Testosterone might be influenced by co-morbidities, not by aging

by

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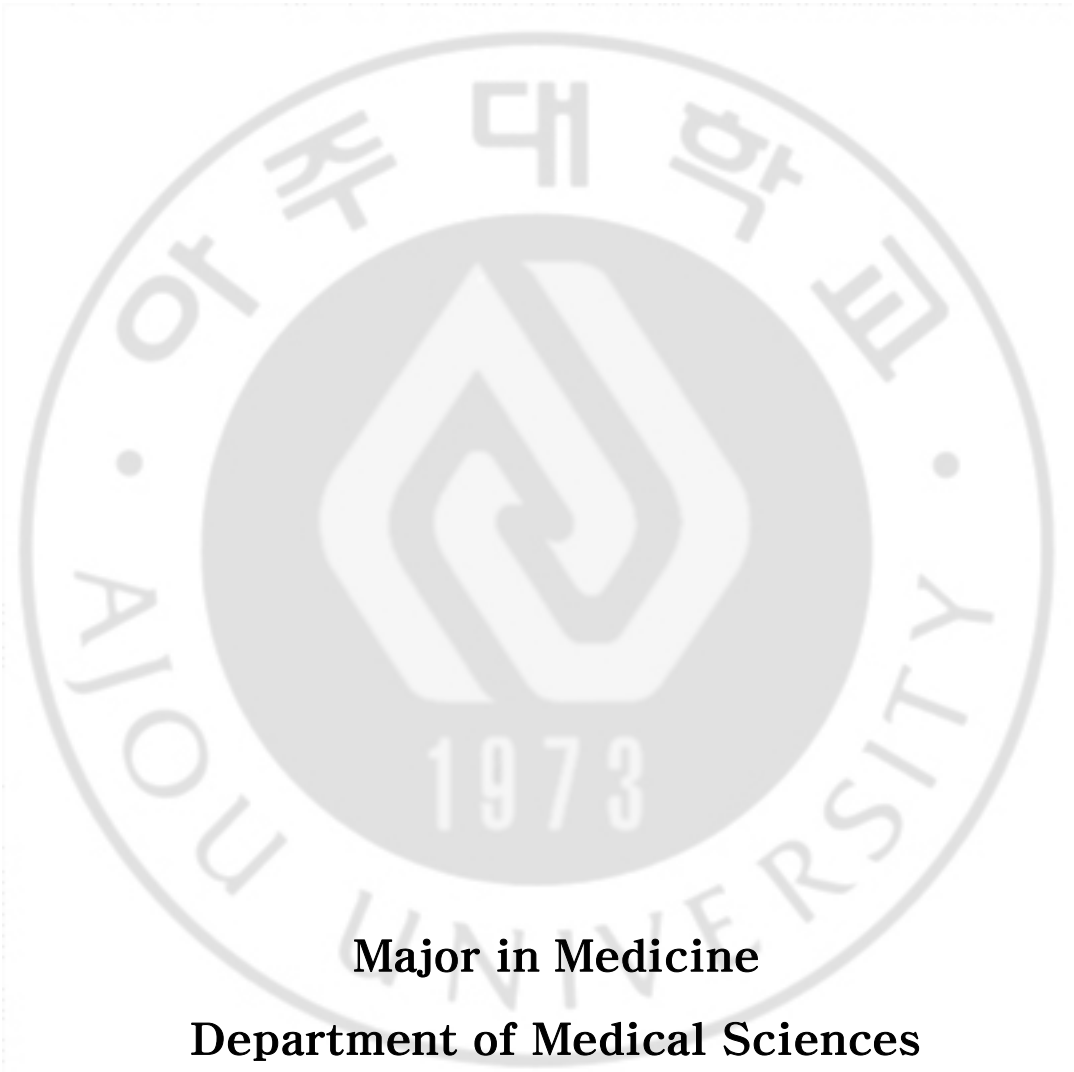

Major in Medicine

Department of Medical Sciences

The Graduate School, Ajou University

아주대학교
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This certifies that the dissertation
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- Abstract -

Testosterone might be influenced by co-morbidities, not by aging

1) Background

Total testosterone in men decreasing with age is well-established. However, observations on aging-related decrease in total testosterone (TT) are not consistent. The aim of this study is to seek the relationship between testosterone and health status and investigate the influence of the chronic disease to testosterone level.

