Relationship between androgenic hormones and arterial stiffness, based on longitudinal hormone measurements

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Hougaku, Hidetaka, Jerome L. Fleg, Samer S. Najjar, Edward G. Lakatta, S. Mitchell Harman, Marc R. Blackman, and E. Jeffrey Metter. Relationship between androgenic hormones and arterial stiffness, based on longitudinal hormone measurements. Am J Physiol Endocrinol Metab 290: E234–E242, 2006. First published September 13, 2005; doi:10.1152/ajpendo.00059.2005.—Circulating testosterone levels (T) decrease with age in men. Low T has been associated with coronary disease and with risk factors for atherosclerosis. This study examines the relationship in men between androgenic hormones and arterial stiffness, a major risk factor for cardiovascular events. T, sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulfate (DHEAS) were measured longitudinally over 33 yr (follow-up 11.8 ± 8.3 yr) in 901 men from the Baltimore Longitudinal Study of Aging, of whom 206 (68.1 ± 13.7 yr) underwent carotid duplex ultrasonography. The 901 men were used to characterize age-associated hormone levels by means of mixed-effects models. Hormone values were estimated for the 206 men at the time of ultrasonography. Free T index (FTI) was calculated by dividing T by SHBG. The arterial stiffness index was calculated from peak systolic and end diastolic diameters of the common carotid artery and simultaneous brachial artery blood pressure. T, FTI, and DHEAS were correlated negatively with age, pulse pressure (PP), and stiffness index (each P < 0.01), whereas SHBG was correlated positively with age and stiffness index (P < 0.01). However, T was the only hormone that predicted the stiffness index after adjustment for age, PP, fasting plasma glucose, body mass index, and total cholesterol. T values 5–10 yr before the carotid study also predicted the stiffness index (P < 0.05). Thus the adverse influence of low T on the cardiovascular system in men may be mediated in part via the effects of T on vascular structure and function.

testosterone; dehydroepiandrosterone; carotid ultrasonography; intimal medial thickness; coronary heart disease

AGING IS ASSOCIATED WITH an increasing risk for atherosclerotic cardiovascular (CV) disease. There is considerable evidence that some of this risk is related to the age-associated decline in sex hormone activity. Testosterone (T), free T, and their precursor dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) have been reported to have an antiatherosclerotic effect in men. Men with CV disease have significantly lower levels of each hormone (18, 46), and lower T levels have been associated with a higher risk for all-cause or CV death (5). On the other hand, androstenedione, another precursor to T, which has recently been marketed as a natural alternative to anabolic steroids for increasing blood T concentrations, has been reported to produce adverse health effects (44). Recent studies have shown that sex hormone-binding globulin (SHBG) also plays a role in CV risk (8, 15, 24, 26, 29, 68). However, how androgenic hormones assert these effects on atherogenesis remain unclear. The most commonly accepted explanation at present is that these hormones affect conventional CV risk factors (22, 25, 30, 52, 53, 73), rather than exerting a direct effect on the arterial tree. To our knowledge, no study has examined the relationships between androgenic steroids and traditional risk factors and arterial wall properties simultaneously.

In this study, we hypothesized that androgenic hormones exert a salutary CV effect, at least in part, by preventing or reducing arterial stiffness. Increased arterial stiffness is increasingly recognized as an early risk factor for CV disease. Increased stiffness of large elastic arteries mechanically leads to systolic blood pressure elevation (51) and, thence, left ventricular hypertrophy (50). An association has been shown between arterial stiffness and atherosclerosis (9), hypertension (3), diabetes (59), hyperlipidemia (43), and smoking (67). Increased arterial stiffness is reported not only in patients with coronary artery disease (33) and stroke (42) but also in healthy young subjects with a family history of myocardial infarction (55) or diabetes mellitus (34). Previous studies from our laboratory suggested that age-associated increases in arterial stiffness are attenuated by postmenopausal estrogen replacement therapy (47, 60). However, a previous study in men from the Baltimore Longitudinal Study of Aging (BLSA) did not detect an association of lower T or DHEAS with subsequent onset of CV disease (13). In the current study, we examined the relationship between an arterial stiffness index derived from carotid ultrasonography and CV risk factors and androgenic hormone levels that had been longitudinally evaluated from male volunteers in the BLSA.

