The relationship between sex hormone levels and subclinical coronary artery calcification in non-obese Korean men

Byoung-Jin Park

Department of Medicine

The Graduate School, Yonsei University

The relationship between sex hormone levels and subclinical coronary artery calcification in non-obese Korean men

Directed by Professor Hye-Ree Lee

The Master's Thesis submitted to
the Department of Medicine
the Graduate School, Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Byoung-Jin Park

December 2011

This certifies that the Master's Thesis of
Byoung-Jin Park is approved.

Thesis Supervisor : Hye-Ree Lee

[Sang-Yol Mah: Thesis Committee Member#1)

[Soon-Won Hong: Thesis Committee Member#2)

The Graduate School
Yonsei University

December 2011

ACKNOWLEDGEMENTS

First of all, I would like to thank God for having made everything possible. I am heartily thankful to my supervisor, Professor Hye-Ree Lee, whose encouragement, guidance and support from the initial to the final level enabled me to complete this thesis. Also sincere thanks to Professor Sang-Yol Mah and Professor Soon-Won Hong who generously offered guidance and supports. In addition, I really appreciate Professor Jae-Yong Shim, Professor Yong-Jae Lee and Professor Dong-Hyuk Jung. Without their help, the outcome of this thesis could not be made. At last, I want to give my love to my family who all gave me courage and support. I'd like to dedicate this paper to all of you with all my heart.

Byoung-Jin Park

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE

ABSTRACT

The relationship between sex hormone levels and subclinical coronary artery calcification in non-obese Korean men

Byoung-Jin Park

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hye-Ree Lee)

Background: Although low testosterone levels in men have been associated with high risk for cardiovascular disease (CVD), little is known about the association between male sex hormones and subclinical coronary atherosclerosis. This study was performed to investigate associations between male sex hormones and subclinical coronary artery calcification measured as coronary calcium score (CCS) in non-obese Korean men.

Methods: We examined the relationship of total testosterone, sex hormone-binding globulin (SHBG), bioavailable testosterone (BT), free testosterone (FT) and free testosterone index (FTI) with CCS in 291 non-obese Korean men (mean age, 52.8 ± 9.3 years) not having a history of CVD. Using multiple linear regression, we evaluated associations between log(sex hormone) levels and log(CCS) after adjusting for confounding variables.

Results: In multiple linear regression analysis, BT and FTI were inversely associated with CCS (p=0.046 and p=0.018, respectively) after adjusting for age, body mass index, smoking status, alcohol consumption, regular exercise, mean blood pressure, resting heart rate, C-reactive protein, fasting plasma glucose, albumin, total cholesterol, triglyceride and HDL-cholesterol, whereas

total testosterone, SHBG and FT were not (p=0.674, p=0.121 and p=0.102, respectively).

Conclusions: Our findings indicate that BT and FTI are inversely associated with subclinical coronary artery calcification in non-obese men. Accordingly, early detection of decreased BT and FTI is important in the assessment of potential cardiovascular risk and could be an initiative for CVD prevention and vascular health management.

Key words: male sex hormone, testosterone; coronary calcium score; subclinical coronary artery calcification; cardiovascular disease

The relationship between sex hormone levels and subclinical coronary artery calcification in non-obese Korean men

Byoung-Jin Park

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Hye-Ree Lee)

I. INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death around the world, especially in developed countries. In upcoming aging society, the importance of CVD would be more noticed because it is implicated by decreased quality of life and social burden for a long time. Thus, identification of risk factors and early detection of CVD are very important, which could be an initiative for the prevention and slow progression of CVD.

A non-invasive marker of early coronary arterial wall alteration is now available. The coronary calcium score (CCS) measured by multidetector computed tomography (MDCT) is a sensitive marker of coronary artery atherosclerosis and reflects the severity of coronary artery stenosis to some extent.[1, 2] Recent epidemiological evidence suggests that CCS helps identify patients with cardiovascular risks in addition to the Framingham risk score.[3, 4]

An increasing body of evidence suggests that low testosterone levels in men are associated with high cardiovascular risk.[5-7] Although many studies have

been focused on the association between testosterone and CVD event, little is known about the association between sex hormone and subclinical coronary atherosclerosis in male adults with low cardiometabolic risk.

Therefore, we examined the associations of male sex hormones with subclinical coronary artery calcification in non-obese Korean men as measured by CCS.

II. MATERIALS AND METHODS

1. Study sample

We retrospectively reviewed the medical records of 328 males who voluntarily participated in a physical examination including male sex hormones and MDCT at the Health Promotion Center of Gangnam Severance Hospital, Yonsei University College of Medicine in Seoul, Korea, between October 2007 and November 2008.