2) Methods

A total of 4,284 aged ≥ 40 year old men were included between 2008 and 2013. The subjects divided to two groups (chronic disease group versus normal group). Blood tests results and clinical data, including serum total testosterone, were checked and compared between the groups.

3) Results

Our data showed that 2,041 subjects had chronic diseases (47.6%), and 2,243 were normal (52.4%). Total testosterone and age(r=0.032, P=0.034), HDL(r=0.133, P<0.001) had positive correlation, respectively. On the other hand, BMI(r=-0.198, P<0.001), waist circumference(r=-0.184, P<0.001), blood pressure, ALT(r=-0.132, P<0.001), fasting sugar(r=-0.105, P<0.001), Triglyceride(r=-0.119, P<0.001) and albumin(r=-0.108, P<0.001) showed negative correlation with total testosterone, respectively. Total testosterone level did not decrease with age. People who had metabolic syndrome, hypertension and diabetes were had lower total testosterone than normal population. Odds ratio of the hypogonadism in chronic disease group compared to normal group was 1.595(95% CI, 1.355-1.876, P<0.001).

4) Conclusion

The total testosterone level was lower in chronic disease group compared to healthy subjects. Total testosterone level influenced by disease status, not by aging.

Keyword: Testosterone, Chronic disease, Hypogonadism, Aging

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I. Introduction

Testosterone deficiency syndrome (TDS), also regard as the late onset hypogonadism (LOH), is a common but often unrecognized syndrome that affects as many as 38.7% of aging men(Mulligan et al., 2006). Since the elderly population has been increasing recently, old male patients with LOH has a significantly decreasing quality of life(민권식, 2011). Many of the physical and behavioral changes that occur in men as they age are similar to those that occur in younger men with hypogonadism. These changes include decreases in muscle mass, strength, bone mass and sexual function and increases in body fat, fatigue, and depressed mood(Bremner, 2010).

Generally, total testosterone in men decreases with age that is well-established (Harman and Tsitouras, 1980; Kaufman and Vermeulen, 2005). According to the Massachusetts Male Aging study, total testosterone decreases 1.6% by year(Kaufman and Vermeulen, 2005). The reason for the decline in testosterone concentrations with aging is not fully understood but multiple mechanisms including primary testicular changes, altered neuroendocrine regulation of Leydig cell function and increase in plasma SHBG binding capacity have been proposed(Nieschlag et al., 2005).

Regardless of age, there are some factors causing low testosterone. Some drugs, obesity related conditions, hyperprolacinemia, estrogen excess, toxin exposure, etc. can cause low testosterone(Pantalone and Faiman, 2012). However, in some studies, the level of testosterone did not fall significantly with age in healthy men (Harman and Tsitouras, 1980; Sparrow et al., 1980). Consider all these findings, we can estimate that the late onset hypogonadism (LOH) is not only caused by aging process. In other studies, including a recent study, there were some evidences that showed low testosterone caused by other factors, not by aging(Sparrow et al., 1980; Kim et al., 2012). In addition, there were correlation between low testosterone status and many common diseases. These include type 2 DM, ischemic heart disease, dyslipidemia and hypertension, Alzheimer's disease, osteoporosis,

peripheral artery disease, rheumatoid arthritis, chronic obstructive pulmonary disease, severe liver disease(Kamischke et al., 1998; Svartberg et al., 2003; Grossmann et al., 2012; Maggio et al., 2012; Pikwer et al., 2013). In recent report, Kim et al. illustrated that total testosterone may not decline with aging(Kim et al., 2012).

The aim of this study is to seek the relationship between testosterone level and health status. We try to figure out the subjects who had chronic disease and then compare the testosterone level to normal subjects.

