Study of the relation between serum testosterone level and carotid atherosclerosis in elderly men

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Objective

The aim of the present study was to evaluate the relationship between serum testosterone concentration and carotid atherosclerosis in elderly men.

Participants and methods

The current study included 40 participants who were classified into two groups; the first group comprised 30 elderly healthy men (the case group) and the second group comprised 10 young males (the control group). Serum level of total testosterone was measured using a commercial immunoassay kit cobas testosterone II; sex hormone binding globulin (SHBG) was measured using a commercial immunoassay kit cobas. SHBG and free androgen index (FAI) were calculated by dividing the total testosterone value by SHBG value and then multiplying it by 100 [total testosterone (nmol/l)/SHBG (nmol/l)×100%]. Ultrasonographic measurement of carotid intima–media thickness (IMT) was also carried out.

Results

Total testosterone level was significantly lower in the case group than in the control group ($t = 5.354$, $P < 0.001$). SHBG was significantly higher in the case group than in the control group ($t = 4.796$, $P < 0.001$). FAI was significantly lower in the case group than in the control group ($z = 4.686$, $P < 0.001$). IMT was significantly higher in the case group than in the control group ($t = 3.513$, $P = 0.001$). As regards the number of plaques, 10 men participants (33.3%) from the case group did not have any plaques, 13 (43.3%) had one plaque, and seven (23.3%) had two plaques; however, in the control group, nine participants (90%) did not have any plaques and only one (10%) had one plaque; therefore, the case group had significantly higher number of plaques than did the control group ($z = 3.007$, $P = 0.003$). There was a significant negative correlation between total testosterone and SHBG ($R = –0.856$, $P < 0.001$), a significant positive correlation between total testosterone and FAI ($R = 0.957$, $P < 0.001$), and a significant negative correlation between testosterone and both IMT ($R = –0.501$, $P = 0.005$) and number of plaques ($R = –0.358$, $P = 0.52$). SHBG was negatively correlated with FAI ($R = –0.845$, $P < 0.001$) but positively correlated with both IMT ($R = 0.392$, $P = 0353$) and the number of plaques ($R = 0.032$, $P = 0.056$). There were significant negative correlations between FAI and both IMT ($R = –0.601$, $P < 0.001$) and the number of plaques ($R = –0.461$, $P = 0.010$). IMT was positively correlated with the number of plaques ($R = 0.760$, $P < 0.001$).

Conclusion

These findings suggest that normal physiologic testosterone levels may help to protect men from atherosclerosis. In elderly men, low plasma testosterone is associated with elevated carotid IMT. A negative correlation has been demonstrated between endogenous testosterone levels and IMT of the carotid arteries. These findings suggest that men with lower levels of endogenous testosterone may be at a higher risk for developing atherosclerosis.

Keywords:
atherosclerosis, carotid artery, free androgen index, sex hormone binding globulin, total testosterone

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Introduction

Among men, testosterone secretion from the Leydig cells in the testes has a central role in developing secondary sexual characteristics, supporting spermatogenesis, and regulating libido [1]. Synthesis and secretion are under the stimulation of the gonadotropin luteinizing hormone from the anterior pituitary gland and only 1–2% of circulating testosterone is not bound to protein. This fraction is termed free testosterone. Approximately 40–50% of circulating testosterone are weakly bound to albumin. The free and albumin-bound testosterone is referred to as bioavailable. The remaining testosterone in circulation is strongly bound to sex hormone binding globulin (SHBG). The amount of SHBG in circulation,

therefore, influences the amount of bioavailable testosterone. SHBG can be altered by factors such as age, hepatic cirrhosis and hepatitis, hyperthyroidism, obesity, and the use of anticonvulsants. Total testosterone refers to circulating, bioavailable, and SHBG-bound testosterone [2].

