Associations of Total Testosterone, Sex Hormone-Binding Globulin, Calculated Free Testosterone, and Luteinizing Hormone with Prevalence of Abdominal Aortic Aneurysm in Older Men

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Context: Abdominal aortic aneurysm (AAA) is associated with mortality in older adults, and increasing aortic diameter predicts incident cardiovascular events. Although AAA occurs predominantly in men, its association with male sex hormones is unclear.

Objective: The objective of the study was to examine whether male sex hormones are independently associated with AAA or increased abdominal aortic diameter.

Design: This was a cross-sectional analysis.

Setting and Participants: Participants included 3620 community-dwelling men aged 70–88 yr.

Main Outcome Measures: Abdominal aortic diameter was measured with ultrasound. Early morning sera were assayed for total testosterone, SHBG, and LH. Free testosterone was calculated using mass action equations.

Results: AAA (aortic diameter ≥30 mm) was present in 262 men (7.2%). Men with AAA had lower serum total and free testosterone (mean ± SD 14.5 ± 6.0 *vs.* 15.5 ± 5.6 nmol/liter, $P = 0.005$ and 256 ± 87 *vs.* 280 ± 97 pmol/liter, $P < 0.001$, respectively) compared with men without. LH was higher in men with AAA (median, interquartile range: 4.9, 3.1–7.9 *vs.* 4.3, 3.0–6.4 IU/liter, $P = 0.013$). In multivariate analysis adjusting for potential confounders, free testosterone was negatively associated with AAA (odds ratio per 1 SD increase: 0.84, 95% confidence interval 0.72–0.98, $P = 0.026$). LH was positively associated (odds ratio 1.14, 95% confidence interval 1.03–1.25, $P = 0.008$). Comparable results were seen with aortic diameter analyzed as a continuous variable.

Conclusions: Lower free testosterone and higher LH levels are independently associated with AAA in older men. Impaired gonadal function may be involved in arterial dilatation as well as occlusive vascular disease in older men. Additional studies are needed to clarify direction of causality and determine possible scope for preventive intervention. (***J Clin Endocrinol Metab*** **95: 1123–1130, 2010)**

Testosterone in the circulation is bound to SHBG or albumin, with a small fraction unbound or free. As men grow older, testosterone levels fall, with a steeper decline in free compared with total testosterone (1, 2). Lower total or free testosterone levels have been associated with ill health in older men (3, 4). Specifically, lower testosterone levels predict increased incidence of metabolic syndrome and type 2 diabetes, both conditions as-

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Abbreviations: AAA, Abdominal aortic aneurysm; CHD, coronary heart disease; CI, confidence interval; OR, odds ratio.

sociated with increased risk of cardiovascular disease (5, 6). Men with lower testosterone levels have greater carotid intima-media thickness reflecting preclinical atherosclerosis and more evidence of atherosclerotic vascular disease in the form of abdominal aortic calcification and lower extremity arterial disease (7–9).

Another manifestation of vascular disease, abdominal aortic aneurysm (AAA), is associated with mortality in older adults due to both aortic rupture and also other cardiovascular events (10). AAA primarily affects men, who have a 5-fold greater prevalence of AAA compared with women in studies using ultrasound screening (11–13). Recently increased abdominal aortic diameter, even below the threshold for definition of AAA, has been identified as a predictor of overall mortality and incident cardiovascular events (14, 15). However, it is unclear whether higher testosterone levels in men compared with women may contribute to the male preponderance of AAA or whether in men lower testosterone levels are associated with aortic dilatation in the same manner lower testosterone is associated with occlusive vascular disease (16, 17). To address this question, we examined the association between male sex hormones with both the presence of AAA and abdominal aortic diameter in a large population-based cohort of older men.