II. Materials and methods

Study population

This cross sectional study conducted a database analysis of 4,284 men aged over 40 year old visited Health promotion center of Ajou University Hospital, Suwon, South Korea, between January 2008 and February 2013. Self-report questionnaires were used to obtain clinical information including medical history, medication history, smoking and alcohol consumption, and body mass index was calculated. Total testosterone was assayed in subjects who voluntarily added the aging-related module to the routine medical examination program. Total testosterone was measured by radioimmunoassay using Coat-a-Count Total Testosterone (Siemens Healthcare Diagnostic Inc., NY, USA). Exclusion criteria included known cancer, acute diseases or acute exacerbation of chronic disease within 3 months, and LOH patients who got testosterone replacement therapy within 6 months. This study designed for non-identical subjects.

Define the chronic disease and the late onset hypogonadism

Subjects were classified as two major groups, chronic disease group and normal group. The subjects who had metabolic syndrome, hypertension, diabetes, and stroke assorted as chronic disease group. Hypertension included who had systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90 mmHg(Chobanian et al., 2003). Diabetes included who had fasting blood sugar ≥ 126mg/dL(Federation, 2006).

Metabolic syndrome was defined as three or more of the following criteria, according to the American Heart Association/Updated National Cholesterol Education Program Third Adult Treatment Panel guidelines (NCEP ATP III) triglyceride level ≥150 mg/dl, HDL cholesterol <40 mg/dl, BP ≥130/85 mmHg or the use of BP medications, fasting glucose level ≥110 mg/dl or undergoing treatment for hyperglycemia, and waist circumference ≥ 90 cm. The criteria of waist circumference were corrected for Asians according to World Health Organization suggestion for redefining central obesity(Region,

2000).

To measure the serum total testosterone, it should be tested between 7 a.m. and 11 a.m.(Vermeulen, 2005). Serum total testosterone less than 12nmol/L (3.5ng/mL) defined as the late onset hypogonadism (Svartberg et al., 2003).

Statistical analysis

Descriptive statistics were computed for all clinical and demographic variables. Comparisons among age groups were performed using a one-way ANOVA test, and comparisons between two groups were carried out using an unpaired Student't-test. Pearson correlation coefficients were computed to determine the strength and form of associations. Multivariate logistic regression analysis was used to figure out the odds ratio of hypogonadism according to health status. All analyses were conducted using SPSS Statistics version 19.0.0. for Windows. Significance determined at 0.05 was used throughout all statistical tests.

III. Results

The clinical, laboratory and demographic data of two groups are listed in table 1. 4,284 over 40 year old men were included. 2,041 subjects had chronic diseases (47.6%) and 2,243 were normal (52.4%). Disease group was older (normal 52.6 ± 7.9 vs. Diseased 58.2 ± 8.7) and they had lower total testosterone (normal 4.99 ± 1.53 vs. diseased 4.79 ± 1.49). Moreover, chronic disease group were more obese and had higher level of blood sugar.

Table 1. General characteristics.

	Normal group	Disease group	P value
Number of cases	2,243	2,041	
Age (years)	52.4 ± 7.9	55.6 ± 8.6	< 0.001
Total testosterone (ng/mL)	5.15 ± 1.55	4.72 ± 1.46	< 0.001
Body Mass Index (kg/m^2)	23.8 ± 2.5	25.5 ± 2.9	< 0.001
Height (cm)	169.9 ± 5.8	169.3 ± 6.0	0.001
Weight (kg)	68.8 ± 8.5	73.1 ± 10.1	< 0.001
Waist circumference (cm)	83.8 ± 6.7	88.5 ± 7.4	< 0.001
Systolic BP (mmHg)	115 ± 11	128 ± 14	< 0.001
Diastolic BP (mmHg)	77 ± 7	86 ± 10	< 0.001
Total cholesterol (mg/dL)	193.4 ± 34.0	194.6 ± 36.1	0.237
HDL cholesterol (mg/dL)	50 ± 12	47 ± 11	< 0.001
Triglyceride (mg/dL)	117 ± 82	161 ± 106	< 0.001
Fasting glucose (mg/dL)	95 ± 9	113 ± 33	< 0.001

