/DBP values >140/90 mmHg; isolated systolic hypertensives (ISH; $n$=117), with SBP values >140 mmHg and DBP values < 90 mmHg. The normotensives studied here all belonged were subjects belonging to the same working community and all underwent periodic physical examinations; the hypertensives were all outpatients referred to our Hypertension Center due to a diagnosis of hypertension.

Body weight was rounded to the nearest 0.1 kg and height

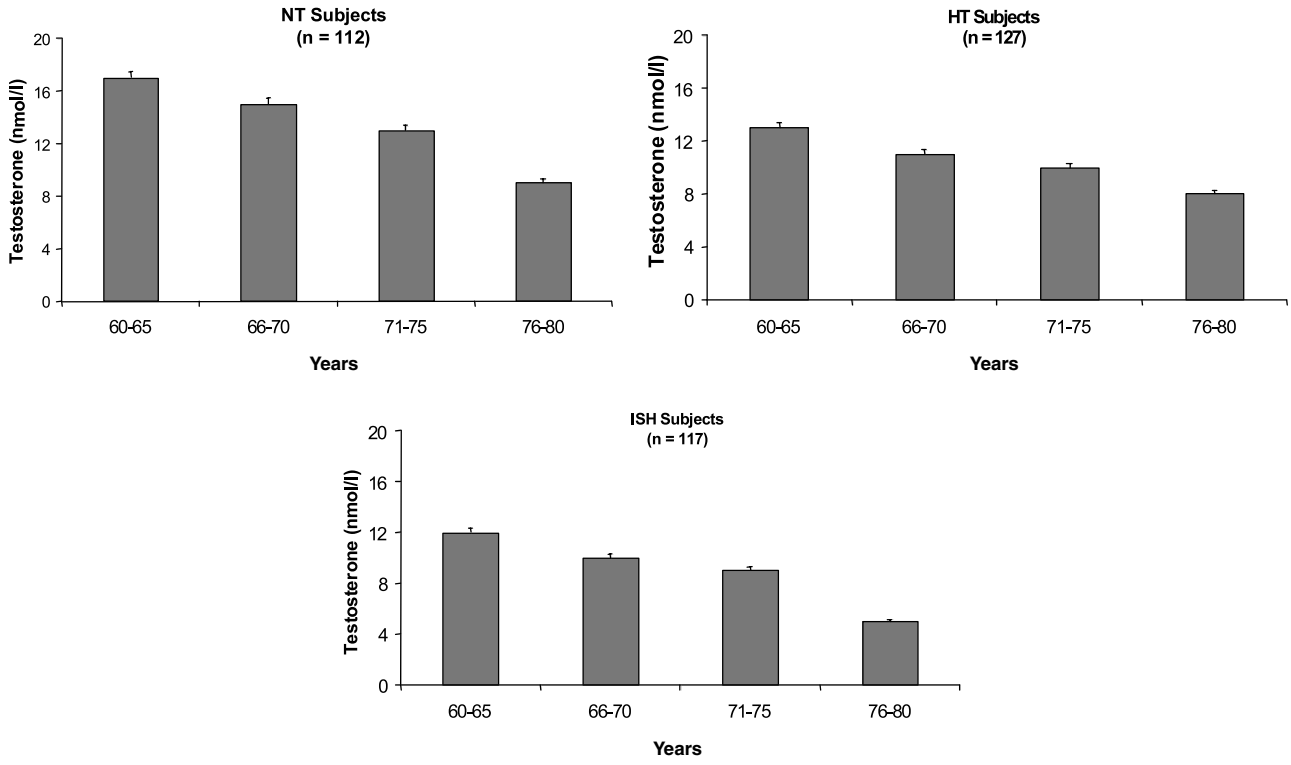


**Fig. 2.** *Mean±SEM of plasma free testosterone with increasing age in normotensive (NT), systolic/diastolic hypertensive (HT) and isolated systolic hypertensive (ISH) men.*

was rounded to the nearest 1 cm; these values were measured while the subjects were barefoot and wearing light clothing. The BMI was calculated as weight (kg)/height $(m)^2$.

To limit the influence of fluctuations in plasma testosterone levels due to episodical secretion, blood samples for the evaluation of testosterone levels were always drawn at the same time of the day, between 8:30 AM and 9:30 AM. Plasma was obtained by venipuncture from fasting subjects, and the sample were frozen at −70°C and stored in tightly sealed containers. Free plasma testosterone was measured by a radioimmunoassay method involving an analog ligand (*27*) (Diagnostic Products Corporation, Los Angeles, USA). The maximum storage time before measurement was 4 days.