SUBJECTS AND METHODS

Subjects. Subjects consisted of 206 male BLSA volunteers who underwent both common carotid artery ultrasound examination and measurement of serum levels of androgenic hormones. The BLSA is
comprised of community-dwelling, predominantly white, college-educated volunteers who are examined at regular intervals with 2–2.5 days of extensive medical, physiological, and psychological studies and who have serum samples banked for future investigation (62). The BLSA was started in 1958 and has recruited participants continuously since that time.

A total of 833 carotid duplex sonograms were performed from February 1994 to January 2000 in 678 BLSA subjects. For the current analysis, the 425 sonograms on women were excluded. From the remaining 366 male subjects (408 examinations), 80 men were excluded who did not have androgenic hormone data. In addition, 76 subjects were excluded in whom carotid diameter was not measured, three who had undergone carotid endarterectomy, and one with severe carotid stenosis (>60%), based on duplex ultrasonography. Only the initial carotid study was included in 10 men who underwent carotid examinations on two visits. Thus 206 men aged 33.5–95.0 yr (mean 68.1 ± 13.7 yr, with 5 men 30–39 yr of age, 23 men 40–49 yr, 30 men 50–59 yr, 44 men 60–69 yr, 59 men 70–79 yr, and 45 men 80 yr or older) formed the basis of this study.

Blood sampling. Serum T, SHBG, and DHEAS were measured longitudinally in 901 men over a 35-yr period (1963–1998, mean follow-up 11.8 ± 8.3 yr) as part of a BLSA prostate study (26). Blood samples were drawn between 0600 and 0800 after an overnight fast and stored at −70°C. A total of 3,621 samples were assayed for these hormones in 1995 (28). Serum samples were taken from each subject’s most recent three visits, and visits closest to 10, 15, 20, 25 and 30 yr prior to the most recent visit. All hormone measurements were performed at Hazleton Laboratories (now Covance Laboratories, McLean, VA). The free T index (FTI) was calculated by dividing serum T by SHBG. The FTI reasonably approximates bioavailable T by means of equilibrium dialysis (70). Calculated free T (calc-FT) was calculated on the basis of the mass action models suggested by Vermeulen et al. (70). The intraclass correlation between calc-FT and FTI was 0.67 for the entire 3,651 T measurements from the 901 men (adjusted for the repeated measurements within subjects) and 0.92 for the 206 measurements included in this report.

Details of the hormonal assay have been previously published (28). T levels were determined in duplicate using 125I-labeled RIAs kits obtained from Diagnostic Systems Laboratories (Webster, TX). Minimum detectible T levels averaged 0.42 nmol/l, with intra- and interassay coefficients of variation (CoVs), respectively, of 4.8 and 5.7% at concentrations of 7.74 and 7.29 nmol/l, and 3.3 and 6.4% at concentrations of 44.7 and 42.9 nmol/l. SHBG concentrations were measured using RIA kits purchased from Radim (Liege, Belgium), which employ 125I-labeled SHBG and polyethylene glycol (PEG)-complexed second antibody. The sensitivity of the SHBG assay was ~10 nmol/l. The CoV was 22% at 5 nmol/l and 5% at 25 nmol/l, with intra- and interassay CoVs, respectively, of 3.4 and 10.8% at concentrations of 22 and 19 nmol/l and 1.8 and 7.7% at concentrations of 117 and 118 nmol/l. Preliminary analysis revealed a significant increase in T level with length of storage, independent of age, which was due to a date-related assay artifact (28). A mixed-effects model was utilized to adjust T for the date effect.

DHEAS was measured using a double-antibody coated-tube assay with reagents from Diagnostic Systems Laboratories. The minimal detectable level was 141.4 nmol/l. The intra-assay COV was 4.3% at 688 nmol/l and 2.0% at 3,340 nmol/l. The interassay COV was 6.6% at 688 nmol/l and 3.9% at 3,340 nmol/l.

