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RELATIONSHIP BETWEEN TESTOSTERONE DEFICIENCY AND THE CARDIOVASCULAR RISK FACTORS, DIABETES, AND HYPERTENSION

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ABSTRACT

Background and objective

Testosterone deficiency (TD) increases the incidence of cardiovascular risk factors such as diabetes and hypertension. Conversely, TD is reported in people with obesity and diabetes. Therefore, this study examines the relationship between TD, diabetes, and hypertension by following a longitudinal design.

Material and methods

In this study, 2242 (1490 middle-aged and 752 elderly) healthy men were followed up for 8 years and the incidence of hypertension or diabetes was determined.

The diagnostic criteria for hypertension were systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg, and the criterion for diabetes was a fasting blood glucose level ≥126 mg/dL; the men who took medication for hypertension or diabetes were considered diseased. The threshold for TD was 2.5 ng/mL of serum testosterone. Subsequently, the relative risk (RR) of disease according to the testosterone level was analyzed. In addition, the RR of TD according to glucose and blood pressure levels was analyzed for men with normal testosterone at the initial examination.

Results

The TD incidence rates were 12.2 and 16.8% for middle-aged and elderly men, respectively. Among the middle-aged men, the diabetes incidence rates were 11.7 and 5.7% in the TD and non-TD (NTD) groups, respectively; the RR of diabetes increased by 1.771 times in the TD group relative to the NTD group ($p<0.001$). Among the elderly men, the RR of hypertension and diabetes increased by 1.573 and 1.649 times, respectively, in the TD group, compared to the NTD group. Among those with normal testosterone

levels at the initial examination, prehypertension (PHTN) increased the RR of TD by 2.421 and 3.091 times for middle-aged and elderly men, respectively, compared to those with normal blood pressure. Moreover, an impaired fasting glucose level at baseline increased the RR of TD by 1.710 times in middle-aged men and 2.187 times in elderly men, compared to those with normal glucose levels.

Conclusion

In men, TD increased the risk of diabetes and hypertension, which are cardiovascular risk factors.

Keywords: *cardiovascular disease; diabetes; hypertension; risk; testosterone*

INTRODUCTION

Cardiovascular disease is a major cause of death, and hypertension and diabetes are two of the major risk factors for cardiovascular disease. It is estimated that, worldwide, 34.9 and 8.8% of the adult population have high blood pressure and diabetes, respectively.[1,2] Testosterone is the primary sex hormone in men. Secreted predominantly by the testes, testosterone regulates sexual desire, fertility, muscle mass, and personality in men.[3–5] Testosterone deficiency (TD), a condition in which testosterone levels are below normal, has adverse health effects.[6,7] The incidence of TD is reported to be 6–9.5% in men aged 40–70 years and to increase to 15–30% in men with diabetes or obesity.[8] In a study measuring testosterone in South Koreans aged 40–80 years old, <2.5 ng/mL people were 13.4%.[9] The representative causes of TD or low testosterone levels are aging and genetic factors; furthermore, people with cardiovascular risk factors, such as obesity, diabetes, and high blood pressure, have a high propensity for TD.[10–12] Conversely, TD is known to increase the risk of cardiovascular disease,[13] as the incidence of chronic and cardiovascular diseases, as well as TD, is closely related to aging. Therefore, the action of various aging-related physiological, psychological, and socio-environmental factors makes the elucidation of the causality between TD and cardiovascular disease very challenging, although many studies have examined this aspect. We examined the hypothesis that TD would increase the risk of hypertension and diabetes, which are cardiovascular risk factors. This study used a longitudinal research design to investigate the relationship among TD, diabetes, and hypertension. Their relative risks (RRs) of hypertension and diabetes according to the presence or absence of TD were analyzed. In addition, RR of TD according to high blood pressure and glucose was analyzed in participants with normal testosterone.

METHODS

Participants and Process

The men who participated in health screening from 2005 to 2008 were followed up till 2016. Among the 29,364 men aged 40–79 years who participated in the initial examination, 6772 underwent the testosterone test. The study also considered men with systolic and diastolic pressures in the normal range, that is, <140 and <90 mmHg, respectively.[14] The study excluded men with hypertension (systolic pressure ≥140 mmHg, diastolic pressure ≥90 mmHg) or diabetes (fasting glucose level ≥126 mg/dL) and those who had been previously diagnosed with hypertension or diabetes and were taking relevant medication. Finally, the study included 2242 men (middle-aged men of 40–59 years: 1490; elderly men of 60–79 years: 752) who agreed to participate in follow-up examinations and allow the use of their test results for research purposes. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki,

and the protocol was approved by the Institutional Review Board (AMC IRB center 2016-0084).