### Statistical Analysis

The results are expressed as means±SD. Statistical analysis of the data was performed using the SAS 6.12 program package (SAS Corp., Cary, USA). The results were analyzed using analysis of variance, Student's *t*-test, Pearson's correlation test, and multiple regression analysis. Based on the principal idea that testosterone deficiency plays a causal role in hypertension—although reverse causality is also possible—multiple regression analysis was performed with testosterone as an independent variable and BP as a dependent variable. The level of significance was taken as $p<0.05$.

## Results

The main demographic and clinical characteristics of the study sample are shown in Table 1. Both men with systolic/diastolic hypertension (HT) and men with isolated systolic hypertension (ISH) had significantly lower levels of free testosterone than normotensive (NT) men (−15% and −21%, respectively) (Fig. 1). The difference between means was 1.968 (95% confidence interval: −3.629 to 0.306), $p<0.05$ for NT *vs.* HT subjects, and 2.838 (95% confidence interval: −4.533 to 1.144), $p<0.05$ for NT *vs.* ISH subjects. No significant difference was found between the two hypertensive groups: the difference between means was 0.870 (95% confidence interval: −0.771 to 2.512), NS.

Plasma testosterone values decreased with increasing age in all 3 groups, and this decrease was evident in men 66 years old or older (Fig. 2). Pearson's correlation analysis showed a significant negative correlation between testosterone and age in the NT group ($r=-0.54$, $p<0.001$), HT ($r=-0.35$, $p<0.001$) and ISH ($r=-0.42$, $p<0.001$).

The BMI was significantly higher in HT and ISH subjects than in NT subjects (+14.5% to +15.7%, respectively). The difference between means was −0.384 (95% confidence interval: −0.742 to −0.026, $p<0.05$) for NT *vs.* HT subjects, and −0.407 (95% confidence interval: −0.733 to −0.042,

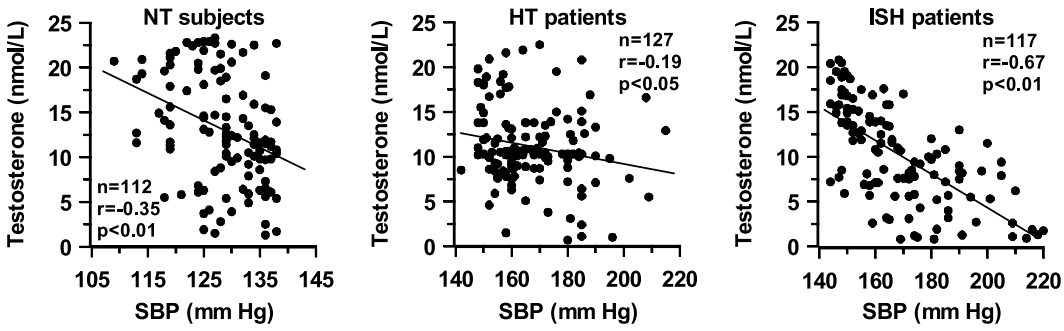


**Fig. 3.** *Relationship between plasma free testosterone levels and systolic (SBP) and diastolic blood pressure (DBP)(Pearson's correlation analysis) in normotensive (NT), systolic/diastolic hypertensive (HT) and isolated systolic hypertensive (ISH) men.*

$p<0.05$) for NT *vs.* ISH subjects. No significant difference in the BMI was observed between the hypertensive groups: the difference between means was −0.023 (95% confidence interval: −0.377 to 0.330), NS. Pearson's correlation analysis showed that in each group, free testosterone levels were significantly negatively correlated with the BMI ($r=-0.61$ in NT, $r=-0.76$ in HT, and $r=-0.72$ in ISH, all $p<0.001$ in each case).

A significant negative correlation was also found in each group between free testosterone and SBP values (NT: $r=-0.35$, $p=0.0002$; HT: $r=-0.19$, $p=0.029$; ISH: $r=-0.67$, $p<0.001$) (Fig. 3); however a negative correlation with DBP was observed only in the NT subjects, albeit at a lower degree of statistical significance ($r=-0.19$, $p=0.039$).

Due to the close tight relationship between testosterone levels and BMI, it was necesseray to exclude any interference of BMI on the relationship between testosterone and BP values. Therefore, the results were adjusted for BMI, and a significant difference in plasma free testosterone levels between NT and ISH subjects was confirmed (mean difference: 3.699, $p<0.001$) and between ISH and HT subjects (mean difference: 2.243, $p=0.025$); however, no such difference was observed between NT and HT (mean difference: 1.587, $p=0.113$, NS).

The results of the multiple regression analysis using free testosterone as an independent variable and both SBP and DBP as dependent variables are reported in Tables 2 and 3. This analysis confirmed a strong relationship between plasma testosterone levels and SBP values in all the three study groups, whereas a significant relationship between testosterone and DBP values was found only in the NT group.