Arterial stiffness index and intimal medial thickness. The common carotid artery (CCA) was examined bilaterally by high-resolution B-mode ultrasonography with a linear array 5- to 10-MHz duplex-type scanner (Ultramark 9 HDI; Advanced Technology Laboratories, Bothell, WA) as previously reported (47). The examination was performed with the subjects in the supine position in a dark and quiet room starting after at least 5–10 min of bed rest. The transducer was manipulated so that the near and far walls of the artery were parallel to the transducer footprint and the lumen was maximized in the longitudinal plane ~1.5 cm proximal to the bifurcation. Intimal medial thickness (IMT) of the far wall was measured on frozen frames of a suitable longitudinal image with the image magnified to achieve higher resolution. IMT was measured at five contiguous sites at ~1-mm intervals as the distance between the luminal-intimal interface and the medial- adventitial interface. The average of the measurements from both arteries was used in the analysis. The maximum (systolic) and minimum (diastolic) diameters were measured visually with the help of electrocardiogram (ECG; in mid or late systole, and in end diastole). Diameter was measured between both endothelial layers, perpendicular to the course of the vessel. The measurements were repeated on three different cardiac cycles for both the right and the left CCA and averaged. Blood pressure (BP) was measured in the brachial artery 15 min after the onset of testing by the oscilometric method (Critikon 1846SX/P, version 085; Dinamap, Tampa, FL). All measurements were performed by a trained sonographer who was unaware of medical profiles of examinees.

CCA stiffness was evaluated by the stiffness index (33, 38), as has been previously reported by our group (47). It was calculated as follows:

\[
\text{stiffness index} = \ln(\text{SBP/DBP})/\Delta d/D
\]

where SBP and DBP are systolic and diastolic BP and \(\Delta d/D\) (change in arterial diameter/diastolic diameter) is the strain. The average value of the six measurements was used for analysis. Intraobserver correlation between repeated stiffness measurements from 10 subjects was 0.96 \((P < 0.01)\), with similar averages for the two sets of readings \([6.37 \pm 2.59 \text{ vs. } 6.43 \pm 2.58, P = \text{ not significant (NS)}]\). The intraclass correlation was 0.92 \((P < 0.01)\), and Bland-Altman plots (9) were flat across the range of measurements.

CV risk factors and coronary artery disease assessment. Common CV risk factors for atherosclerotic disease assessed included age, serum total cholesterol (T-chol), fasting plasma glucose (FGP), pulse pressure (PP), mean BP (MBP), and body mass index (BMI). T-chol was assessed by the methods described by Sorkin et al. (66). FGP was measured after an overnight fast. Brachial artery BP was taken in the right arm in the sitting position after ~5 min of resting during the health evaluation. This pressure, rather than the pressure taken during the sonography, was used because it more closely reflects how BP is measured to assess CV risk. PP was calculated as SBP − DBP. MBP was calculated as DBP + 1/3−PP. Body height and weight were measured on a standard balance beam scale. BMI calculated as weight (kg) divided by height squared (m²).

Subjects were classified into one of three coronary artery disease (CAD) categories on the basis of medical history, resting electrocardiogram (ECG), and maximal treadmill exercise ECG. Men were classified as having no CAD if they gave no history of angina pectoris or myocardial infarction, resting ECG showed no pathological Q waves, and exercise ECG showed no horizontal or downsloping ST-segment depression ≥1 mm. They were classified as having possible CAD if they had asymptomatic ischemic ST-segment depression ≥1 mm without clinical symptoms or resting ECG evidence of myocardial infarction. They were classified as having definite CAD if they had a history of acute myocardial infarction, ECG evidence of silent myocardial infarction (Minnesota Code 1:1 or 1:2), unequivocal angina pectoris as defined by the Rose questionnaire, or a history of coronary artery revascularization. Statistical analysis. Cohort characteristics were expressed as means and standard deviations. The cohort was compared with the subjects who had T measurements but not the carotid ultrasonography by use of Student’s \(t\)-test with a Bonferroni adjustment for 12 comparisons.