Whether healthy adult men maintain serum testosterone concentrations throughout life, and the implications of a postulated decline and thus its potential for therapy, have been widely debated but remain unclear [3,4]. In contrast to the dramatic fall in estrogen levels at the time of menopause in women, testosterone concentrations in men decline gradually with age. Many adverse aspects of male aging have been attributed to the decrease in endogenous testosterone, stimulating a surge of interest in testosterone therapy for middle-aged and older men. However, solid evidence linking testosterone insufficiency to health-related outcomes in older men is just beginning to emerge, and even less information is available on testosterone and mortality. A number of studies have reported decreasing testosterone levels in men with age. These studies reported low levels (<11.3 nmol/l) of total testosterone in up to 20% of men over 60, 30% over 70, and 50% over 80 years of age, and suggested that further investigation of testosterone replacement in aged men, perhaps targeted at those with the lowest serum testosterone concentrations, was justified [5]. Massachusetts Male Aging Study also showed a decrease in total testosterone with increasing age [6], particularly when accompanied by increasing obesity, which is often accompanied by undesirable signs and symptoms such as low bone and muscle mass; increased fat mass (especially central adiposity); low energy; and impaired physical, sexual, and cognitive functions. These complaints have clinical consequences, and are supported by prospective cohort studies showing that men with low testosterone are at an increased risk for falls [7]; hip fracture (if estradiol is also low) [8]; anemia [9]; type 2 diabetes [10]; depressive illness [11]; and, in some studies, Alzheimer's disease [12,13]. The decline in both serum and total testosterone with age have been linked to several disease states in men [14,15]. In particular, cardiac failure and ischemic heart disease have been linked to this natural biochemical decline in testosterone [16,17]. Previously, the higher cardiovascular risk in men had been attributed in part to the negative effects of systemic testosterone; however, more recent research has highlighted the protective nature of testosterone against cardiovascular disease [18]. The magnitude and mechanism of action by which low testosterone in men is influential in the pathogenesis of cardiovascular risk and the potential benefits of testosterone therapy are yet to be fully determined.

Low testosterone is associated with an increased risk for coronary artery disease through the promotion of a proatherosclerotic environment [19]. Some studies have identified testosterone as a vasodilator and an endothelium-repairing hormone within many regions in the body, including the coronary arteries [20,21]. Recent studies depict testosterone as important in decreasing the production of inflammatory cytokines such as tumor-necrosis factor-α, interleukin-1β, and interleukin-6, which are influential in atherosclerotic profiles [22]. Although it is believed that the reduction in inflammatory cytokines is related to a decreased atherosclerotic profile, the full explanation of this mechanism requires further research [23].

Testosterone has also been shown to be effective as an antiatherosclerotic through preventing aortic cholesterol deposition in both rabbits fed with high cholesterol diets and mice with low-density lipoprotein gene knockout. Fatty deposition within the aorta associated with low endogenous testosterone has been determined to be independent of the androgen receptor. Although the mechanism is yet to be fully determined, aromatase activity and the activation of estrogen receptor-α is partially responsible for the atherosclerotic profile characteristic of low testosterone [24].

To our knowledge, the relationship between serum testosterone concentration and carotid atherosclerosis, determined by ultrasonographically evaluated intima–media thickness (IMT) and plaque score, has been explored in very few studies conducted on healthy elderly men. The aim of the current study was to evaluate the relationship between serum testosterone concentration and carotid atherosclerosis in healthy elderly men.

Participants and methods

The current study included 40 participants who were classified into two groups; the first group comprised 30 elderly healthy men (the case group) and the second group comprised 10 young males (the control group). This study was conducted in the Department of Internal Medicine, Alexandria University Hospital, Egypt; after being approved by the local Research Ethics Committee, and informed consent was obtained from all participants. The exclusion criteria included patients with diabetes mellitus; thyroid diseases; dyslipidemia; patients on drugs such as ketoconazole, cimetidine, spironolactone, chemotherapy, and statins; and drugs that are used to treat enlarged prostate; certain antidepressants such as selective serotonin reuptake inhibitors, and tricyclic antidepressant. All participants

were subjected to thorough history-taking and clinical examination. Laboratory investigations were carried out for all participants, which included the following: complete blood picture, fasting and postprandial blood sugar, lipid profile tests, renal function tests, liver function tests, and specific tests [measuring serum level of total testosterone, SHBG, and free androgen index (FAI)]. Ultrasonographic measurement of carotid IMT was carried out. Serum level of total testosterone was measured using a commercial immunoassay kit cobas testosterone II. Blood samples were collected from all participants, and then 20 μl of samples were incubated with biotinylated monoclonal testosterone-specific antibody. The binding site of the labeled antibody became occupied by the sample analyte (depending on its concentration). The second incubation after the addition of streptavidin-coated microparticles and a testosterone-derivated labeled with ruthenium complex became bound to the solid phase through interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Unbound substances were then removed with ProCell/ProCellM. Application of a voltage to the electrode then induced chemiluminescent emission, which was measured by a photomultiplier. Results were determined using a calibration curve, which was generated instrument specifically by using a two-point calibration and a master curve, provided via the reagent par code [25].