## Discussion

Consistent with previous observations, the results of this study of a relatively homogeneous sample of elderly non-diabetic, non-smoking subjects, indicated that plasma testosterone levels decreased with increases in age (*24*, *25*). In addition, in the same age range, the plasma testosterone levels were significantly lower in both HT and ISH subjects than in the NT subjects (*18*–*21*). The finding that hypertensive patients had lower levels of plasma testosterone might sinify one or more of the following: 1) testosterone influences BP regulation; 2) elevated BP negatively affects steroidogenesis or clearance; and/or 3) there are genes involved in the regulation of BP that also affect steroidogenesis. This latter possibility is supported by data demonstrating that Natriuretic Peptide Receptor A gene deficiency in male mice is characterized by both high BP and low circulating testosterone levels (*28*). Moreover, men with a family history of hypertension have been shown to have lower than normal testosterone levels (*13*)

In the NT, HT, and ISH groups, a highly significant negative correlation was found between testosterone levels and the BMI, which is in agreement with previous findings in both obese (*29*, *30*) and non-obese subjects (*31*). A high BMI may lead to hypotestosteronemia *via* a number of different mechanisms, *e.g.* increased conversion in the body fat of androstenedione to oestrone by the enzyme aromatase (*32*); impaired expression of sex hormone binding globulin (SHBG) due to hyperinsulinemia, which is often present in overweight subjects (*29*, *31*); and inhibition of the hypothalamic-pituitary-gonadal axis, possibly *via* agents such as leptin (*33*).

Pearson's correlation analysis showed a significant negative relationship between plasma testosterone levels and SBP in all three groups, whereas testosterone levels were negatively correlated with DBP only in the NT subjects. Adjusting for the BMI confirmed significantly lower testosterone levels in ISH subjects. A multiple regression analysis employing BP as a dependent variable confirmed a strong relationship between plasma testosterone and SBP in all 3 groups, whereas a significant relationship between plasma testosterone and DBP was observed only in the NT group.

These results suggest that in the elderly subjects with ISH, the reduced plasma levels of testosterone might contribute to increased arterial stiffness. In the present study, we obtained no direct evidence (*e.g.* pulse wave velocity data) demonstrating the relationship between serum testosterone levels and arterial stiffness. However some findings reported in the liter-

**Table 2. Results of Multiple Regression Analysis Having Systolic Blood Pressure (SBP) as Dependent Variable**

| Variable | Normotensives | | Systolic/diastolic hypertensives | | Isolated systolic hypertensives | |
|---|---|---|---|---|---|---|
| | *F* value | Pr>F | *F* value | Pr>F | *F* value | Pr>F |
| Free testosterone | 15.94 | 0.0002 | 5.86 | 0.0206 | 92.66 | <0.0001 |
| BMI | 4.12 | 0.0413 | 4.23 | 0.0342 | 3.98 | 0.0461 |
| Age | — | NS | — | NS | 4.71 | 0.0399 |

BMI, body mass index.

**Table 3. Results of the Multiple Regression Analysis Having Diastolic Blood Pressure (DBP) as Dependent Variable**

| Variable | Normotensives | | Systolic/diastolic hypertensives | | Isolated systolic hypertensives | |
|---|---|---|---|---|---|---|
| | *F* value | Pr>F | *F* value | Pr>F | *F* value | Pr>F |
| Free testosterone | 4.44 | 0.0386 | 2.35 | 0.1075 | 7.06 | 0.053 |
| BMI | — | NS | 3.29 | 0.048 | — | NS |
| Age | — | NS | 2.98 | 0.063 | — | NS |

BMI, body mass index.

ature support such a relationship (*34–36*). Furthermore, an interaction between androgens and the vessel wall has been hypothesized because: 1) androgen withdrawal in men is associated with decreased central arterial compliance (*37*); 2) in animal models, testosterone supplementation inhibits atheroma formation (*6*); 3) testosterone has been suggested to act as a protective factor against atherosclerosis due to its immunomodulating effects that influence plaque development and stability (*38*); 4) long-term oral administration of testosterone induces both endothelium-dependent and -independent vasorelaxation (*39*); and 5) intravenous administration of testosterone has been demonstrated to produce coronary vasodilation and increase the angina threshold in men with coronary artery disease (*7–9*). According to these observations, testosterone appears to exert a protective role against the development of atherosclerosis and its clinical complications. Reduction in plasma testosterone with advancing age might contribute to increased arterial stiffness, which in turn has been associated with increased cardiovascular risk and the development of ISH (*40–42*).

In conclusion, the present results indicate that elderly men with ISH have lower plasma testosterone levels than do normotensive subjects in the same age range and a strong inverse relationship appears to exists between testosterone levels and SBP. Although clarification of the physiological and clinical significance of any such relationship will require further investigation, it is thought that low testosterone levels contribute to the increased arterial stiffness typical of ISH patients.

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