The timing of the collection of blood samples did not correspond to the timing of the carotid study in most of the 206 men. To estimate the hormone value at the time of carotid study, a mixed-effects model was developed for each hormone by using the longitudinal data available from 901 men (including the 206 men from this study) as previously reported by Harman et al. (28). The model considered initial age, year,
and elapsed time from first measurement in the prediction. These analyses were performed using MLwiN (beta version 1.10.0005, Multilevel Models Project Institute of Education). The resulting equations were as follows:

\[ T = (639.083 + u_0) - 3.417 \cdot \text{iage} + (-5.5 + u_1) \cdot \text{time} + (0.056 + u_2) \cdot \text{time}^2 + e \]

\[ \text{FTI} = (15.207 + u_0) - 0.15217 \cdot \text{iage} + (-0.1387 + u_1) \cdot \text{time} + (0.0000238 + u_2) \cdot \text{time}^2 + e \]

\[ \text{DHEAS} = (1994.089 + u_0) - 15.693 \cdot \text{iage} + (48.442 + u_1) \cdot \text{time} + 1.219 \cdot \text{time}^2 + (-1.266 + u_2) \cdot \text{time} \cdot \text{iage} + e \]

\[ \text{SHBG} = (52.6502 + u_0) + 0.5886 \cdot \text{iage} + (-1.942 + u_1) \cdot \text{time} + (0.0190 + u_2) \cdot \text{time}^2 + (0.04161 + u_3) \cdot \text{time} \cdot \text{iage} + e \]

where iage is initial age and u0 to u3 are random effects that reflect individual variation from the mean effect. To examine the reliability of the equations, hormone values predicted by these equations were compared with hormone values measured at the time of the carotid study in those men who had blood analyzed at the same visit as the carotid study. Pearson’s correlations between the estimated values and the actual values were 0.997 for T, 0.998 for FTI, and 0.95 for SHBG with no evidence of bias in the parameter estimates.

RESULTS

Aging, sex hormones, and risk parameters. Table 1 shows subject characteristics for selected CV risk factors and androgenic hormone at the time of the carotid study. The men on average were overweight and had normal BP. Twelve men (6%) had FPG in the diabetic range, and 21 (10%) were in the impaired glucose tolerance range. Six men (2.9%) were current and 116 (56.3%) were former cigarette smokers. Thirty-seven men (18%) had SBP >140 mmHg, of whom nine had BP >160. One hundred twenty men (58%) had used CV medications, 90 (44%) at the time of the carotid visit, including antihypertensives and cholesterol-lowering agents. One hundred sixteen men (56%) had no coronary heart disease, whereas 64 (31%) had possible and 26 (13%) had definite disease. No differences were found in T, FTI, SHBG, or DHEAS levels based on coronary disease status or the use of CV medicines when adjusted for age.

The study cohort differed on body mass and CV risk factors from the 695 men who had T measurements but not a carotid study or were excluded for other reasons. Of these men, 9.5% were current and 51.0% were former smokers, whereas 55.8% had no evidence of coronary heart disease, 21.9% had possible, and 22.2% had definite disease.

Relationship of sex hormones to carotid stiffness index and IMT. Table 2 shows the bivariate relationships among risk parameters, IMT, and stiffness index. Carotid stiffness index was positively correlated with age and PP (each P < 0.01). It
was also negatively correlated with T, FTI, and DHEAS ($P < 0.01$, respectively), although positively correlated with SHBG ($P < 0.01$, Table 2). IMT correlated positively with carotid stiffness index and age and negatively with T, FTI, and DHEAS. IMP and the carotid stiffness index differed on their influences on CCA stiffness. However, the levels of these hormones are interrelated and highly (inversely) correlated in the long-term effect of androgenic hormones on the arterial stiffness index after adjustment for all CV risk parameters at the time of carotid study in multiple regression analysis ($P < 0.05$). Similar analyses for FTI, DHEAS, or SHBG did not find independent contributions for these hormones on the stiffness index.