SHBG was measured using a commercial immunoassay kit cobas SHBG. First incubation of 10 μl of sample biotinylated monoclonal SHBG-specific antibody and monoclonal SHBG-specific antibody labeled with a ruthenium complex formed a sandwich complex. Then, second incubation after the addition of streptavidin-coated microparticles resulted in the complex becoming bound to the solid phase through an interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Unbound substances were then removed with ProCell/ProCellM. Application of a voltage to the electrode then induced chemiluminescent emission, which was measured by using a photomultiplier. Results were determined using a calibration curve, which was generated instrument specifically by using a two-point calibration and a master curve provided through the reagent par code [26].

FAI was calculated by dividing the total testosterone value by SHBG value and then multiplying it by 100 [total testosterone (nmol/l)/SHBG (nmol/l) ×100%] [27].

Carotid Doppler B mode ultrasonography was carried out for all participants using an Acuson Sequoia 512 at Diagnostic Radiology Department, Faculty of Medicine, Alexandria University. IMT of common carotid artery, carotid bulb, and internal carotid arteries were assessed. IMT was defined as the distance between the lumen–intima interface and the media–adventitia interface [28]. Common carotid artery IMT is defined as the mean of the maximum IMT in both right and left sides of common carotid artery. The plaque of carotid artery (common carotid artery, carotid bulb, and internal carotid artery) is defined as a localized protrusion of the internal part of the vessel wall into the lumen of 50% of the surrounding IMT value. Plaque presence was defined as greater than or equal to 1 plaque in any of the carotid arteries [29].

Statistical analysis

Data were fed to the computer and analyzed using the IBM SPSS software package version 20.0 (Alexandria, Egypt). Qualitative data were described as number and percent. Quantitative data were described as range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at 5% level.

Following tests were used in the present study:

(1) The χ^2-test:
It was used for categorical variables to compare between different groups.
(2) Monte–Carlo correction:
It was used for the correction for χ^2 when more than 20% of the cells had an expected count less than 5.
(3) Student *t*-test:
For normally quantitative variables, the Student *t*-test was used to compare between two studied groups.
(4) Pearson coefficient:
This test was used to correlate between two normally quantitative variables.
(5) Mann–Whitney test:
For abnormally quantitative variables, the Mann–Whitney test was used to compare between two studied groups.

Results

A total of 40 males participated in the current study and were divided into two groups; the first group comprised 30 elderly healthy men (the case group) and 10 young males (the control group). The age of the participants in the case group was 66–81 years,

with a mean of 71.30 ± 3.88 years. The age of the participants in the control group was 28–41 years, with a mean of 35.0 ± 4.24 years. Age of the case group was statistically higher than that of the control group (t = 25.054, P < 0.001). Fasting blood sugar was 76–104 mg/dl with a mean of 87.37 ± 6.86 for the participants of the case group but in controls fasting blood sugar was 76–90 mg/dl with a mean of 82.60 ± 5.06, with no significant difference between the two groups (t = 2.012, P = 0.051). Postprandial blood sugar in the case group was 125–150 mg/dl with a mean of 136.47 ± 6.30, but in the control group it was 131–145 mg/dl, with a mean of 137.70 ± 4.67. There was no significant difference between the two groups (t = 0.567, P = 0.574). Table 1 shows the comparison between the two studied groups according to lipid profile and kidney functions. There was no significant statistical difference between the two groups as regards serum triglyceride level (t = 0.095, P = 0.925) but cholesterol was significantly higher in the case group than in the control group (t = 11.424, P < 0.001). Blood urea was significantly higher in the case group (t = 3.285, P = 0.006) and serum creatinine also was significantly higher in the case group (t = 2.900, P = 0.006). Serum glutamic pyrovic transaminase (SGPT) level in the case group was 21–34 U/l with a mean of 26.63 ± 3.32, but in the control group it was 24–30 U/l with a mean of 26.8 ± 2.25, with no significant difference between the two groups (t = 1.032, P = 0.309). Serum glutamic oxalacitic transaminase (SGOT) level was 20–30 U/l with a mean of 25.97 ± 2.71 in the case group, but in the control group it was 21–29 U/l with a mean of 24.9 ± 2.85, with no significant difference between the two groups (t = 1.065, P = 0.294). Table 2 shows the