The inclusion criteria were community-dwelling men with body mass index below 25 kg/m^2, which is a cut-off value for generalized obesity in Asian.[8] Subjects meeting any of the following criteria were excluded (n=37): a history of testosterone therapy and/or a history of diabetes, angina pectoris, myocardial infarction or cerebrovascular diseases. After the exclusion, 291 participants were included in the final analysis. This study was approved by the Institutional Review Board of Yonsei University College of Medicine.

The examinations were performed by medical staff according to standard procedures. The participants were asked about lifestyle behaviors (including cigarette smoking, alcohol consumption and exercise) and about ongoing treatment for diabetes, hypertension and hyperlipidemia. If the participants were under treatment, they were asked for the date of diagnosis and a list of current medications. Trained staff reviewed the completed questionnaires and entered the responses into a database. Participants were classified as non-smokers,

ex-smokers or current smokers and were categorized by alcohol consumption as non-drinkers or abstainers (alcohol drinking <140 g/week) and current drinkers (alcohol drinking ≥140 g/week). Regular exercise was defined as more than twice a week. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, with subjects wearing light indoor clothing and no shoes. Body mass index (BMI) was calculated as the ratio of weight to height squared (kg/m^2). Blood pressure and resting heart rate were measured with the participants in the sitting position after 5 minutes of rest using an automated device (TM-2665P, A&D Co., Ltd., Tokyo, Japan).

2. Laboratory measurement

Blood samples were taken from the antecubital vein early in the morning after a 12-hour overnight fast. Fasting plasma glucose, total cholesterol, HDL-cholesterol, triglyceride and albumin were measured using a Hitachi 7600-110 chemistry autoanalyzer (Hitachi, Tokyo, Japan). C-reactive protein (CRP) was measured using a latex-enhanced immunoturbidimetric method. Framingham risk score was calculated using available table format.[9]

Total testosterone and sex hormone-binding globulin (SHBG) concentrations were measured using an electrochemiluminescence assay with a Modular Analytics E170 system (Roche Diagnostic Systems, Basel, Switzerland). Bioavailable testosterone (BT) and free testosterone (FT) were calculated using the computerized Vermeulen formula,[10] which is available on the ISSAM web site (www.issam.ch). Free testosterone index (FTI) was

calculated using this formula: 100 x total testosterone/SHBG .[11]

3. Coronary calcium score measurement

MDCT was performed to measure CCS (Philips Brilliance 64; Philips Medical System, Best, Netherlands). A ß-blocker (40-80 mg propranolol hydrochloride; Pranol, Dae Woong, Seoul, Korea) was administered orally one hour before the examination to reduce the heart rate in patients who had a heart rate of more than 65 beats/minute. We used a prospective ECG-gating protocol with a step-and-shoot technique. With the participants in the supine position, MDCT scanning was performed in the craniocaudal direction within a single breath-hold at end-inspiratory suspension. A 1.0 ml/kg of iodinated contrast medium (Optiray 350; Tyco Healthcare, Kantata, Canada) was administered intravenously. Imaging was performed by using a real time bolus tracking technique. The scans were started 7 seconds after a trigger threshold of 110 Hounsfield Unit was reached. The breath-hold was achieved by all participants.

The image reconstruction was performed on the scanner's workstation using commercially available software (Extended Brilliance Workstation, Philips Medical System, Best, Netherlands). Reconstructed images were analyzed for the presence and extent of coronary artery calcification by using coronary calcium quantification software (Aquarius Workstation, TeraRecon, Inc., USA).

4. Statistical Analysis

Demographic and biochemical characteristics of the study population were described as percentages for categorical variables, and as the mean ± SD in the case of normal distribution and as median [interquartile range] or geometric mean ± SD in the case of non-normal distribution. In addition, we divided the subjects into two groups as follows: the control (CCS=0) and the coronary calcification group (CCS≥1). The basic characteristics of each group were compared using the Student's t-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation coefficients were calculated to evaluate the relationship between serum male sex hormone levels and Framingham risk score. Univariate regression analysis was performed to measure the strength of the relationship between coronary calcification and surrogate markers for CVD. Additionally, associations between sex hormone levels and CCS were evaluated using multiple linear regression analysis after log-transformation of sex hormones and CCS. All analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, NC, USA). All statistical tests were two-sided and statistical significance was determined with a p value < 0.05.

III. RESULTS

The mean subject age was 52.8 ± 9.3 years. The median serum concentration of total testosterone was 17.0 nmol/L, SHBG was 40.7 nmol/L, BT was 7.29 nmol/L and FT was 0.29 nmol/L. The geometric mean CCS was 36.6 ± 5.0. All male sex hormones and CCS were positively skewed. Age, systolic blood pressure, diastolic blood pressure and fasting plasma glucose were significantly higher in the group with coronary calcification. The mean BMI was similar in both groups (Table 1).

