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ORIGINAL ARTICLE

The relationship between testosterone, metabolic syndrome, and mean carotid intima-media thickness in aging men

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Abstract

We studied relationships between testosterone, metabolic syndrome, and mean carotid intima-media thickness (IMT) in aging men. We enrolled 935 men who had participated in a health examination. The median age was 57.0 years. Mean IMT showed a significant and negative linear correlation with testosterone (correlation co-efficiency = −0.067, $p = 0.039$). There was a significant increase in the percentage of men with hypogonadism in the second and third tertiles of mean IMT (p trend = 0.022). Logistic regression revealed a greater likelihood of hypogonadism in the third tertile mean IMT group when compared to the first tertile mean IMT group after adjusting for age and metabolic syndrome (OR = 1.700, $p = 0.044$). After adjusting for age and testosterone level, mean IMT was significantly higher in metabolic syndrome group as compared to non-metabolic syndrome group (0.733 mm versus 0.764 mm; $p < 0.001$). Mean testosterone level was significantly lower in metabolic syndrome group as compared to non-metabolic syndrome group after adjusting for age and mean IMT (5.52 ng/mL versus 4.89 ng/mL; $p < 0.001$). Mean IMT, testosterone, and metabolic syndrome were significantly and independently correlated with each other in aging male. Further studies are needed to confirm our results and to elucidate their causative relationship.

Keywords

Carotid artery, intima-media thickness, metabolic syndrome, testosterone

History

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Introduction

Testosterone plays an important role in the physiology of various organs and tissues including muscle, skin, bone, liver, and sexual organs [1–3]. Recent clinical studies have indicated that low testosterone levels are positively correlated with the severity of coronary atherosclerosis and stroke in addition to the occurrence of advanced heart failure. However, at present there are scant data available to support this observation [4].

Carotid intima-media thickness (IMT) is a widely used predictor of cerebral vascular and cardiovascular disease [5]. Previous studies have demonstrated that low testosterone is correlated with increased IMT [6–14]. However, most data were obtained from relatively small populations [6–11]. One large-scale study has been performed, but the methodology failed to calculate serum testosterone in the early morning hours, despite the fact that testosterone levels fluctuate according to circadian rhythms [12–14]. Furthermore, when evaluating the relationship between testosterone and IMT, no consideration was given to metabolic syndrome, which is known to be a risk factor for carotid artery disease [6–14]. Therefore, we examined the relationship between testosterone and IMT in a relatively large population, using optimal testosterone sampling coupled with a full metabolic workup.

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Materials and methods

Study subjects

This study was approved by the institutional review board in June 2014 (IRB number: 16222-201408-HR-001). Our study group included 1002 men with available testosterone and carotid duplex ultrasound data who had received routine health check-ups at the Health Promotion Center of the National Police Hospital (Seoul, Korea), from January 2013 to May 2014. Patients who had taken a drug related to testosterone such as testosterone replacement therapy, 5-alpha reductase inhibitors, and steroids were excluded, in addition to those who had taken anti-psychotics. Participants who had undergone scrotal surgery, and/or carotid surgery were also excluded. Participants with documented coronary atherosclerosis or with personal history for cardiovascular event were also excluded. Finally, 935 men of the original 1002 were included in the study.

Carotid artery assessment

Carotid ultrasound was performed as previously described [15]. In short, the carotid arteries were evaluated by ultrasonography (model iE33; Philips Medical Systems, Eindhoven, The Netherlands). The relevant measurements were determined by a single experienced sonographer who was blinded to all clinical information. Longitudinal images of the carotid arteries, including the common carotid arteries and internal and external carotid arteries, were acquired. Mean carotid IMT was calculated by taking the arithmetic mean of 6 (3 from each side) measurements. We divided participants into tertiles based on their mean IMT measurements: first tertile mean IMT ($\leq$0.687 mm), second tertile mean IMT (>0.687 mm, $\leq$0.775 mm) and third tertile mean IMT (>0.775 mm).

Testosterone assay

Serum testosterone was measured by radioimmunoassay using a kit from Cisbio Bioassays, Inc. (Parc Marcel Boiteux, Codolet). The intra-assay coefficients of variation for all assays were less than 9%, and the inter-assay coefficients of variation were less than 12%. For each assay, all samples from each subject were analyzed in the same run. We defined hypogonadism as a testosterone level of lower than 3.5 ng/mL [16,17].

Metabolic syndrome assessment

Medical histories were collected using a standardized structural questionnaire. Two blood pressure (mmHg) measurements, obtained 5 min apart and averaged, were taken using a mercury sphygmomanometer on the right arm. Waist circumference (cm) to the nearest 0.1 cm was measured midway between the lowest rib and the iliac crest. Blood samples were collected with the subject in a fasted state between 09:00 and 10:00 h. Biochemical analyses included serum glucose, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Aspects of metabolic syndrome were classified according to the National Cholesterol Education Program Adult Treatment Panel III criteria [18]: (1) blood pressure $\geq$130/85 mmHg and/or receiving anti-hypertensive medication, (2) fasting blood sugar $\geq$110 mg/dL and/or receiving anti-diabetic medication, (3) waist circumference $\geq$90 cm, (4) high-density lipoprotein cholesterol <40 mg/dL and/or receiving anti-hypercholesterolemic medication, and (5) triglyceride level $\geq$150 mg/dL and/or receiving anti-hypercholesterolemic medication.