Table 1 Comparison between the two studied groups according to lipid profile and kidney function

Items	Cases (n = 30)	Control (n = 10)	t	P
TG (mg/dl)				
Minimum–maximum	103.0–145.0	99.0–142.0	0.095	0.925
Mean ± SD	123.13 ± 12.14	122.70 ± 13.56		
Median	121.50	123.50		
Cholesterol (mg/dl)				
Minimum–maximum	163.0–193.0	122.0–156.0	11.424*	<0.001*
Mean ± SD	179.40 ± 8.48	140.60 ± 11.56		
Median	182.0	139.50		
Urea (mg/dl)				
Minimum–maximum	20.0–35.0	22.0–28.0	3.285*	0.002*
Mean ± SD	28.87 ± 3.28	25.20 ± 2.20		
Median	29.0	25.0		
Creatinine (mg/dl)				
Minimum–maximum	0.80–1.20	0.70–1.10	2.900*	0.006*
Mean ± SD	1.02 ± 0.11	0.90 ± 0.12		
Median	1.0	0.90		

t, Student's t-test; TG, triglyceride; *Statistically significant at $P \leq 0.05$.

Table 2 Comparison between the two studied groups according to different parameters

Items	Cases (n = 30)	Control (n = 10)	Test of significance	P
Total testosterone (nmol/l)				
Minimum–maximum	3.50–11.60	8.50–32.80	t = 5.354*	<0.001*
Mean ± SD	6.94 ± 1.84	20.89 ± 8.17		
Median	6.95	21.15		
SHBG (nmol/l)				
Minimum–maximum	38.0–97.0	23.50–56.80	t = 4.796*	<0.001*
Mean ± SD	64.0 ± 15.08	38.91 ± 11.58		
Median	62.0	36.55		
FAI (%)				
Minimum–maximum	4.02–30.50	34.40–65.90	Z = 4.686*	<0.001*
Mean ± SD	11.87 ± 6.17	52.57 ± 11.53		
Median	11.18	57.35		
IMT (mm)				
Minimum–maximum	0.70–1.08	0.71–1.0	t = 3.513*	0.001*
Mean ± SD	0.96 ± 0.13	0.80 ± 0.10		
Median	1.02	0.78		

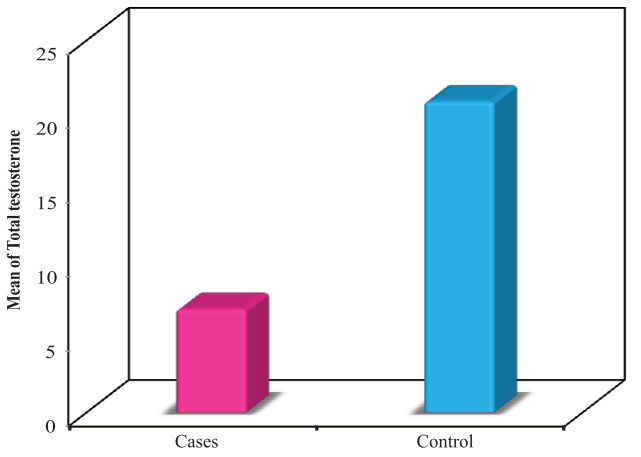
FAI, free androgen index; IMT, intima–media thickness; SHBG, sex hormone binding globulin; t, Student's t-test; Z, Z for Mann–Whitney test; *Statistically significant at $P \leq 0.05$.

comparison between the two studied groups according to different parameters; total testosterone level was significantly lower in the case group than in the control group ($t = 5.354$, $P < 0.001$), as shown in Fig. 1. SHBG was significantly higher in the case group than in the control group ($t = 4.796$, $P < 0.001$), as shown in Fig. 2. FAI was significantly lower in the case group than in the control group ($z = 4.686$, $P < 0.001$). IMT was significantly higher in the case group than in the control group ($t = 3.513$, $P = 0.001$), as shown in Fig. 3. Table 3 shows the comparison between the two studied groups according to the number of plaques; 10 males (33.3%) from the case group did not have any plaques, 13 (43.3%) had one plaque, and seven (23.3%) had two plaques; however, in the control group, nine participants (90%) did not have any plaques and only one (10%) had one plaque; therefore, the case group had a significantly higher number of plaques than did the control group ($z = 3.007$, $P = 0.003$). Table 4 shows a significant negative correlation between total testosterone and SHBG ($R = -0.856$, $P < 0.001$), a significant positive correlation between total testosterone and FAI ($R = 0.957$, $P < 0.001$), and a significant negative correlation between testosterone and both IMT ($R = -0.501$, $P = 0.005$) and the number of plaques ($R = -0.358$, $P = 0.52$), as shown in Fig. 4. SHBG was negatively correlated with FAI ($R = -0.845$, $P < 0.001$) but it was positively correlated with both IMT ($R = 0.392$, $P = 0353$) and the number of plaques ($R = 0.032$, $P = 0.056$). There was a significant negative correlation between FAI and both IMT ($R = -0.601$, $P < 0.001$) and the number of plaques ($R = -0.461$, $P = 0.010$). IMT was positively correlated with the number of plaques ($R = 0.760$, $P < 0.001$).