HbA1C (%)	5.7 ± 0.2	6.3 ± 1.0	< 0.001
AST (U/L)	26 ± 8	28 ± 10	< 0.001
ALT (U/L)	27 ± 13	32 ± 15	< 0.001
ESR (mm/hr)	9.3 ± 0.15	10.5 ± 0.16	< 0.001
CRP (mg/L)	0.17 ± 0.05	0.13 ± 0.04	0.573
Current smoker (%)	39.6	36.3	< 0.001
Alcohol use (%)	74.4	76.0	< 0.001
Exercise (%)	83.9	83.2	< 0.001

Data are mean ± standard deviation unless otherwise indicated.
ESR and CRP showed mean ± standard error.
Abbreviations: HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Correlation between total testosterone and other variables was listed in table 2. Total testosterone and age(r=0.032, P=0.034), HDL(r=0.133, P<0.001) showed positive correlation, respectively. On the other hand, BMI(r=-0.198, P<0.001), waist circumference(r=-0.184, P<0.001), blood pressure, ALT(r=-0.132, P<0.001), fasting sugar(r=-0.105, P<0.001), TG(r=-0.119, P<0.001) and albumin(r=-0.108, P<0.001) showed negative correlation with total testosterone, respectively.

Table 2. Correlations between serum total testosterone and other variables.

Variable	r	p-value
Age	0.032*	0.034
Body Mass Index	-0.198†	<0.001

Waist circumference	-0.184†	<0.001
Systolic BP	-0.102†	<0.001
Diastolic BP	-0.085†	<0.001
AST	-0.009	0.567
ALT	-0.131†	<0.001
Fasting sugar	-0.105†	<0.001
HbA1C	-0.078	0.072
Total cholesterol	-0.016	0.284
HDL cholesterol	0.133†	<0.001
Triglyceride	-0.119†	<0.001
Albumin	-0.108†	<0.001

*. Correlation is significant at the 0.05 level (2-tailed).

†. Correlation is significant at the 0.01 level (2-tailed).

Abbreviations: HDL, high density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Total testosterone does not increase with age (Figure 1). Among the age groups, there was no statistically significant difference (P=0.25, performed by one way ANOVA).