Subjects and Methods

Study population

We studied participants from the Health In Men Study, which consists of a cohort of men who originally participated in a trial of screening for AAA (18). Between 1996 and 1999, 12,203 community-dwelling men aged 65–83 yr from Perth, Western Australia, attended for screening for AAA. Each man completed a questionnaire assessing aspects of history and lifestyle relevant to AAA including smoking status, diet, history of (or treatment for) coronary heart disease (CHD), stroke, hypertension, dyslipidemia, or diabetes. Between 2001 and 2004, 4,263 of the original cohort of 12,203 men completed a follow-up visit at which time a fasting blood sample for biochemical analysis was collected (19). The Human Research Ethics Committee of the University of Western Australia approved the study protocol, and all men gave written informed consent. For this analysis we excluded men for whom serum was not available (n = 98), men who were receiving either testosterone or antiandrogen therapy (n = 149), and men who had a history of prostate cancer (n = 378). Men with prostate cancer were excluded because we were concerned that they may have been receiving unreported therapies that influenced circulating sex hormones. Another 13 men with incomplete clinical data and five men with prior surgical repair of AAA were excluded.

Assessment of medical comorbidities

Medical comorbidity data were collected by questionnaire in 1996–1999 and reassessed in 2001–2004. Hypertension was defined as a recorded blood pressure of 140/90 mm Hg or greater, having a diagnosis of hypertension, or receiving treatment for high blood pressure. Dyslipidemia was defined as having high-density lipoprotein less than 0.9 mmol/liter, low-density lipoprotein of 3.4 mmol/liter or greater, triglycerides of 1.8 mmol/liter or greater, or total cholesterol of 5.5 mmol/liter or greater or receiving lipid-lowering therapy. Diabetes was defined as having been diagnosed with or receiving treatment for diabetes, fasting glucose level greater than 7 mmol/liter, or nonfasting glucose greater than 11.1 mmol/liter. Additional information on medical comorbidities was obtained from the Western Australian Data Linkage System (20). Briefly, this system links together records from the Mental Health Information System, cancer register, death register, and hospital morbidity data (which includes codes for multiple medical diagnoses for all admissions to private and public hospitals). Linked data were reviewed for all men in the study cohort. CHD was defined by a history of myocardial infarction, angina, or treatment for coronary artery disease. Chronic pulmonary disease was defined by a past history or treatment of recurrent bronchitis or asthma for more than 3 months. Smoking history was categorized as ever smoker or lifelong nonsmoker. Subjects' waist and hip circumference were measured in accordance with guidelines of the International Society for the Advancement of Kinanthropometry (21).

Measurement of abdominal aortic diameter

The greatest transverse and anteroposterior diameter of the infrarenal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 M Hz probe (Toshiba Australia, North Ryde, New South Wales, Australia). The reproducibility of ultrasound measurements were assessed every 4 months during the initial screening period and during surveillance of cases of AAA. On each of these occasions, 10 men were selected at random for assessment of intra- and interrater agreement of aortic diameter measurements. Each man was scanned twice by each of three observers as well as by a senior vascular sonographer. All scans were performed with the operators blinded to previous aortic diameter measurements. Nonparametric tests were used to compare mean intra- and interrater differences in aortic diameter measurements. No significant differences were found between observers, with 95% of measurement differences being less than 3 mm, as previously reported (22). An AAA was considered present if the abdominal aortic diameter was 30 mm or greater (14, 23).

Laboratory assays

Blood samples were collected between 0800 and 1030 h. Serum was prepared immediately after phlebotomy and stored at −80 C until assayed. Biochemical and hormone assays were performed in the Biochemistry Department, PathWest, Royal Perth Hospital, Perth, Western Australia, Australia, as previously described (24). Briefly, serum total testosterone, SHBG, and LH were determined by chemiluminescent immunoassays on an Immulite 2000 analyzer (Diagnostic Products Corp.-Biomediq, Doncaster, Australia). Between-day imprecision (coefficient of variation) for testosterone was 11.2% at 7.2 nmol/liter and 8.9% at 18 nmol/liter, for SHBG, 6.7% at 5.2 nmol/liter and 6.2% at 81 nmol/liter, and for LH, 6.4% at 2.3 IU/liter and 5.8% at 19 IU/liter. The working range of the testosterone assay was 0.7–55 nmol/liter; the sensitivities of the SHBG and LH assays were 2 nmol/liter and 0.1 IU/liter, respectively. The established refer-