Discussion

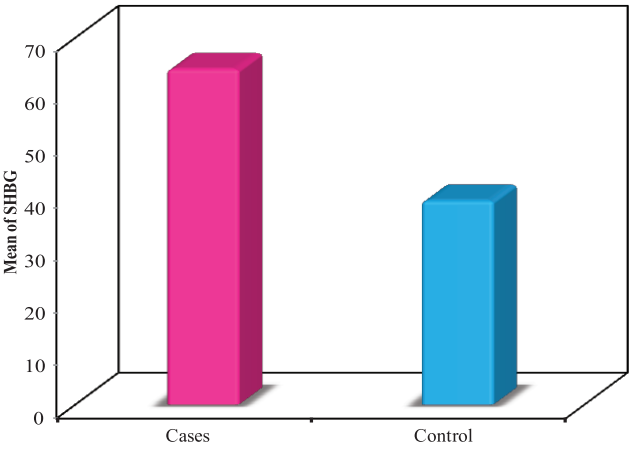
The current study was carried out on 30 healthy elderly men with a mean age of 71.30 ± 3.88 years (the case group) and 10 young males with a mean age of 35.0 ± 4.24 years (the control group). There was no significant difference between the studied groups as regards blood sugar level ($t = 2.012$, $P = 0.051$) or triglyceride level, but cholesterol level, blood urea, and serum creatinine were significantly higher in the case group than in the control group; however, they were within the normal range. Total testosterone level was significantly lower in the case group than in the control group ($t = 5.354$, $P < 0.001$), whereas SHBG was significantly higher in the case group than in the control group ($t = 4.796$, $P < 0.001$). This was in agreement with the findings of a study conducted by Haddad *et al.* (2007) [30], who stated that total testosterone level decreased with advancing age, and also with the study by Travison *et al.* [31], who observed a cross-sectional testosterone decline of 0.4%

Figure 1



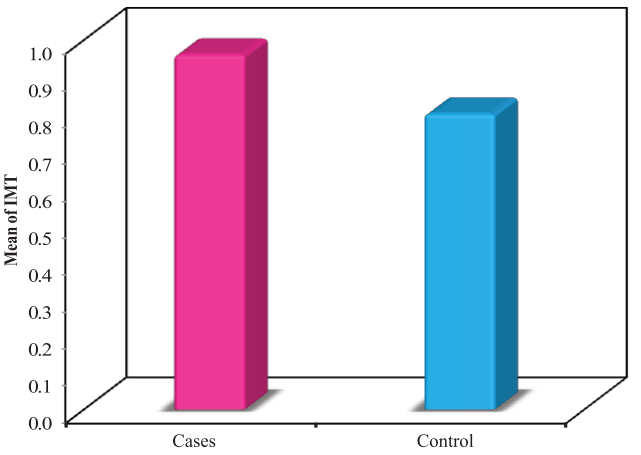
Comparison between the two studied groups according to total testosterone.

Figure 2



Comparison between the two studied groups according to sex hormone binding globulin (SHBG).

Figure 3



Comparison between the two studied groups according to intima–media thickness (IMT).