### Longitudinal hormone effect on arterial stiffness

To examine the long-term effect of androgenic hormones on the arterial tree, the hormone levels 5–10 yr before the carotid examination were regressed on the stiffness index (Table 5). The mean serum T level 5–10 yr (mean 8.1 ± 1.2 yr) before the carotid study ($T_{5–10}$) was significantly higher than T was at the time of the carotid examination (428.5 vs. 399.8 ng/dl, $P < 0.01$ by paired-samples $t$-test) and was an independent negative predictor of the arterial stiffness index after adjustment for all CV risk parameters at the time of carotid study in multiple regression analysis ($P < 0.05$). Simultaneous analysis of relationships among parameters by path analysis. The multiple regression models in Table 3 examine whether the androgenic steroids exert independent influences on CCA stiffness. However, the levels of these hormones are interrelated and highly (inversely) correlated with age, and the actions of these hormones on arterial stiffness are likely related to their effects on other factors. Furthermore, increasing arterial stiffness has an effect on increasing PP (14). A path analysis was performed to examine the relationships among these hormone indexes, risk parameters, and stiffness changes in each analysis except age in model 6. The models were unchanged by the addition of coronary heart disease status or the use of antihypertensive medications (data not shown). T, FTI, DHEAS, and SHBG were not significantly associated with IMT after adjustments for age, FPG, PP, MBP, T-chol, or BMI (Table 4). K-fold validation found no evidence that the parameter estimates were significantly biased, and in no instance did the observations in either Table 3 or Table 4 change.

### Table 3. Multiple regression models to estimate effect of each androgenic hormone and their combination on stiffness index after adjustment for CV risk parameters

<table>
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<tr>
<th>Hormone(s) Used in Model</th>
<th>Model 0</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
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$\chi^2$ values are $P$ values. calc-FT, calculated free T; FPG, fasting plasma glucose; NS, not significant (note: $P$ in 0.05 to 0.1 range, although nonsignificant, are shown as <0.1). Each regression model uses age, FPG, PP, MBP, T-chol, and BMI as independent variables and hormone(s) as independent variables for predicting stiffness index.
index simultaneously. Table 6 shows the initial model with the direction of the proposed relationships. Our assumptions in the initial model were that 1) age would act directly on each variable; 2) BMI would impact the other measurements except age; 3) each hormone would act directly on each risk parameter, IMT, and stiffness index; 4) stiffness index would be affected by all variables; and 5) IMT would be affected by all variables except for arterial stiffness. The initial model assumed all of these relationships. Paths were subsequently removed if they had a P value >0.1.

Figure 1 presents the final model. Aging is directly associated with every factor except MBP, FPG, and T-chol. Serum levels of T, FTI, and DHEAS, but not SHBG, are negatively associated with age. T had a direct effect on the arterial stiffness index and PP. It also influenced FPG, which through an effect on T-chol impacted MBP and then PP. Decreased DHEAS also increased PP. Stiffness and IMT were not related. Arterial stiffness was found to have a positive impact on PP, in contrast to our initial assumption. MBP, but not PP, was related to IMT. Boot-strapping the model with 1,000 randomly drawn samples found no evidence that the parameters reported in Fig. 1 were biased. A model replacing FTI with calc-FT gave the same relationships for free T.

**DISCUSSION**

The major observation in this study is that higher serum T is independently associated with lower arterial stiffness. Furthermore, the effect of T on arterial stiffness was present when T was measured 5–10 yr prior to the carotid measurement, suggesting a long-term influence of T on the artery. In addition, DHEAS exerted a weak, independent impact on PP but not on stiffness or MBP. The relationships of androgens to arterial stiffness may explain, at least in part, the mechanism of the apparent antiatherosclerotic effect of sex hormones noted in some (6, 18, 46) but not other (54) epidemiological studies. Findings that men with overt CAD have lower T levels may represent the effects of chronic illness on hypothalamic-pituitary-gonadal function rather than of T on CAD risk, although some (6, 18, 46) but not other (54) epidemiological studies. The modest nature of the salutary effects on arterial stiffness in the current study is consistent with observations that the beneficial influence of T on atherosclerotic processes is not consistently observed (72) and with the failure to detect significant prospective differences in T, FTI, or DHEAS levels in men who later did or did not develop CAD in the present and previous (13) BLSA study. The observations offer no justification for the therapeutic use of T replacement for older men.