TABLE 1. Comparison of physical and biochemical variables in 3620 men with and without AAA

Characteristic	AAA	No AAA	*P* value
Number	262	3358	
Aortic diameter (mm)	33.7 (31.5–39.2)	21.4 (20.0–23.1)	<0.001
Age (yr)	78.2 ± 4.1	76.9 ± 3.5	<0.001
Hypertension	210 (80.2%)	2,553 (76.0%)	0.130
Diabetes mellitus	59 (22.5%)	504 (15.0%)	0.001
Dyslipidemia	210 (80.2%)	2,332 (69.5%)	<0.001
Ever smoker	231 (88.2%)	2,179 (64.9%)	<0.001
CHD	154 (58.8%)	1,046 (31.2%)	<0.001
Body mass index (kg/m^2)	27.0 ± 3.8	26.4 ± 3.6	<0.001
Waist to hip ratio	0.99 ± 0.07	0.97 ± 0.07	<0.001
Chronic pulmonary disease	90 (34.4%)	934 (27.8%)	0.024
Total testosterone (nmol/liter)	14.5 ± 6.0	15.5 ± 5.6	0.005
Free testosterone (pmol/liter)	256 ± 87	280 ± 97	<0.001
SHBG (nmol/liter)	42.6 ± 18.5	42.4 ± 16.5	0.830
LH (IU/liter)	4.9 (3.1–7.9)	4.3 (3.0–6.4)	0.013
Creatinine (μmol/liter)	95 (82–115)	88 (78–100)	<0.001

Nominal variables are presented as numbers (percent) and compared with the χ^2 test. Continuous variables are presented as mean ± SD or median (interquartile range).

ence intervals for these assays are total testosterone 8–35 nmol/liter, SHBG 10–70 nmol/liter, and LH 1–8 IU/liter. Free testosterone, specifically the portion not bound to either SHBG or albumin, was calculated from total testosterone and SHBG using mass action equations as described by Vermeulen *et al.* (25).

Stratification of men based on testosterone and LH levels

Clinical assessment of hypogonadal men requires confirmatory testing should an initial early morning blood sample reveal abnormal testosterone levels. For the purpose of this analysis based on a single blood sample, men were classified as having primary hypogonadism if their total testosterone was less than 8 nmol/liter and LH greater than 12 IU/liter, Leydig cell impairment if total testosterone was 8–15 nmol/liter and LH greater than 12 IU/liter, and hypogonadotrophic hypogonadism if total testosterone was less than 8 nmol/liter and LH 12 IU/liter or less according to previously published Australian criteria (26).

Statistical analysis

We investigated the association of serum concentrations of total and free testosterone, SHBG, and LH with the presence of AAA and with aortic diameter as a continuous variable using the statistical package Stata, version 10.0 (StataCorp, College Station, TX). Multivariate logistic regression analysis was used to assess the association of total and free testosterone, SHBG and LH with presence of AAA after adjusting for other risk factors (age, smoking status, hypertension, dyslipidemia, diabetes, CHD, chronic pulmonary disease, body mass index, waist to hip ratio, and serum creatinine), which may be implicated in AAA (27). Hormonal parameters were entered into the models as Z-scores (numerical value of the variable minus the mean divided by the SD), placing them on a common, metric-free scale. Odds ratios reflect the effect of a 1 SD increase in hormone level. Multivariate linear regression analysis was used to assess associations between hormone levels and aortic diameter (log transformed) after adjustment for covariates as above. All statistical tests were two tailed, and $P < 0.05$ was considered statistically significant.

Results

Characteristics of study population

Of 3620 men included in the analysis, 262 (7.2%) had an AAA (Table 1). Men with AAA were older and were more likely to have diabetes, dyslipidemia, CHD, chronic pulmonary disease, and a history of smoking. Men with AAA had higher waist to hip ratio and serum creatinine, lower total and free testosterone levels, and higher LH levels than men who did not have AAA. SHBG levels were similar in both groups.