Figure 1 shows the relationship between male sex hormone levels and Framingham risk score in non-obese men. A significant correlation was not present in total testosterone (A) and SHBG (B). However, BT (C), FT (D) and FTI (E) were significantly inversely related with Framingham risk score.

According to univariate analysis (Table 2), old age, high blood pressure, high fasting plasma glucose, high SHBG, low BT, low FT and low FTI were associated with coronary artery calcification, whereas total testosterone was not. Upon multivariate linear regression analysis (Table 3), BT, FT and FTI were found to be independently and inversely related with CCS after adjusting for age and BMI (model 2), whereas total testosterone and SHBG were not. We also assessed associations between male sex hormones and CCS after additional adjusting for smoking status, alcohol consumption, regular exercise, mean blood pressure, resting heart rate, fasting plasma glucose, total cholesterol, HDL-cholesterol, triglyceride, C-reactive protein, albumin, hypertension medication and hyperlipidemia medication (model 3). These inverse and

independent associations remained in BT and FTI after using model 3. A 2.72-fold (1 log-unit greater) BT and FTI was negatively associated with a 1.07- and 1.22-fold geometric mean CCS, respectively.

Table 1. Characteristics of the study population

	Coronary calcification group (N=105)	Control group (N=186)	Total (N=291)	*p*-value
[a]Age, years	58.7 ± 9.3	49.5 ± 7.6	52.8 ± 9.3	<0.001
[a]Body mass index, kg/m^2	22.8 ± 1.8	23.0 ± 1.5	22.9 ± 1.6	0.394
[a]Current smoker, %	24.8	39.8	34.4	0.009
[a]Alcohol consumption[*], %	16.2	30.7	25.4	0.006
[a]Regular exercise[†], %	59.1	58.1	58.4	0.870
[a]Systolic blood pressure, mmHg	125.4 ± 15.0	121.9 ± 13.7	123.2 ± 14.2	0.046
[a]Diastolic blood pressure, mmHg	79.1 ± 9.2	77.0 ± 8.4	77.8 ± 8.7	0.047
[a]Resting heart rate, beats/min	75.9 ± 11.9	74.5 ± 12.3	75.0 ± 12.2	0.332
[a]Fasting plasma glucose, mg/dL	99.7 ± 22.0	93.1 ± 18.3	95.5 ± 19.9	0.009
[a]Total cholesterol, mg/dL	191.5 ± 34.8	191.4 ± 35.3	191.4 ± 35.1	0.975
[a]HDL-cholesterol, mg/dL	48.8 ± 10.1	50.2 ± 11.1	49.7 ± 10.8	0.286
[a]Triglyceride, mg/dL	127.4 ± 66.7	119.7 ± 59.2	122.5 ± 62.0	0.307
[a]C-reactive protein, mg/L	1.7 ± 3.0	2.5 ± 6.7	2.2 ± 5.7	0.145
[a]Albumin, g/dL	4.7 ± 0.3	4.7 ± 0.3	4.7 ± 0.3	0.329
[b]Total testosterone, nmol/L	16.9 [13.9-20.3]	17.1 [13.6-20.6]	17.0 [13.7-20.5]	
[b]Sex hormone-binding globulin, nmol/L	43.7 [34.0-53.9]	38.3 [29.7-48.0]	40.7 [31.9-51.2]	
[b]Bioavailable testosterone	6.89 [5.72-\8.40]	7.42 [6.32-9.85]	7.29 [5.97-9.26]	
[b]Free testosterone	0.28 [0.23-0.33]	0.29 [0.25-0.38]	0.29 [0.24-0.36]	
[b]Free testosterone index	36.7 [34.0-53.9]	45.2 [35.4-55.6]	41.2 [32.2-52.5]	
[c]Coronary calcium score	36.6 ± 5.0		36.6 ± 5.0	

Data are expressed as [a]the mean ± SD or percentage, [b]Median [interquartile range] and [c]Geometric mean ± SD

[*]Alcohol drinking ≥ 140g/week. [†]Regular exercise ≥ twice/week.

Table 2. Univariate analysis of factors associated with coronary artery calcification