A relationship between T and arterial stiffness has been suggested but not examined directly. Rosano et al. (56) reported that short-term intravenous administration of T induced a beneficial effect on exercise-induced myocardial ischemia in men with coronary heart disease, which they related to a direct coronary artery-relaxing effect. T infused into coronary arteries in men with CAD causes vasodilatation, possibly mediated by a direct effect via sex steroid receptors (56, 44). Dockery et al. (16) reported that androgen withdrawal was associated with a reduction in central arterial compliance in 24 men. Our study showed an inverse relationship between T and CCA stiffness.
On the basis of the path analysis (Fig. 1), one of many models that could potentially explain the data, T exerted an inverse direct influence on both carotid arterial stiffness and PP. Decreased T with advancing age increased PP, which was further increased by the stiffness index. The model was not improved by adding a path from PP to stiffness. Close relationships between T and blood pressure have been reported in previous studies (61, 63).

The path analysis indicated that decreased T correlated with higher FPG (Fig. 1). Several studies have reported that decreased T is associated with hyperinsulinemia and glucose intolerance and leads to FPG elevation (27, 63). Taken together with the aforementioned findings, these data suggest that T exerts indirect antiatherosclerotic effects on several CV risk factors (e.g., PP and FPG). However, there is a well-described inverse relationship of total T with obesity (1, 2, 21), most (2, 20), if not all (69), of which appears to be caused by an obesity-related decrease in SHBG such that FTI remains constant. The apparent influence of T on obesity-associated CV risk factors may be explained by this effect.

FTI, or calc-FT, was not independently associated with the arterial stiffness index. There are several possible explanations for this finding. First, it is possible that T and free T exert different effects on CV risk factors. Kabakci et al. (36) reported

Table 6. Parameters used in initial model of path analysis with direction of relationship

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<th>T</th>
<th>FTI</th>
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On the basis of the path analysis (Fig. 1), one of many models that could potentially explain the data, T exerted an inverse direct influence on both carotid arterial stiffness and PP. Decreased T with advancing age increased PP, which was further increased by the stiffness index. The model was not improved by adding a path from PP to stiffness. Close relationships between T and blood pressure have been reported in previous studies (61, 63).

The path analysis indicated that decreased T correlated with higher FPG (Fig. 1). Several studies have reported that decreased T is associated with hyperinsulinemia and glucose intolerance and leads to FPG elevation (27, 63). Taken together with the aforementioned findings, these data suggest that T exerts indirect antiatherosclerotic effects on several CV risk factors (e.g., PP and FPG). However, there is a well-described inverse relationship of total T with obesity (1, 2, 21), most (2, 20), if not all (69), of which appears to be caused by an obesity-related decrease in SHBG such that FTI remains constant. The apparent influence of T on obesity-associated CV risk factors may be explained by this effect.

FTI, or calc-FT, was not independently associated with the arterial stiffness index. There are several possible explanations for this finding. First, it is possible that T and free T exert different effects on CV risk factors. Kabakci et al. (36) reported
that T was inversely associated with HDL cholesterol level, whereas free T was positively associated with total cholesterol and LDL cholesterol. Another possibility is that FTI, or calc-FT, and similar indexes may not be reliable indicators of an active form of T, especially in men (11, 70). However, in previous work in the BLSA using these hormonal data, we observed that FTI had a clearer relationship with muscle strength (58) and was associated with a higher rate of hypogonadism compared with T (28). The methodology used to estimate FTI at the time of the carotid evaluation and the strong relationship between age and FTI suggest that age is a confounder for FTI that could mask any modest relationship. The path analysis is primarily designed to address the issue of covariance, and the models evaluated found no evidence for a direct role of FTI but rather an indirect effect primarily through age. It is possible that, because total T but not FTI is reduced in obesity due to a decrease in SHBG (1, 2, 20, 21), the association that we observed is also an indirect effect of total or abdominal obesity (24). However, SHBG was not associated with arterial stiffness in the current study, which is compatible with the lack of a relationship between these hormones and CV events (12, 23). Nonetheless, there is increasing evidence of relationships between SHBG and risk factors for atherosclerosis (8, 15, 24, 29, 68).