Probability of AAA according to hormone levels

The probabilities and 95% confidence intervals of having AAA according to quintiles of total and calculated free testosterone, SHBG, and LH are shown in Fig. 1. Probabilities were adjusted for age in these analyses. The probability of having an AAA increased with lower total and free testosterone levels (Fig. 1, A and B) and with higher LH levels (Fig. 1D). Probability of having an AAA did not appear to change substantially across quintiles of SHBG (Fig. 1C).

Associations between hormone levels and AAA

Serum total testosterone and free testosterone were positively correlated ($r = 0.78$, $P < 0.001$). Free testosterone and LH were negatively correlated ($r = -0.20$, $P < 0.001$). We examined nonhormonal factors associated with AAA (Table 2) and then in separate logistic regression analysis evaluated associations between total or free testosterone, SHBG, and LH levels with AAA after adjusting for these risk factors (Table 2). In the adjusted analyses, higher free testosterone concentration was associated with lower risk [odds ratio (OR) 0.84 per 0.096 nmol/liter,

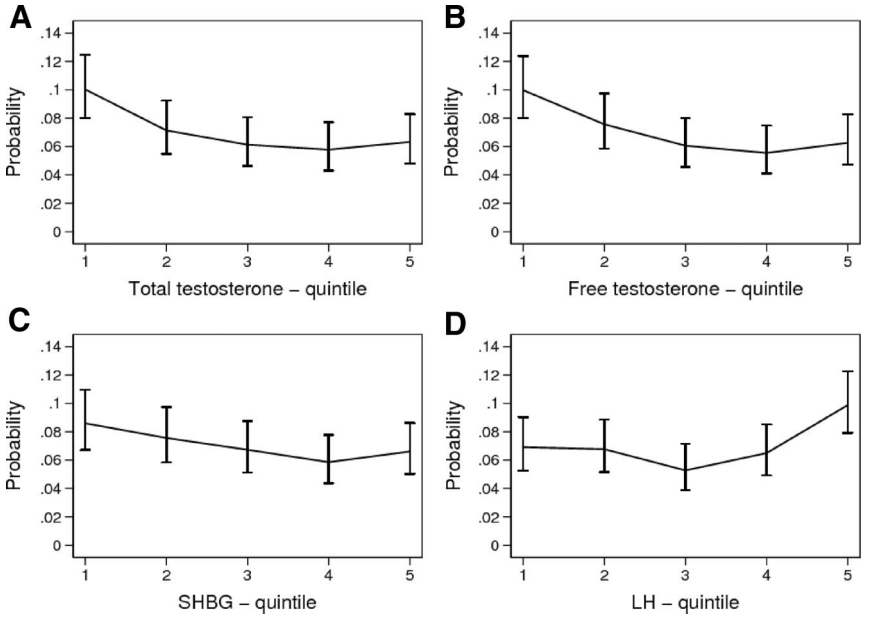

FIG. 1. Probability of AAA being present according to quintiles of total testosterone (A), free testosterone (B), SHBG (C), and LH (D) in 3620 community-dwelling older men. Quintile 1 contains the lowest values. Results are shown as probabilities adjusted for age and 95% CIs.

95% confidence interval (CI) 0.72–0.98] and higher LH with higher risk (OR 1.14 per 5.3 IU/liter, 95% CI 1.03–1.25) of AAA, respectively (Table 2). In the adjusted analysis, total testosterone (OR 0.95 per 5.6 nmol/liter, 95% CI 0.82–1.09) was not associated with AAA, nor was SHBG. The difference in total testosterone levels in men with AAA compared with those without (Table 1) reflected subtle confounding by several covariates including waist to hip ratio.

We performed a sensitivity analysis to determine whether exclusion of men with preexisting CHD would affect the results. There were 1200 men with CHD, of whom 154 (12.8%) had an AAA. Of the 2420 men without CHD, 108 (4.5%) had an AAA ($P < 0.001$). In men without existing CHD, after adjusting for nonhormonal risk factors, there was no association between total testosterone, SHBG, or LH with AAA. In the absence of CHD, the adjusted OR for AAA in men with higher free testosterone was similar to that seen in the cohort as a whole (OR 0.83), but statistical power was reduced with the smaller number of men (95% CI 0.65–1.05, $P = 0.117$).