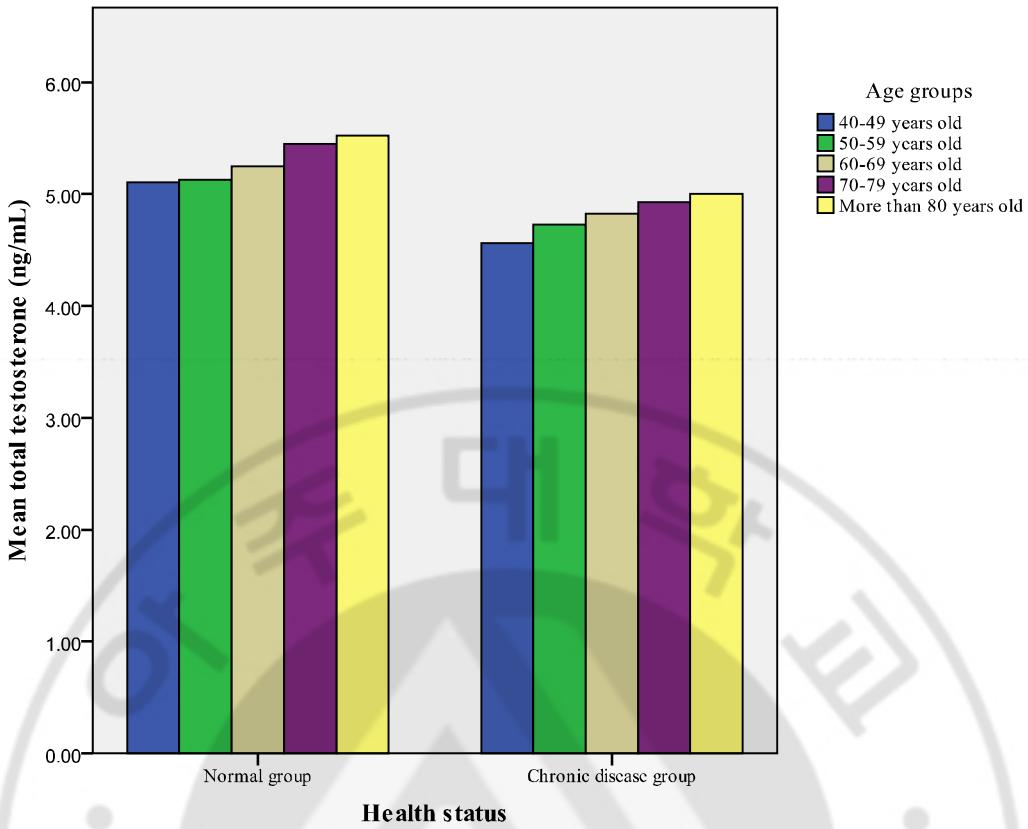

Fig 1. Mean total testosterone according to health status by age groups. Figure 1 illustrates the mean total testosterone between normal group and diseased group by age groups. Total testosterone did not decrease with age. Compare among the age groups, one way ANOVA test was used. P=0.25

Comparing the total testosterone level in disease subgroups and normal groups, subjects who had metabolic syndrome, hypertension and diabetes had lower mean total testosterone than normal group (Table 3).

Table 3. Mean total testosterone according to health status.

		Metabolic syndrome	Hypertension	Diabetes	Stroke
Mean value of total testosterone (ng/mL)	Normal	5.15 (n=2241)			
	Disease	4.55 (n=991)	4.74 (n=1505)	4.64 (n=518)	4.70 (n=24)
P value		< 0.001	< 0.001	< 0.001	0.16

To compare between normal group and chronic disease group, independent sample t-test was used.

Odds ratios and 95% CI of hypogonadism according to health status were listed in Table 4. Control group was the reference group. The unadjusted odds ratio of the hypogonadism compared with normal versus diseased group was 1.595(95% CI, 1.355-1.876, P<0.001). After adjustment for age, BMI, smoking status, waist circumference, systolic blood pressure, diastolic blood pressure, high density lipoprotein, and fasting blood sugar, odds ratio was 1.273(95% CI, 1.033-1.570, P=0.024).

Table 4. Odds ratio of hypogonadism according to health status

	Model 1	Model 2	Model 3	Model 4
	Odds ratios (95% CI)			
LOH in normal population	1.00			

LOH in chronic disease population	1.595(1.355-1.876)	1.681(1.424-1.984)	1.451(1.218-1.728)	1.273(1.033-1.570)
p-value	<0.001	<0.001	<0.001	0.024

Abbreviations: LOH, late onset hypogonadism; WC, Waist circumference; BMI, Body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein.

Model 1: Unadjusted, Model 2: Adjusted for age, Model 3: Adjusted for age, BMI and smoking status, Model 4: Adjusted for age, BMI, smoking status, WC, SBP, DBP, HDL, and fasting blood sugar

IV. Discussion

Our results show that total testosterone does not decrease with age. It is influenced by chronic diseases. Compared to the normal population, people having chronic diseases seemed to have 1.6 times higher probability to affect hypogonadism. So we can estimate that the hypogonadism is easier to be affected in people who have chronic diseases.

Multiple mechanisms might explain that people with co-morbidities have low total testosterone. TNF-α, Interleukin-1 and Interleukin-6 in systemic inflammation have been shown to independently reduce testosterone level(Balasubramanian and Naing, 2012). Variety of medications that they take including ACE inhibitors, ARBs, spironolactones, ketoconazoles, steroids, and statins also alter the synthesis of testosterone(Carrero and Stenvinkel, 2012). As observed in several chronic diseases, low testosterone might have a protective role by turning off energy consuming T-dependent functions such as reproduction and physical labor(Buvat et al., 2013).