DHEAS also exhibited no independent relationship with the arterial stiffness index, although it was related to PP. Furthermore, we found a modest direct relationship between DHEAS and T (Fig. 1), although they were moderately correlated (Table 2). Several large, community-based prospective studies have examined the relationship between DHEA(S) and CV risk factors and events. Some studies have detected no apparent influence of DHEA(S) on the development of human atherosclerosis (39) or nonfatal CV disease (4, 6, 35, 41, 48). Other studies have reported an inverse relationship between endogenous DHEA(S) and CV risk factors (65), CV events (46), angiographic stenosis (31), and allograft vasculopathy (32) in young and old men and/or women. Moreover, higher mortality was observed in men with lower DHEAS levels (7, 45, 57). Recent studies suggest that DHEA exerts genomic and non-genomic effects on vascular endothelial cells not mediated by other steroid hormone receptors, leading to increases in nitric oxide production (62), and improves vascular function and insulin sensitivity (37). In contrast, DHEA has also been reported to increase human macrophage foam cell formation, which is potentially proatherogenic (49). As for the interrelationships among androgenic hormones, it has been reported that an intake of DHEAS did not raise T level (40). Phillips et al. (52) reported that DHEAS was not associated with T, free T, and SHBG.

Several methodological issues and limitations need to be addressed in regard to this report. The arterial stiffness index used as an indicator of CCA stiffness in the present study is conceptually similar to the Peterson’s pressure-strain elastic modulus but exhibits the additional characteristic of being independent of transient changes in BP (33, 36). Wada et al. (71) reported that, among four indexes that measure the properties of the arterial wall by use of carotid ultrasound (pressure-strain elastic modulus, distensibility coefficient, cross-sectional compliance, and stiffness index beta), stiffness index was the least dependent on BP. The index is only approximate and is dependent on the relationship between brachial and carotid arterial pressure. We reviewed data from 26 subjects who had pulse wave pressure of the carotid artery with brachial BPs measured at the same visit but not concurrently with the Doppler assessment. Brachial SBP (116 ± 14 mmHg) exceeded central SBP (103 ± 14 mmHg), consistent with the well-known peripheral amplification of SBP that occurs in humans. However, the correlation between central and brachial measurements of ln(SBP/DBP), the numerator in the stiffness index, was 0.92 (central = 0.36 ± 0.09, brachial = 0.48 ± 0.10), which suggests a fixed difference in ln(SBP/DBP), which should lead to a fixed, systematic error in the stiffness index.

The hormone values at the time of carotid examination were determined using mixed-effects modeling because the timing of the blood samples did not correspond to the timing of the carotid study in most men. The resulting T is the best linear unbiased predictor of the actual hormonal level, with less error than in the observed measurement. Such estimates take advantage of all the information available on a subject. Using this approach allowed for examining the effect of T at the time of the stiffness measure and also the long-term impact of T.

The FTI has been argued to be an unreliable indicator of free T (70). For this reason we examined both FTI and calc-FT. Calc-FT has been argued to be a reliable indicator of free T (70). Both approaches for estimating free T gave similar results, suggesting that using FTI in this report was not the reason for the poor association between free T and arterial stiffness or IMT.

Another potential issue in this report is the difference between the subjects included and excluded from the study. The study subjects showed less CV risk than the excluded subjects, with the major reason for exclusion being the lack of having the ultrasonography. The inclusion of healthier subjects suggests that the observed relationships more likely represent what is normal between arterial properties and T and less to CV pathology. Furthermore, the healthier nature of the subjects suggests that the observations may not apply to men with CAD.

In summary, our results are consistent with the hypothesis that decreasing T with advancing age is correlated with increasing arterial stiffness. These findings suggest that maintaining T at a favorable level could have a protective effect on arterial aging. Thus T replacement therapy in hypogonadal men, a common condition in the elderly, may have a salutary impact on arterial stiffness and perhaps on CV events. Further research is needed to establish the extent that T and T replacement impact on arterial aging.

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REFERENCES