Associations between hormone levels and abdominal aortic diameter

To examine associations between hormone levels and aortic diameter as a continuous variable, multivariate linear regression analysis was performed (Table 3). In the adjusted analysis, total testosterone was not associated with aortic diameter (Table 3). Free testosterone was inversely associated with aortic diameter (coefficient −0.008, $P = 0.007$), whereas SHBG and LH were positively associated (coefficient 0.006, $P = 0.047$ and coefficient 0.013, $P < 0.001$, respectively).

Stratification of men according to total testosterone and LH levels

After stratifying men according to total testosterone and LH concentrations, a higher proportion of men in abnormal categories had AAA compared with the reference group (Table 4). Of note, those with low total testosterone and elevated LH had the highest proportion of men with AAA (20 *vs.* 6%). Of the other categories, 12–15% of men classified as having abnormal hormone levels had AAA, compared with 6% for those without. However, the majority of men with AAA had normal total testosterone and LH levels.

Discussion

This study, undertaken in a large, well-characterized, population-based cohort of older men, reveals a significant and independent inverse association between circulating free testosterone concentration and presence of AAA. Because male gender is an important risk factor for AAA, the potential relationship of male sex hormones to AAA is of interest, particularly because there are animal data supporting a role of male sex hormones in AAA development (28, 29). For example, elastase perfusion of the aorta in male rats resulted in larger AAAs with higher frequency than in female rats (28), and androgens promoted AAA development in apolipoprotein-ε-deficient mice infused with angiotensin II (29). In contrast, our findings indicate that in humans, higher total or free testosterone levels are not associated with AAA; in fact, having higher serum free testosterone reduced the OR of AAA in older men. To our knowledge this is the first published report examining the association of circulating testosterone and AAA in men, and it supports the concept that in aging men adequate exposure to circulating androgens predicts better health outcomes.

Previous studies reported an inverse correlation between total testosterone levels and carotid intima-medial thickness, a marker of preclinical atherosclerosis, in middle-aged and older men (7, 30). A study of 1302 men aged 55 yr or older found that those with total and bioavailable (free and albumin bound) testosterone levels in the highest

TABLE 2. Multivariate logistic regression analysis of factors associated with AAA in 3620 older men

	Odds ratio	95% CI	*P* value
Multivariate model			
Age per 3.6 yr[a]	1.35	1.20, 1.53	<0.001
Hypertension	1.12	0.81, 1.56	0.481
Diabetes mellitus	1.24	0.90, 1.71	0.193
Dyslipidemia	1.44	1.03, 1.99	0.031
CHD	2.52	1.93, 3.30	<0.001
Ever smoker	3.66	2.48, 5.40	<0.001
Chronic pulmonary disease	1.14	0.86, 1.50	0.367
Body mass index per 3.6 kg/m^{2a}	1.01	0.96, 1.05	0.766
Waist to hip ratio per 0.07[a]	1.19	1.03, 1.37	0.020
Creatinine per 32 μmol/liter[a]	1.16	1.07, 1.27	<0.001
Logistic regression analyses			
Total testosterone per 5.6 nmol/liter[a]	0.95	0.82, 1.09	0.463
Free testosterone per 96 pmol/liter[a]	0.84	0.72, 0.98	0.026
SHBG per 16.7 nmol/liter[a]	1.09	0.95, 1.24	0.206
LH per 5.3 IU/liter[a]	1.14	1.03, 1.25	0.008

Multivariate model includes age, body mass index, hypertension, diabetes mellitus, dyslipidemia, CHD, smoking status, chronic pulmonary disease, waist to hip ratio, and serum creatinine. Separate logistic regression analyses evaluate associations between total or free testosterone, SHBG, and LH levels with AAA adjusting for all covariates shown in multivariate model.

[a] Approximately 1 SD.