Variables	Odds ratio (95% CIs)	*p*-value
Age, years	1.14 (1.10-1.18)	<0.001
Body mass index, kg/m^2	0.93 (0.81-1.08)	0.364
Systolic blood pressure, mmHg	1.02 (1.00-1.04)	0.048
Diastolic blood pressure, mmHg	1.03 (1.00-1.06)	0.048
Resting heart rate, beats/min	1.01 (0.99-1.03)	0.331
Fasting plasma glucose, mg/dL	1.02 (1.00-1.03)	0.011
Total cholesterol, mg/dL	1.00 (0.99-1.01)	0.975
HDL-cholesterol, mg/dL	0.99 (0.97-1.01)	0.286
Triglyceride, mg/dL	1.00 (0.99-1.01)	0.307
C-reactive protein, mg/L	0.97 (0.91-1.03)	0.250
Albumin, g/dL	0.63 (0.25-1.60)	0.328
[a]Total testosterone, nmol/L	0.93 (0.46-1.89)	0.845
[a]Sex hormone-binding globulin, nmol/L	2.47 (1.33-4.60)	0.004
[a]Bioavailable testosterone, nmol/L	0.44 (0.21-0.92)	0.030
[a]Free testosterone, nmol/L	0.42 (0.20-0.89)	0.024
[a]Free testosterone index	0.27 (0.13-0.56)	<0.001

[a]Values have been analyzed after log-transformation.

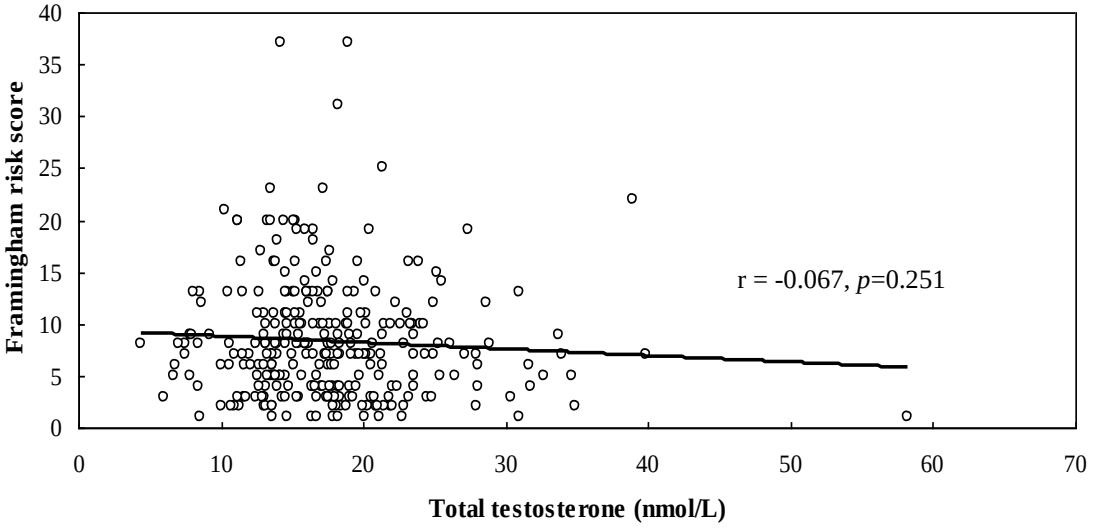
Table 3. Multiple regression analysis showing the independent contribution of sex hormones to coronary artery calcification in non-obese men

	Model 1[*]		Model 2[†]		Model 3[‡]	
	[b]β ± SE	*p*-value	[b]β ± SE	*p*-value	[b]β ± SE	*p*-value
[a]Total testosterone, nmol/L	- 0.713 ± 0.535	0.186	- 0.596 ± 0.517	0.252	- 0.225 ± 0.535	0.674
[a]Sex hormone-binding globulin, nmol/L	0.945 ± 0.496	0.059	0.365 ± 0.540	0.501	0.908 ± 0.579	0.121
[a]Bioavailable testosterone, nmol/L	- 1.830 ± 0.498	<0.001	- 1.330 ± 0.548	0.017	- 1.157 ± 0.572	[c]0.046
[a]Free testosterone, nmol/L	- 1.674 ± 0.532	0.002	- 1.156 ± 0.563	0.042	- 0.983 ± 0.595	0.102
[a]Free testosterone index	- 1.883 ± 0.519	<0.001	- 1.328 ± 0.606	0.031	- 1.581 ± 0.658	[d]0.018