This study shows that the mean total testosterone was lower in disease group. Disease group also were older, more obese and had higher blood pressure. Comparing the mean total testosterone of normal people to the subgroups of chronic disease, people who had metabolic syndrome, hypertension, and diabetes had lower testosterone, respectively.

Some cross-sectional studies, including a Korean study, could not find the decline of total testosterone with age(Kang et al., 2003; Li et al., 2005; Halmenschlager et al., 2011). In recent report, Kim et al. illustrated that total testosterone may not decline with aging(Kim et al., 2012). These studies are consistent with our results. High BMI, central adiposity and metabolic syndrome were reported to predict low total testosterone(Haring et al., 2009). In our study, the disease group had higher BMI, central obesity, and they had low total testosterone. Also, in metabolic syndrome population, total testosterone was lower than normal population. So in our study, we suggest that the total testosterone was influenced by

disease status, not by aging.

Our study has some limitations. First, the population is not representative of the general population. The subjects participated voluntarily in the health promotion program. So they may be relatively healthier. Second, the definition of diseased group was too limited. We only included the subjects who met the categories of metabolic syndrome, hypertension, diabetes, and stroke. Other testosterone associated diseases could not be included. Third, we only considered total testosterone. SHBG and free testosterone may play some roles. But in our study, we did not consider it. Fourth, a single testosterone measurement in the study subjects may inadequately reflect the average sex hormone release. Fifth, it was a cross-sectional study, which explains associations but not causality.

V. Conclusion

In conclusions, in the observations of over 40 year old men, the total testosterone level was lower in chronic diseased group compared to healthy subjects. The total testosterone was influenced by disease status, not by aging. Especially in metabolic syndrome, hypertension and diabetes, total testosterone levels were lower than normal population. Further studies including various disease categories are needed.

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– 국문요약 –

노화가 아니라 질환이 남성호르몬과 관련이 있을 수 있다

아주대학교 대학원의학과

최정우

(지도교수: 김광민)

1) 연구배경:

일반적으로 테스토스테론은 나이가 들수록 감소한다고 알려져 있다. 하지만 최근의 연구에 따르면 테스토스테론의 감소 및 남성갱년기는 노화와의 연관성 보다는 만성질환을 포함한 다른 조건에 의할 것이라고 조심스럽게 언급되고 있다. 그러므로 본 연구는 남성호르몬에 영향을 주는 주요 인자 중 질환에 의한 영향을 알아보고자 한다.

2) 방법:

2008년부터 2013년까지 40세 이상의 남성 4,283명을 대상으로 질병군 및 정상군으로 나누어 총 테스토스테론을 포함한 혈액검사 및 임상자료를 두군간에 비교하였다.

3) 결과:

금번 연구에서 2,041명이 질병군(47.6%), 2,243명이 정상군(52.4%)이며 총 테스토스테론과 나이(r=0.032, P=0.034), HDL(r=0.133, P<0.001) 은 각각 양의 상관관계를 보이며, BMI(r=-0.198, P<0.001), 복부둘레(r=-0.184, P<0.001), 혈압, ALT(r=-0.132, P<0.001), 공복혈당(r=-0.105, P<0.001), TG(r=-0.119, P<0.001) 및 알부민(r=-0.108, P<0.001)은 각각 총 테스토스테론과 음의 상관관계를 보였다. 총 테스토스테론은 나이에 따라 증가하지 않았으며, 대사증후군, 고혈압, 및

당뇨병이 있는 사람들은 정상군에 비해 총 테스토스테론이 낮았다. 질병군이 남성갱년기에 이환될 확률이 정상군이 남성갱년기에 이환될 확률보다 1.595(95% CI, 1.355-1.876)배 높았다.

4) 결론:

정상군에서보다 질병군에서 총테스토스테론이 낮았다. 총테스토스테론은 나이가 아니라 질병에 의해 영향을 받는다.

핵심어 : 총 테스토스테론, 만성질환, 남성갱년기, 노화