TABLE 3. Multivariate linear regression analysis of factors associated with aortic diameter in 3620 older men

	Coefficient	95% CI	*P* value
Multivariate model			
Age per 3.6 yr[a]	0.020	0.015, 0.026	<0.001
Hypertension	−0.006	−0.020, 0.007	0.363
Diabetes mellitus	−0.003	−0.013, 0.019	0.692
Dyslipidemia	−0.002	−0.015, 0.011	0.761
CHD	0.039	0.026, 0.051	<0.001
Ever smoker	0.039	0.027, 0.051	<0.001
Chronic pulmonary disease	−0.001	−0.013, 0.012	0.920
Body mass index per 3.6 kg/m^{2a}	0.004	0.002, 0.006	<0.001
Waist to hip ratio per 0.07[a]	0.005	−0.002, 0.012	0.144
Creatinine per 32 μmol/liter[a]	0.016	0.011, 0.022	<0.001
Linear regression analyses			
Total testosterone per 5.6 nmol/liter[a]	−0.003	−0.009, 0.003	0.323
Free testosterone per 96 pmol/liter[a]	−0.008	−0.014, −0.002	0.007
SHBG per 16.7 nmol/liter[a]	0.006	0.001, 0.012	0.047
LH per 5.3 IU/liter[a]	0.013	0.007, 0.019	<0.001

Multivariate model includes age, body mass index, hypertension, diabetes mellitus, dyslipidemia, CHD, smoking status, chronic pulmonary disease, waist to hip ratio, and serum creatinine. Separate linear regression analyses evaluate associations between total or free testosterone, SHBG, and LH levels with aortic diameter adjusting for all covariates shown in multivariate model.

[a] Approximately 1 SD.

tertile had a lower risk of severe aortic atherosclerosis (detected by radiography as abdominal aortic calcification) than those with the lowest testosterone levels (8). Also, in a study of 3014 men aged 69–80 yr, those with free testosterone in the lowest quartile had an OR of 1.65 (95% CI 1.22–2.23) for lower extremity peripheral arterial disease, defined as an ankle-brachial index less than 0.90 (9). These reports are consistent with the higher overall and cardiovascular mortality described in middle-aged and older men with lower testosterone levels (31–33). Possible mechanisms by which lower testosterone levels could contribute to an increased burden of cardiovascular disease range from the loss of beneficial effects of testosterone on endothelial function to adverse influences on circulating lipids and vascular inflammation (3, 16, 34, 35). Therefore, whereas lower testosterone levels have previously been linked with atherosclerotic plaque formation, our findings implicate male sex hormones in a distinct pathological process involving aortic dilatation.

Testosterone does enhance beneficial physiological processes such as maintenance of muscle mass and reduction in accumulation of visceral fat (36). Thus, it is possible that anabolic actions of testosterone within the vasculature could promote maintenance of vascular smooth muscle cells and extracellular matrix, thus countering the aortic medial destruction found in AAA. In addition, increased inflammation associated with lower testosterone levels would also facilitate development of AAA (37). Therefore, the age-related decline in circulating testosterone may promote pathological processes favoring aortic dilatation, which are normally inhibited by testosterone. In some regards AAA may be viewed as an advanced manifestation of normal aging because aortic diameter is known to increase with age and is a marker of all-cause mortality (14, 15).

Lower free or total testosterone levels have been associated with less optimal health outcomes including re-

TABLE 4. Prevalence of AAA in men stratified according to testosterone and LH levels from a single blood sample

Hormone status	Number[a]	Number with AAA	Percent with AAA	*P* value
Normal hormone levels Total testosterone 8 nmol/liter or greater LH 12 IU/liter or less	3210	206	6.4	Reference
Hypogonadotrophic hypogonadism Total testosterone less than 8 nmol/liter LH 12 IU/liter or less	133	20	15.0	<0.001
Leydig cell impairment Total testosterone 8–15 nmol/liter LH greater than 12 IU/liter	125	15	12.0	0.014
Hypergonadotrophic hypogonadism Total testosterone less than 8 nmol/liter LH greater than 12 IU/liter	55	11	20.0	<0.001

Proportions of men with AAA in each category of hypogonadotrophic hypogonadism, Leydig cell impairment, and hypergonadotrophic hypogonadism were compared with the reference group of men with normal hormone status using Pearson's χ^2 test.