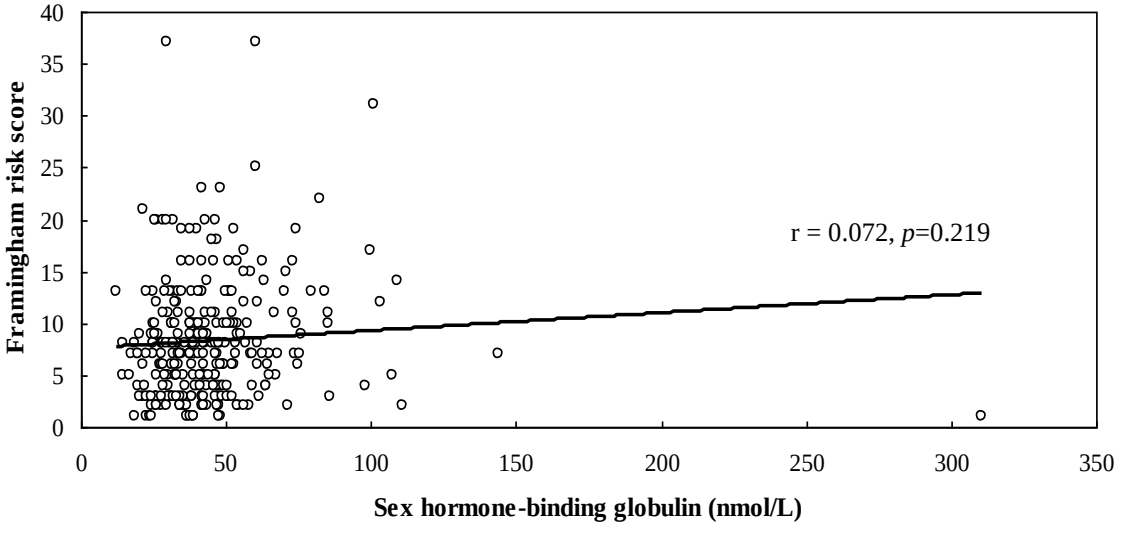
[a]Values have been analyzed after log-transformation. [b]Coronary calcium score (units of beta are log-unit increased CCS per 1 log unit greater sex hormone level) [C]Negatively 1.07-fold geometric mean CCS/2.72-fold(1 log-unit greater) BT. [d]Negatively 1.22-fold geometric mean CCS/2.72-fold(1 log-unit greater) FTI. [*]Model 1: unadjusted. [†]Model 2: adjusted for age and body mass index. [‡]Model 3: adjusted for age, body mass index, smoking status, alcohol consumption, regular exercise, mean blood pressure, resting heart rate, fasting plasma glucose, total cholesterol, HDL-cholesterol, triglyceride, C-reactive protein, albumin, hypertension medication and hyperlipidemia medication.

Figure 1. The correlation between Framingham risk score and total testosterone (A), sex hormone-binding globulin (B), bioavailable testosterone (C), free testosterone (D) and free testosterone index (E) in non-obese men.

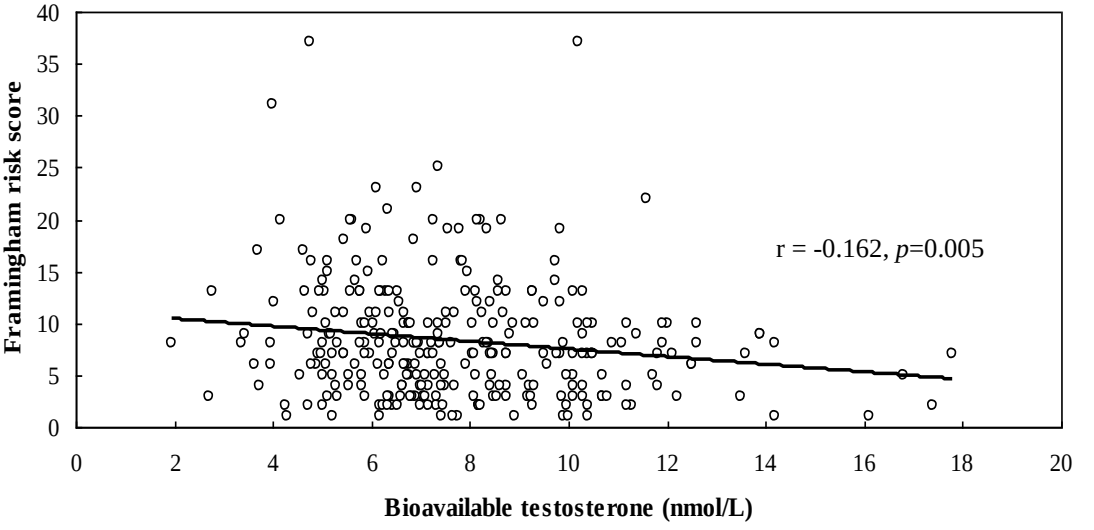
(A)