Statistical analysis

First, the 935 male subjects were analyzed to evaluate simple relationships between age, mean IMT, and testosterone using the Pearson correlation test. Then, we compared the ratio of hypogonadism among the tertiles (classified according to mean IMT using the Mantel–Haenszel Extension test). Finally, the odds ratio (ORs) for hypogonadism occurrence in each IMT tertile [15] was calculated using logistic regression, after adjusting for age and metabolic syndrome. Additionally, we compared the mean IMT between the absence and presence of metabolic syndrome groups. Then, the mean IMT adjusted for age and testosterone was also compared between these two groups using a multiple linear regression test. To assess the relationship between testosterone and metabolic syndrome, we compared testosterone levels between the absence and presence of metabolic syndrome groups. The mean IMT, adjusted for age and testosterone, was also compared between these two groups using a multiple linear regression test.

All statistical analyses were performed using SPSS version 11.0 (SPSS, Chicago, IL). $p < 0.05$ was considered to be statistically significant.

Results

Patient characteristics

The characteristics of the study population are shown in Table 1. The median age was 57.0 years. The median testosterone and median mean IMT were 5.1 ng/mL and 0.725 mm, respectively. Metabolic syndrome was present in 39.4% of participants.

Relationship between mean IMT and testosterone

Univariate analysis revealed a significant and negative linear correlation between mean IMT and testosterone (Table 2). There was a significant increase in the percentage of hypogonadism in the second and third tertiles of mean IMT (p trend = 0.022; Table 3). Logistic regression (Table 4) demonstrated a greater likelihood of hypogonadism in the third tertile of mean IMT than in the first tertile after adjusting for age and metabolic syndrome (OR = 1.700, $p = 0.044$).

Table 1. Patient characteristics ($n = 935$).

Variable	
Age, years	57.0 (55.0–58.0)
Testosterone (ng/mL)	5.1 (4.2–6.3)
Height (cm)	170.3 (168.0–174.0)
Body weight (kg)	73.0 (68.0–78.4)
Waist circumference (cm)	90.0 (86.0–94.0)
Systolic blood pressure (mmHg)	123.0 (114.0–136.0)
Diastolic blood pressure (mmHg)	81.0 (74.0–88.0)
Triglyceride (mg/dL)	127.0 (91.0–179.0)
High-density lipoprotein cholesterol (mg/dL)	40.0 (35.0–47.0)
Fasting blood sugar (mg/dL)	102.0 (95.0–114.0)
Metabolic syndrome (%)	39.4 (368)
Mean IMT (mm)	0.725 (0.669–0.800)

IMT, intima-media thickness.
The values are presented as the median (interquartile range) or % (number).

Table 2. Pearson's correlations between mean IMT and age or testosterone.

	Age	Testosterone
Mean IMT	0.195 (<0.001)	−0.067 (0.039)

IMT, intima-media thickness. The values are presented as the correlation co-efficiency (p value).

Table 3. The relationship between late onset hypogonadism and severity of mean IMT.

	Mean IMT			
	Tertile 1	Tertile 2	Tertile 3	*p**
Testosterone <3.5 ng/mL	9.0 (28)	13.3 (44)	15.1 (44)	0.022

IMT, intima-media thickness; Tertile 1, first tertile; Tertile 2, second tertile; Tertile 3, third tertile.
*Mantel–Haenszel Extension test.
The values are presented as the % (*number*).

Table 4. The OR for late onset hypogonadism according to severity of mean IMT.

	Mean IMT		
	Tertile 1	Tertile 2	Tertile 3
Testosterone <3.5 ng/mL			
OR*	1.000 (reference)	1.506 (0.908–2.497)	1.700 (1.015–2.848)
p Value†	–	0.113	0.044

Odds ratios are listed as 95% confidence intervals with absence of plaque as the reference category.
IMT, intima-media thickness; OR, odds ratio; Tertile 1, first tertile; Tertile 2, second tertile; Tertile 3, third tertile.
*OR, adjusting for age and metabolic syndrome.
†*p* value, logistic regression analysis.

Table 5. Mean IMT according to the presence of metabolic syndrome.

	Metabolic syndrome		
	Absent	Present	*p*
Unadjusted mean* (mm)	0.733 (0.112)	0.764 (0.118)	<0.001
Adjusted mean† (mm)	0.733 (0.724–0.742)	0.764 (0.752–0.775)	<0.001

Data are presented as mean (standard deviation) or mean (95% confidence interval).
IMT, intima-media thickness.
**t* test; †multiple linear regression test: adjusted for age and testosterone.

Table 6. Testosterone according to the presence and absence of metabolic syndrome.