[a] Total number of men is 3523 because 97 men with total testosterone greater than 15 nmol/liter and LH greater than 12 IU/liter were not included in this classification.

duced cognitive performance, diminished muscle mass, visceral adiposity, and osteoporosis and increased mortality from cardiovascular and other causes (for reviews see Refs. 3 and 4). Free testosterone declines more rapidly than total testosterone as men grow older, partly due to the age-related rise in SHBG levels (1, 2, 24). However, whether one is a more informative marker of androgen status over the other remains unclear. The free hormone hypothesis maintains that dissociation of testosterone from SHBG and weaker affinity binding to albumin in the circulation provides the free hormone, which enters cells and activates the androgen receptor. This concept has been debated with the identification of a putative cell surface receptor for SHBG, megalin, which could possibly bind and facilitate internalization of SHBG to provide an avenue for SHBG to modulate intracellular availability of testosterone (for discussion, see Refs. 38 and 39). In multivariate analysis including adjustment for age and other covariates, we found that lower serum free testosterone level and higher LH level were independently associated with presence of AAA, whereas total testosterone and SHBG were not. These observations support retention of calculated free testosterone as an informative hormonal parameter for studies of male aging. However, further studies are needed to clarify its role in the diagnosis of androgen deficiency in aging men as an adjunct to measurement of total testosterone.

Strengths of this study include the large sample size, direct assessment of aortic diameter using ultrasound, and early morning blood sampling to minimize possible confounding from circadian variation in hormone concentrations. Furthermore, we evaluated possible confounders including age, measures of body composition, hypertension, diabetes, smoking, dyslipidemia, and CHD in the multivariate analyses. We acknowledge several limitations of this study. Blood testing was performed 4–5 yr after aortic diameter measurement; however, the incidence of new AAA is very low (~0.4% pa) (40) and the small number of interval cases of AAA are unlikely to have influenced the results. We did not have the opportunity to undertake serial assessments of aortic diameter or collect multiple blood samples for analysis; this limits our ability to assess direction of causality. Also, we did not measure other hormones such as estradiol. Furthermore, total testosterone was measured by immunoassay and free testosterone calculated using mass action equations. Different testosterone immunoassays may give varying results, and calculated free testosterone may not provide a precise estimate of free testosterone measured by equilibrium dialysis. However, these methods are frequently used in large-scale studies in which assay of total testosterone by mass spectrometry and free testosterone via equilibrium dialysis might be impractical.

We stratified men according to whether they would meet criteria for hypogonadotrophic hypogonadism, Leydig cell impairment, or primary gonadal failure, albeit based on the single blood sample (26). Men with both low total testosterone and elevated LH had an approximately 3-fold greater risk of having AAA than other men. All the other categories of men classified as having abnormal hormone levels had an approximately 2-fold greater risk of having AAA compared with other men. Therefore, the association between AAA and abnormalities of pituitary-gonadal axis function are not limited to men with evidence of testicular failure but involve men more generally who had lower testosterone without elevated LH and also men with low-normal testosterone levels and raised LH.

In summary, our findings from this cross-sectional study are consistent with the hypothesis that reduced circulating androgens are independently associated with ar-

terial disease during male aging. This is in keeping with previous cross-sectional studies linking lower testosterone levels and coronary artery disease (41). Prospective studies are needed to determine whether preserving circulating testosterone in older men might reduce their burden of ill health. At present, only men who meet accepted criteria for the diagnosis of androgen deficiency, encompassing symptoms suggestive of hypogonadism and confirmed low early morning serum testosterone should be offered testosterone therapy (42). Additional studies are needed to clarify the relationship between lower testosterone level and AAA, particularly to evaluate the direction of causality. Finally, consideration could be given to the feasibility of incorporating aortic diameter as an end point in prospective trials of interventions that improve circulating testosterone levels.

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