Table 3 Comparison between the two studied groups according to the number of plaques

Items	Cases (n = 30) [n (%)]	Control (n = 10) [n (%)]	Test of significance	P
Number of plaques				
0	10 (33.3)	9 (90.0)	χ^2 = 8.802*	^{MC}P = 0.007*
1	13 (43.3)	1 (10.0)		
2	7 (23.3)	0 (0.0)		
Minimum–maximum	0.0–2.0	0.0–1.0	Z = 3.007*	0.003*
Mean ± SD	0.90 ± 0.76	0.10 ± 0.32		
Median	1.0	0.0		

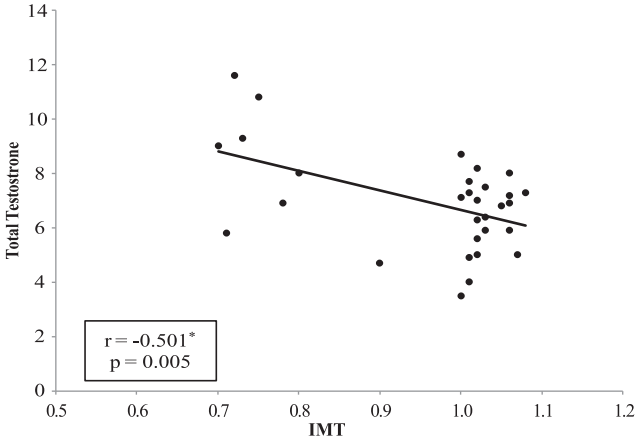
χ^2, χ^2–test; MC, Monte–Carlo; Z, Z for Mann–Whitney test; *Statistically significant at $P \leq 0.05$.

Table 4 Correlation between different studied parameters in the case group

Items	Total testosterone	SHBG	FAI	IMT	Number of plaques
Total testosterone					
R	1.000	−0.856*	0.957*	−0.501*	−0.358
P		<0.001	<0.001	0.005	0.052
SHBG					
R		1.000	−0.845*	0.392*	0.353
P			<0.001	0.032	0.056
FAI					
R			1.000	−0.601*	−0.461*
P				<0.001	0.010
IMT					
R				1.000	0.760*
P					<0.001
Number of plaques					
r					1.000

FAI, free androgen index; IMT, intima–media thickness; *r*, Pearson coefficient; SHBG, sex hormone binding globulin; *Statistically significant at $P \leq 0.05$.

Figure 4



Correlation between intima–media thickness (IMT) with total testosterone in cases group.

per year from 45 years onwards in 2194 men. In addition, studies conducted by Muller *et al.* [32], Mohr *et al.* [33], and Simon *et al.* [34] all reported a small annual decline of 0.4, 0.3, and 0.5%, respectively (n = 400, 1677, 1408, respectively), and showed no increase in variance. But these results were in contrast to the results found in a study by Yeap *et al.* [35], who stated that total testosterone did not decline with advancing age in older men (aged 70–89). Whereas a study by Halmenschlager *et al.* [36] reported both no decline in total testosterone with advancing years and an increase in variance later in life. Studies by Frost *et al.* [37], Boyce *et al.* [38], and Orwoll *et al.* [39] (n = 783, 266 and 2623, respectively) all reported no decline in serum total testosterone with advancing age and no increase in variance. In their study, Rhoden *et al.* [40] not only reported that serum total testosterone falls with advancing age, but also that there is an increase in variance across the lifespan from age 40 onwards. In the current study, FAI (total testosterone/SHBG ×100%) was significantly lower in the case group than in the control group. These findings are in agreement with those of a study by Rosano *et al.* (2007) [41], who found reduction in FAI in elderly men.

FAI was initially proposed as a measure for assessing the circulating testosterone availability in female hirsutism. The extension of its use, by a number of investigators, on males has not been formally justified. An analysis of its derivation from the Law of Mass Action reveals an implied assumption that the binding capacity of SHBG should greatly exceed the concentration of its ligand testosterone. This does not hold true in adult males, for whom the use of FAI is, therefore, inappropriate. A comparison of FAI and free-testosterone (determined by centrifugal ultrafiltration) yielded a correlation coefficient (r) of 0.858 for 20 adult females but only 0.435 for 19 adult males [42]. SHBG was negatively correlated with FAI (R = −0.845, P<0.001) but positively correlated with both IMT (R = 0.392, P = 0353) and the number of plaques (R = 0.032, P = 0.056). There were significant negative correlations between FAI and both IMT (R = −0.601, P<0.001) and the number of plaques (R = −0.461, P = 0.010). IMT was positively correlated with the number of plaques (R = 0.760, P < 0.001). IMT was higher in the case group than in the control group in this study (t = 3.513, P = 0.001), and as regards the number of plaques, 10 elderly men did not have any plaques, 13 had only one plaque, and seven had two plaques; however, in the control group only one participant (10%) had one plaque and nine

(90%) did not have any plaques. In the current study, there were significant negative correlations between testosterone and both IMT ($R = -0.501$, $P = 0.005$) and the number of plaques ($R = -0.358$, $P = 0.52$). These findings were similar to those of studies by Van den Beld *et al.* (2003) [43], De Pergola *et al.* (2003) [44], and Svartberg *et al.* (2006) [45].