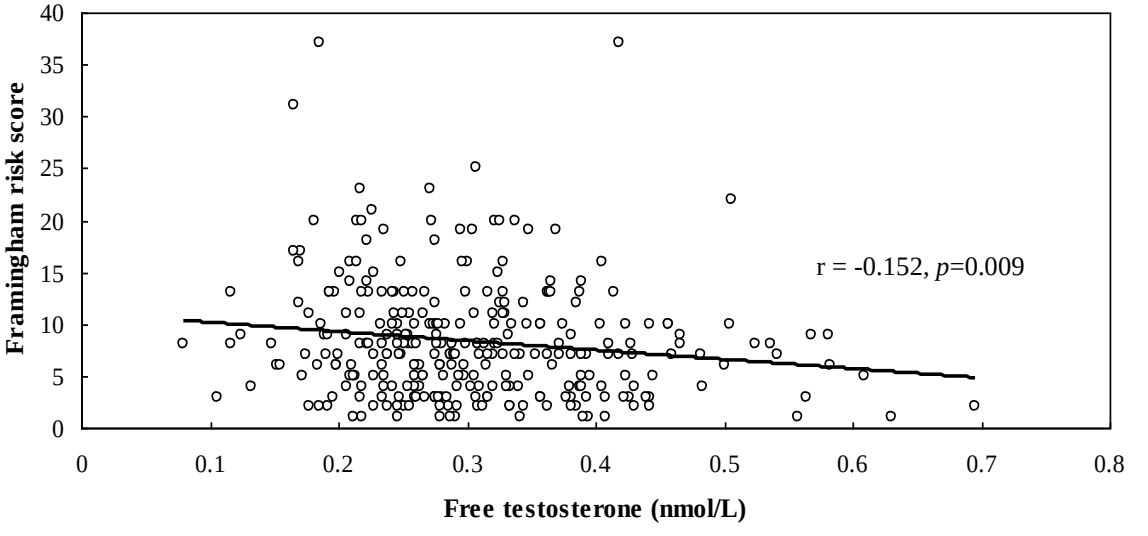
(B)



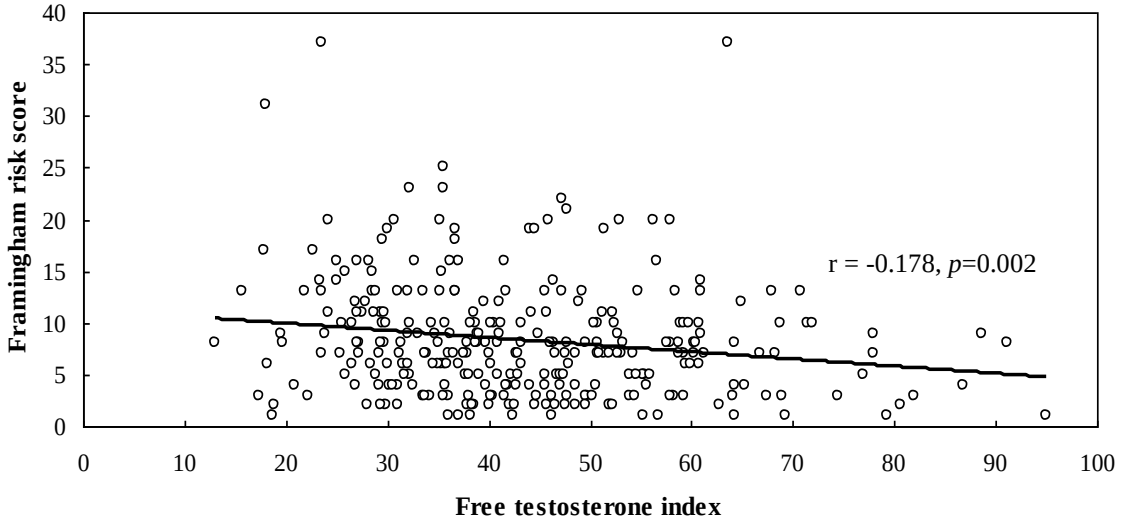
(C)


Framingham risk score
Bioavailable testosterone (nmol/L)
r = -0.162, p=0.005

(D)


Framingham risk score
Free testosterone (nmol/L)
r = -0.152, p=0.009

(E)


Framingham risk score
Free testosterone index
r = -0.178, p=0.002
0
5
10
15
20
25
30
35
40
0
10
20
30
40
50
60
70
80
90
100

IV. DISCUSSION

In this cross-sectional study, we found an inverse association of BT and FTI with CCS independent of classic cardiovascular risk factors in non-obese men. However, we did not find a significant relationship between total testosterone, SHBG and CCS.

A decreased testosterone level has been found to be predictive of subclinical atherosclerosis in some observational studies. Most studies were performed to determine the relationship between testosterone and carotid artery intima-media thickness or abdominal aortic calcification.[12-15] To our knowledge, there was only one previous study that focused on the association between sex hormone and subclinical coronary calcification. Ouyang *et al*.[16] have reported that testosterone is associated with coronary calcium score, but the study was conducted only in postmenopausal women.

