Study of the relation between the serum level of male sex hormone and peripheral vascular disease in elderly men

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Introduction
Testosterone hormone decreases consistently with advancing age. Many studies have shown a possible relationship between decreasing level of testosterone and atherosclerosis.
Objective
The objective of our study was to demonstrate the relationship between male sex hormone [testosterone and sex hormone-binding globulin (SHBG)] concentration and peripheral vascular disease in elderly men.
Background
Few studies have explored the relationship between serum sex hormones and lower-extremity peripheral arterial disease (PAD) in men.
Patients and methods
Our study was conducted on 20 elderly men older than 65 years with peripheral vascular disease and 10 healthy age-matched men as controls. Lower-extremity PAD was defined as ankle brachial index less than 0.90 and diagnosis was confirmed with Doppler ultrasound. Radioimmunoassay measured serum levels of total testosterone and SHBG, and we calculated free androgen index level from the mass action equations.
Results
The results show that serum level of total testosterone, SHBG, and free androgen index were lower in men with peripheral vascular disease than in those without. There is a positive correlation between total testosterone, SHBG, free androgen index, and ankle brachial index.
Conclusion
Low serum level of total testosterone, SHBG, and free androgen index are significantly and independently associated with the presence of PAD in elderly men.

Keywords:
older men, peripheral arterial disease, sex hormone-binding globulin, testosterone

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Introduction

Lower-extremity peripheral arterial disease (PAD) is a highly prevalent condition in the elderly [1]. The presence of PAD is also widely accepted as an indicator of generalized atherosclerosis and is a potential determinant of cardiovascular mortality and morbidity [2] As an early indicator of PAD, a low ankle brachial index (ABI) has also been associated with increased risk for subsequent cardiovascular disease and mortality [3].

The level of testosterone decreases consistently with advancing age. Many studies have shown a possible relationship between decreasing level of testosterone and atherosclerosis [4]. Many mechanisms were postulated, but the definitive mechanisms remain unclear. Several prospective investigations have shown that low total testosterone concentrations in men are associated with obesity [5], incident metabolic syndrome [6], diabetes mellitus [7], and dyslipidemia, [8], which are well-recognized risk factors for coronary and peripheral vascular diseases.

Arterial functions may be directly influenced by testosterone, and, most likely, two independent pathways of testosterone-induced effects within the vessel wall can be assumed (i.e., genomic and nongenomic) [9].

Aim of the work

The aim of the work was to study the relationship between male sex hormone [testosterone and sex hormone-binding globulin (SHBG)] and peripheral vascular disease in elderly men.

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Patients and methods

The present study was conducted on 30 elderly men above 65 years who were divided into two groups: group I, comprising 20 men older than 65 years and suffering from peripheral vascular disease, and group II, comprising 10 healthy elderly men older than 65 years. All individuals, both patients and controls, included in this study were recruited after obtaining informed consent for thorough and full history taking, complete physical examination, ECG examination, and routine laboratory investigations including complete blood picture, fasting and postprandial blood glucose, and renal function tests. The ABI was measured, and vascular studies using ultrasonographic duplex Doppler examination of peripheral arteries were conducted. Peripheral blood was collected, the samples were centrifuged, and serum separated. Serum level of total testosterone and SHBG was measured by means of electrochemiluminescence immunoassay, and free androgen index was calculated. The normal level of total testosterone ranged from 1.93 to 7.40 ng/ml, that of SHBG ranged from 20.6 to 76.7 nmol/l, and free androgen index (FAI) ranged from 24.3 to 72.1.

Ethical approval

The protocol was approved by the ethical committee of the Faculty of Medicine.

Statistical analysis of data

Data were fed into a computer and analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). Qualitative data were described as number and percentage, and quantitative data were described using range (minimum and maximum), mean, SD, and median. Significance of the obtained results was judged at the 5% level. The following tests were conducted:

(1) The χ^2-test: This test was used to compare categorical variables between different groups
(2) Fisher's exact test: This test was used to determine the correction for χ^2 when more than 20% of the cells had expected counts less than 5
(3) The Student *t*-test: This test was conducted to compare normally quantitative variables between two groups
(4) Paired *t*-test: This was used to compare normally quantitative variables between two periods
(5) *Z* for Mann–Whitney test: This test was used to compare abnormally quantitative variables between two groups.

Results

The mean total testosterone level in group I was 3.51 ± 1.76 ng/ml (range 0.36–7.51 ng/ml), and the mean total testosterone level in group II was 8.17 ± 2.17 ng/ml (range 4.46–10.77 ng/ml). There was a statistically significant difference between groups I and II regarding total testosterone (P > 0.001) (Table 1).

The mean SHBG in group I was 53.95 ± 20.41 nmol/l (range 28.31–97.55 nmol/l), and the mean SHBG in group II was 85.86 ± 37.41 (range 45.82–164.50 nmol/l). There was a statistically significant difference between groups I and II regarding SHBG (P = 0.027).

The mean free androgen index of patients in group I was 22.94 ± 9.37% (range 2.60–47.20%), and the mean FAI in group II was 35.26 ± 8.54% (range 22.70–55.50%). There was a statistically significant difference between groups I and II as regards FAI (P = 0.002) (Table 2).