	Metabolic syndrome		
	Absent	Present	*p*
Unadjusted mean* (ng/mL)	5.52 (1.68)	4.88 (1.38)	<0.001
Adjusted mean† (ng/mL)	5.52 (5.36–5.65)	4.89 (4.73–5.06)	<0.001

Data are presented as mean (standard deviation) or mean (95% confidence interval).
**t* test; †multiple linear regression test: adjusted for age and mean intima-media thickness.

Relationship between mean IMT and metabolic syndrome

Mean IMT was significantly higher in patients with metabolic syndrome (Table 5). Mean IMT was also significantly higher in the metabolic syndrome group after adjusting for age and testosterone (Table 5).

Relationship between testosterone and metabolic syndrome

Mean testosterone was significantly lower in patients with metabolic syndrome (Table 6). Mean testosterone was also significantly lower in the metabolic syndrome group after adjusting for mean IMT and age (Table 6).

Discussion

The aim of this study was to evaluate the relationship between testosterone, metabolic syndrome, and mean IMT in aging men. The data analyzed in this study indicated that testosterone, metabolic syndrome, and IMT were significantly and independently associated with each other. To our knowledge, this is the first study to elucidate their relationship simultaneously and synthetically. Our results suggest that carotid artery disease, late-onset hypogonadism, and metabolic syndrome are not separate diseases in aging men. Therefore, patients with one of the aforementioned diseases should receive counseling and assessment concerning the other two in aging men.

Previous data have demonstrated the relationship between testosterone and carotid IMT in men. A cross-sectional study from the Netherlands ($n = 403$) demonstrated that serum testosterone was inversely related to mean IMT [6]. Another cross-sectional study from Finland ($n = 239$) revealed that common carotid IMT was inversely related with testosterone after adjusting for age, total cholesterol, body mass index, blood pressure, and smoking [7]. Results from Norway ($n = 1482$) showed that participants in the lowest testosterone quantile were more likely (OR = 1.51, $p = 0.015$) to be in the highest mean IMT quintile [12]. Other results [14,13] from the same cohort [12] confirmed these results. Additionally, French ($n = 354$) [8] and Japanese ($n = 176$) [9] data showed that free testosterone and total testosterone were significantly and inversely associated with IMT before and after adjusting for confounding factors. Overall, these studies revealed a significant relationship between low testosterone and IMT. However, most of the previous data were obtained from small populations (less than 403 men) [6–11]. Furthermore, in many of the previous studies involving larger populations, testosterone measurements were taken in a non-fasted state between 08:00 and 16:00 h, even though it is optimal to measure testosterone in the early hours [12–14]. Our study assessed a relatively large population ($n = 935$) compared to previous studies, and blood samples for testosterone analysis were collected with the subject in a fasted state between 09:00 and 10:00 h. Our results corroborate the previous data described above.

Inflammation is one possible mechanism behind the relationship between testosterone and IMT. It has been proposed that testosterone might have a role in limiting the vascular inflammation and cytokine activity underpinning the pathophysiology of atherosclerosis [19–21]. In support of this proposition, cytokine-releasing cells such as macrophages, vascular smooth cells, and lymphocytes all possess androgen receptors [19–21]. Additionally, men with late-onset hypogonadism were exposed to a greater degree of inflammatory

activation, including higher serum cytokine levels than healthy controls [19,22]. To confirm causative relation in IMT and testosterone and the role of inflammation, following studies examining the effects of testosterone deprivation therapy or testosterone replacement therapy on IMT would be needed.

Recently, it has also been reported that metabolic syndrome is closely related with IMT [23–26]. In this study, mean IMT was significantly greater in metabolic syndrome before and after adjusting for potential confounding factors in aging men. Our results are in agreement with those of previous studies. Obesity, which contributes to the pathophysiology of metabolic syndrome, leads to the production of proinflammatory cytokines and chemokines by adipocytes. Immune cells then trigger adipose tissue inflammation, which when prolonged progresses to systemic inflammation that affects plaque development [27]. Considering that systemic inflammation also contributes to the pathophysiology of atherosclerosis, inflammation would explain the relationship between metabolic syndrome and IMT in a similar way to the relationship between testosterone and IMT.

Additionally, it is well known that metabolic syndrome is related to low-testosterone levels [28,29]. In accordance with previous studies, mean testosterone was significantly lower in metabolic syndrome. Recently, experimental data using rabbits demonstrated that metabolic syndrome induced by a high-fat diet caused hypogonadotropic hypogonadism [30]. Obesity could therefore be a relevant cause of hypogonadism [4].

Several limitations of the present study deserve mentioning. First, the cross-sectional nature of the dataset makes causal inferences problematic. In addition, as this study included data from a single institution, there is potential for selection bias. Nevertheless, we believe that the results of this study are highly relevant given that a relatively large population was sampled. Samples were collected in an ideal manner and we adjusted for confounding factors such as metabolic syndrome before assessing the relationship between testosterone and IMT.

In conclusion, mean IMT, testosterone, and metabolic syndrome were significantly and independently correlated with each other in aging men. Further studies are needed to confirm our results and to elucidate their causative relationship.

Declaration of interest

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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