Although the reason for the relationship between BT and CCS is unclear, it may be explained by some biological mechanisms. Endothelial dysfunction has been linked to testosterone deficiency. There are two possible mechanisms for this relationship: direct and indirect mechanisms. For the former, testosterone has positive effects on endothelial function by directly stimulating endothelium-derived nitric oxide.[17, 18] Additionally, testosterone could stimulate endothelial progenitor cells, which play a key role in endothelial repair.[19, 20] Lu *et al*.[21] have proposed that decreased testosterone is associated with

ultrastructural damage of the aortic endothelium. In the latter, hypogonadism has been reported to contribute to the development of metabolic syndrome.[22-24] Metabolic syndrome represents a cluster of cardiometabolic risk factors, including central obesity, elevated blood pressure, impaired glucose metabolism and atherogenic dyslipidemia. Thus, testosterone could have an indirect physiological role in heart vessels.

The majority of testosterone exists in the bound form, with only a small portion unbound.[25] The biological effects of testosterone also depend on its conversion to bioactive metabolites.[25] BT is thought to be more biologically active than the bound forms. A previous study has demonstrated that total testosterone and SHBG are significantly associated with metabolic syndrome irrespective of insulin resistance.[26] Our study was performed in subjects with relatively low cardiometabolic risks. Therefore, a direct action of BT on heart vessels may deserve much consideration in the early phase of coronary atherosclerosis.

Our results demonstrate that FT was associated with the severity of CCS independently of age and BMI (p=0.042), but not of other traditional CVD risk factors including blood pressure and fasting plasma glucose (p=0.074). Although all blood samples were drawn early in the morning to minimize the diurnal variation in testosterone levels,[27] FT might be less reliable than BT to represent basal androgenic activity. FTI has been used as a surrogate marker of

BT,[28] but a recent positional statement of the Endocrinology Society has indicated that FTI correlates well with FT in women but not in men.[29] Our study has shown that FTI is significantly associated with CCS. In men with low cardiometabolic risk, FTI might be a complementary to BT in the relationship with coronary artery calcification.

Our study has some limitations. First, our study is a cross-sectional study and the cause-effect relationship between male sex hormones and CCS remains unclear. Second, we used calculated rather than directly measured BT and FT. However, previous studies have demonstrated the validity and reliability of calculated BT and FT.[10] Third, our results cannot be generalized to women. Testosterone levels in women are much lower than in men and women are pronouncedly influenced by estrogen. Therefore, the effect of testosterone on coronary vasculature is not as significant in women as in men or manifested in different manner according to menopausal status.

V. CONCLUSION

Our findings indicate that BT and FTI are inversely associated with subclinical coronary artery calcification in non-obese men. Accordingly, early detection of decreased BT and FTI is important in the assessment of potential cardiovascular risk and could be an initiative for CVD prevention and vascular health management.

REFERENCES

1. Ma ES, Yang ZG, Li Y, Dong ZH, Zhang L, Qian LL. Correlation of calcium measurement with low dose 64-slice CT and angiographic stenosis in patients with suspected coronary artery disease. Int J Cardiol 2008;140:249-52.
2. Budoff MJ, Gul KM. Expert review on coronary calcium. Vasc Health Risk Manag 2008;4:315-24.
3. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-5.
4. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, et al. Arterial stiffness and cardiovascular events: The Framingham Heart Study. Circulation 2010;121:505-11.
5. Simon D, Charles MA, Nahoul K, Orssaud G, Kremski J, Hully V, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: The Telecom Study. J Clin Endocrinol Metab 1997;82:682-5.
6. Khaw K, Dowsett M, Folkerd E, Bingham S, Wareham N, Luben R, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) prospective population study. Circulation 2007;116:2694-701.
7. Malkin CJ, Pugh PJ, Morris PD, Asif S, Jones TH, Channer KS. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821-5.
8. World Health Organization. *The Asia-Pacific perspective. Redefining obesity and its treatment.* Health Communications Australia Pty Limited. Available at: www.obesityasiapacific.com (accessed January

2003). International Diabetes Institute, 2000

9. Framingham Heart Study: Hard coronary heart disease (10-year risk) Framingham Heart Study. Available at www.framinghamheartstudy.org / risk / hrdcoronary.html

10. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666-72.

11. Morley JE, Patrick P, Perry HM. Evaluation of assays available to measure free testosterone. Metabolism 2002;51:554-9.

12. Ma¨kinen J, Jarvisalo M, Pollanen P, Perheentupa A, Irjala K, Koskenvuo M, et al. Increased carotid atherosclerosis in andropausal middle-aged men. J Am Coll Cardiol 2005;45:1603–8.

13. Fukui M, Kitagawa Y, Nakamura N, Kadono M, Mogami S, Hirata C, Ichio N, Wada K, Hasegawa G, Yoshikawa T. Association between serum testosterone concentration and carotid atherosclerosis in men with type 2 diabetes. Diabetes Care 2003;26:1869–73.

14. Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation 2004;109:2074-9.

15. Hak A, Witteman J, de Jong F, Geerlings M, Hofman A, Pols H. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab 2002;87:3632–9.