ABI was positively correlated with serum total testosterone, FAI, and SHBG in all cases (Table 3).

Discussion

The present study was performed on 30 men, who were classified into two groups: group I included 20 elderly men older than 65 years with peripheral vascular disease, and group II included 10 healthy elderly men older than 65 years who were considered as controls.

The results showed that there was a significant difference regarding serum total testosterone and free androgen

Table 1 Comparison between the two groups on the basis of total testosterone and sex hormone-binding globulin

	Group I (cases) (*n*=20)	Group II (control) (*n*=10)	*t*-test	*P*
Total testosterone (ng/ml)				
Minimum-maximum	0.36-7.51	4.46-10.77	6.314*	<0.001*
Mean±SD	3.51±1.76	8.17±2.17		
Median	3.41	8.83		
Sex hormone-binding globulin (nmol/l)				
Minimum-maximum	28.31-97.55	45.82-164.50	2.517*	0.027*
Mean±SD	53.95±20.41	85.86±37.41		
Median	52.18	73.76		

t, Student's *t*-test. *Statistically significant at $P \leq 0.05$. SD, standard deviation.

Table 2 Comparison between the two groups on the basis of free androgen index

	Group I (cases) (*n*=20)	Group II (control) (*n*=10)	*t*-test	*P*
Free androgen index (%)				
Minimum-maximum	2.60-47.20	22.70-55.50	3.492*	0.002*
Mean±SD	22.94±9.37	35.26±8.54		
Median	21.80	33.75		

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

Table 3 Correlation between ankle brachial index and different parameters in each group

	Ankle brachial index			
	Right LL		Left LL	
	R	*P*	*R*	*P*
Total cases				
Total testosterone (ng/ml)	0.716*	<0.001*	0.708*	<0.001*
Sex hormone-binding globulin (nmol/l)	0.475*	0.008*	0.431*	0.017*
Free androgen index (%)	0.504*	0.005*	0.533*	0.002*

r, Pearson's coefficient. *Statistically significant at $P \leq 0.05$.

index among the two groups, with both parameters being significantly lower in group I compared with group II. This agrees with the observations of Tivesten *et al.* [10], who showed for the first time that low serum testosterone was associated with lower-extremity PAD in elderly men. Yeap *et al.* [11] found in a cross-sectional study in men aged 70–89 years that lower T or dihydrotestosterone (DHT) levels, but not E2, are associated with symptoms of intermittent claudication in older men. Price *et al.* [12] in a small nested case–control study investigated the influence of sex hormones on PAD in men and found no significant difference in mean levels of total and free testosterone between cases and controls.

In the present study there was a significant difference regarding the level of SHBG among the two groups, where serum SHBG was significantly lower in group I compared with group II. This agrees with the results of Maggio *et al.* [13] who found that men with PAD had SHBG levels lower than do men without PAD.

Price *et al.* [12] found that the mean level of SHBG was not significantly different in cases compared with controls in either sex ($P > 0.1$).

In the present study we found a significant positive correlation between serum total testosterone in the two studied groups as a whole, on the one hand, and ABI, on the other. In addition, there was a significant positive correlation between the free androgen index in the two studied groups as a whole, on the one hand, and the ABI, on the other. This comes in agreement with the results of Tivesten *et al.* [10], who, in a cross-sectional study on 3014 elderly men, found that low free T and TT concentrations were associated with low ABI and prevalent PAD (defined as an ABI<0.90).

Cross-sectional and longitudinal associations of circulating sex hormone concentrations with ABI and PAD were ascertained by Haring *et al.* [14] in the community-based Framingham Heart Study. Cross-sectional multivariable analyses revealed that men with lower free T and higher estrone (E1) concentrations had a significantly lower ABI. Lower total T and SHBG concentrations were also associated with prevalent PAD in age-adjusted but not in multivariable logistic regression models. This study differs from the MrOS study conducted by Tivesten *et al.* [10] in Sweden, which showed a significant association between TT and prevalent PAD after multivariable adjustment, suggesting that differences in the adjustment set could have mitigated or abolished significant effects of TT on PAD.

Maggio *et al.* [13] demonstrated in a CHIANTI study that in women, but not in men, T was positively associated with PAD (PAD was defined as an ABI<0.90), even after adjusting for multiple confounders.

In the present study we found a significant positive correlation between SHBG in the two studied groups as a whole, on one hand, and the ABI, on the other hand. This is in agreement with the results of Maggio *et al.* [13], who found that SHBG was negatively and independently associated with PAD in men ($P = 0.028$) but not in women.

Haring *et al.* [14] showed in longitudinal multivariable analyses an association of lower SHBG with ABI change in men.

Yeap *et al.* [11] demonstrated that higher SHBG was also associated with reduced odds ratio (OR) of intermittent claudication; however, when total T and SHBG were included in the same model, the association with total T remained significant but the association with SHBG was attenuated.

Conclusion

Serum total testosterone and free androgen index are lower in elderly men suffering from peripheral vascular disease than in those without, which suggests that it may play a role in the pathogenesis of atherosclerosis. Further, there is a positive correlation between SHBG and ABI where serum level of SHBG is lower in elderly men suffering from peripheral vascular disease.

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Conflicts of interest

There are no conflicts of interest.

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