IMT of the carotid artery is considered a marker for preclinical atherosclerosis [46]. Increasing carotid IMT has been associated with generalized atherosclerosis[47], increased incidence of myocardial infarction [48], and stroke [49], and is generally considered a poor prognostic factor for future adverse cardiovascular events. Although some researchers have focused on the association between testosterone levels and IMT of the carotid artery, others have evaluated the association between endogenous testosterone levels and IMT of the aorta. In a large population-based study of 504 nonsmoking men and 528 nonsmoking women (the Rotterdam study), Hak *et al.* [50] demonstrated an inverse correlation between endogenous testosterone levels and atherosclerosis of the abdominal aorta in men. In their study, Hak and colleagues reported decreasing relative risk for severe atherosclerosis of the abdominal aorta with increasing levels of endogenous total testosterone as well as increasing levels of endogenous bioavailable testosterone after adjustment for cardiovascular disease risk factors in men only. No significant association was found between testosterone levels and the presence of severe abdominal aortic atherosclerosis in women in a study by Hak and colleagues. These authors also discovered that men with higher levels of total or bioavailable testosterone experienced a significantly slower rate of progression of abdominal aortic atherosclerosis. In their study, Demirbag *et al.* [51] carried out a similar analysis on 42 men, but instead investigated the association between testosterone and thoracic aorta IMT, discovering an inverse association between total testosterone and thoracic aorta IMT.

It is not clear whether the inverse correlation between endogenous testosterone levels and IMT is cause or effect. Reduced levels of testosterone might cause increased thickness of the intima–media of the vasculature. On the other hand, it can be argued that widespread atherosclerosis may impair adequate blood flow to the testes or to the pituitary gland, which would in turn result in decreased production of testosterone and luteinizing hormone, respectively. In their study, Van den Beld and colleagues have shed some light on this question. They demonstrated that the association between testosterone levels and IMT was independent of cardiovascular disease. Moreover, Van den Beld *et al.* [43] demonstrated that the inverse correlation between endogenous testosterone levels and carotid IMT had similar statistical robustness in patients with and without cardiovascular disease. This finding may suggest that low levels of endogenous testosterone cause increased IMT. However, further follow-up studies are required to confirm these earlier results. Furthermore, the exact mechanism by which testosterone may cause increased IMT of the carotid artery or the aorta is currently unknown. Testosterone may cause decreased IMT by downregulating the inflammatory response, regulating apoptosis, or enhancing vascular smooth muscle cell stability.

Although more research is required, existing data suggest that testosterone deficiency may play some role in the creation and progression of atherosclerosis. Studies have shown that the levels of endogenous testosterone are inversely associated with IMT of the carotid artery [44], as well as both the thoracic and the abdominal aorta. In addition, one study has demonstrated that lower levels of free testosterone are associated with accelerated progression of carotid artery IMT [52], whereas another study has reported that decreased levels of total and bioavailable testosterone are associated with the progression of atherosclerosis in the abdominal aorta [50]. Testosterone treatment of male animals has led to a decrease in atherosclerotic lesion size or the atherosclerosis-related end point studied (e.g. aortic cholesterol content), as in the studies done by Bruck *et al.* (1997) [53] and Nathan *et al.* (2001) [54]. Testosterone has been shown to promote and suppress the proatherogenic and proinflammatory effects on all cell types involved in atherogenesis. It suppresses vascular cell adhesion molecule-1 expression in human endothelial cells through an aromatase/estrogen receptor-dependent mechanism [Hatakeyama *et al.* (2002) [55,56]]. In addition, testosterone has been shown to enhance reverse cholesterol transport [57].

Conclusion

The findings of the present study suggest that normal physiologic testosterone levels may help in protecting men from the development of atherosclerosis. In elderly men, low plasma testosterone is associated with elevated carotid IMT. A negative correlation has been demonstrated between endogenous testosterone levels and IMT of the carotid arteries. These findings suggest that men with lower levels of endogenous testosterone may be at a higher risk for developing atherosclerosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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