16. Ouyang P, Vaidya D, Dobs A, Golden SH, Szklo M, Heckbert SR, et al. Sex hormone levels and subclinical atherosclerosis in postmenopausal women: the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis 2009;204: 255-61.

17. Yue P, Chatterjee K, Beale C, Poole-Wilson PA, Collins P. Testosterone

relaxes rabbit coronary arteries and aorta. Circulation 1995;91:1154–60.

18. Miller VM, Mulvagh SL. Sex steroids and endothelial function: translating basic science to clinical practice. Trends Pharmacol Sci 2007;28:263–70.
19. Foresta C, Caretta N, Lana A, DeToni L, Biagioli A, Ferlin A, et al. Reduced number of circulating endothelial progenitor cells in hypogonadal men. J Clin Endocrinol Metab 2006;91:4599-602.
20. Foresta C, Zuccarello D, De Toni L, Garolla A, Caretta N, Ferlin A. Androgens stimulate endothelial progenitor cells through an androgen-mediated pathway. Clin Endo 2008;68:284–9.
21. Lu YL, Kuang L, Zhu H, Wu H, Wang XF, Pang YP, et al. Changes in aortic endothelium ultrastructure in male rats following castration, replacement with testosterone and administration of 5-alpha-reductase inhibitor. Asian J Androl 2007;9:843–7.
22. Mohr BA, Bhasin S, Link CL, O'Donnell AB, McKinlay JB. The effect of changes in adiposity on testosterone levels in older men; longitudinal results from the Massachusetts Male Aging Study. Eur J Endocrinol 2006;155:443-52.
23. Kalyani RR, Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. Curr Opin Endocrinol Diabetes Obes 2007;14:226-34.
24. Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR, et al. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. J Clin Endocrinol Metab 2007;92;3568-72.
25. Liu PY, Death AK, Handelsman DJ. Androgens and cardiovascular disease. Endocr Rev 2003;24:313-40.
26. Li C, Ford ES, Li B, Giles WH, Liu S. Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. Diabetes Care 2010;33:1618-24.

27. Brambilla DJ, Matsumoto AM, Araujo AB, McKinlay JB. The effect of diurnal variation on clinical measurement of serum testosterone and other sex hormone levels in men. J Clin Endocrinol Metab 2009;94:907-13.

28. Morley JE, Patrick P, Perry HM. Evaluation of assays available to measure free testosterone. Metabolism 2002;51:554-9.

29. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab 2007;92:405-13.

ABSTRACT (IN KOREAN)

비만하지 않은 한국 남성에 있어 성호르몬과 불현성 관상동맥석회화의 상관성

<지도교수 이 혜 리>

연세대학교 대학원 의학과

박 병 진

배경: 총 테스토스테론의 저하가 심혈관질환을 초래할 수 있다는 보고가 여러 차례 이루어진 바 있으나 개별 남성호르몬과 불현성 관상동맥석회화의 관계에 대한 연구는 미미했다. 이번 연구에서는 비만하지 않은 한국 남성에 있어 개별 남성호르몬과 불현성 관상동맥석회화의 상관성에 대해 알아보고자 하였다.

방법: 강남 세브란스 병원 건강증진 센터를 방문하여 심장혈관 및 성호르몬 정밀 검사를 시행한 참가자 중 체질량 지수가 25 kg/m^2 미만이며, 심혈관질환의 과거력이 없는 291명 (52.8 ± 9.3 세)을 대상으로 하였다. 설문지를 통하여 병력을 확인하였고, 혈액검사를 통하여 남성호르몬을 측정 및 계산하였고, 다중검출기 전산화 단층촬영술를 통하여 관상동맥석회화 점수를 산출하였다. 개별 남성호르몬 및 관상동맥석회화 점수를 로그치환한 후 다중회귀분석을

통하여 이들간의 상관성을 규명하였다.

결과: 다중회귀분석결과, 생체활성 테스토스테론과 자유 테스토스테론 지수는 심혈관계 위험인자 및 혼란변수를 보정한 후에도 관상동맥석회화 점수와 유의한 역의 상관관계를 보였으나(p=0.046, p=0.018), 총 테스토스테론, 성호르몬 결합 글로불린, 자유 테스토스테론은 상관성을 보이지 않았다 (p=0.674, p=0.121, p=0.102).

결론: 생체활성 테스토스테론과 이의 대리표지자인 자유 테스토스테론 지수는 비만하지 않은 남성에 있어 불현성 관상동맥석회화와 역의 상관성을 보였다. 생체활성 테스토스테론의 저하는 심혈관질환의 잠재위험인자일 가능성이 있으며, 이를 통해 심혈관질환 예방의 단초를 제공할 수 있을 것이다.

핵심되는 말: 남성 호르몬, 관상동맥석회화 점수, 불현성 관상동맥석회화, 심혈관질환