Examination and Diagnosis

Participants were examined between 8 and 10 am after they had fasted for 8 h. Their blood pressure was measured and hypertension assessed based on the guidelines of the 7th Joint National Committee and the Korean Society of Hypertension.[14,15] Prior to conducting the sitting blood pressure measurement, the participants first sat in a chair and rested for at least 5 min. Subsequently, the cuff was wrapped around the upper arm such that the position of the brachial artery was at the same level as the heart. Prior to inflation, the length of the cuff bladder was approximately 80% of the circumference of the arm. After sufficiently increasing the pressure to the point at which the pulse could not be detected, the examiner decreased the pressure by 2 mmHg per second and recorded the pressure at which the pulse could be re-detected.

Blood samples were collected between 7 and 9 am and analyzed using an enzymatic method through an automated chemical analyzer (TBA-200FR; Toshiba, Tokyo, Japan). To measure serum testosterone, a radioimmunoassay kit (TESTO CT2; Cisbio Bioassays, Codolet, France) was used. Through these processes, the participants' total cholesterol, triglyceride, high-density lipoprotein (HDL), and low-density lipoprotein values were obtained. Diabetes was diagnosed based on fasting glucose levels according to the following criteria: normal glucose (NGL), ≤99 mg/dL; impaired fasting glucose (IFG), 100–125 mg/dL; and diabetes, ≥126 mg/dL or whether the participant was currently taking any medication to control diabetes.[16] PHTN range was systolic 130–139 and diastolic 80–89 mmHg, respectively.[14] The testosterone and glucose levels were collected by a professional nurse. Testosterone reflects the measurement of serum total testosterone. Finally, TD and non-TD (NTD) were defined as ≤2.5 and >2.5 ng/mL testosterone, respectively, based on earlier studies.[9,17]

Data Analysis

All analyses were performed using SPSS version 25.0 (SPSS IBM Corp., New York). General characteristics were reported as averages and standard deviations and compared between the TD and NTD groups using an independent *t*-test. The incidence of hypertension, diabetes, and TD according to the group was evaluated by the Chi-square test, and Cox regression analysis was used for RR. RR was analyzed in two ways. First, RR of diabetes and hypertension according to the presence or absence of TD was analyzed. Next, the incidence of TD was analyzed according to the presence or absence of high blood pressure and glucose in people with normal testosterone levels. The adjustment included variables obtained through multiple regression analysis. Adjusted variables were body mass index (BMI), high-density lipoprotein cholesterol (HDLC), triglyceride, and age. The significance level was set as $p<0.05$.

RESULTS

General Characteristics

Table 1 compares the general characteristics of middle-aged and elderly participants. The results reveal significant differences in age, height, weight, BMI, and testosterone levels. Furthermore, Table 2 compares the participants' general characteristics between TD and NTD groups. The TD incidence rates were 12.2 and 16.8% in middle-aged and elderly men, respectively. There were significant differences in body weight, BMI, glucose levels, HDLC, and triglyceride levels between middle-aged men in the TD and NTD groups ($p<0.05$). Furthermore, significant differences in systolic blood pressure, glucose, and triglyceride were found between elderly men in the TD and NTD groups ($p<0.05$).

RR of Diabetes and Hypertension According to TD

Table 3 reveals the RR of hypertension and diabetes according to the presence or absence of TD.

TABLE 1 General Characteristics of Participants (n = 2242).

Characteristic	MA (n = 1490)	ELD (n = 752)	P
Age, years	49.7 ± 5.1	64.3 ± 3.9	<0.001*
Height, cm	170.3 ± 5.6	168.8 ± 5.8	<0.001*
Weight, kg	71.9 ± 8.3	71.0 ± 7.9	<0.001*
BMI, kg/m^2	24.8 ± 2.4	25.2 ± 2.4	0.012*
Testosterone, ng/mL	7.57 ± 3.2	6.65 ± 3.1	<0.001*

BMI, body mass index; ELD, elderly; MA, middle-aged men.
**p<0.05.*

TABLE 2 Comparison between TD and NTD (n = 2242).

Characteristic	MA (n = 1490)		ELD (n = 752)	
	NTD	TD	NTD	TD
N (%)	1308 (87.8%)	182 (12.2%)	626 (83.2%)	126 (16.8%)
Age, years	49.7 ± 5.1	50.4 ± 5.7	64.2 ± 3.8	65.4 ± 4.9
Height, cm	170.4 ± 5.6	169.7 ± 5.5	168.7 ± 5.7	169.1 ± 7.2
Weight, kg	71.8 ± 8.3	74.6 ± 9.6*	69.9 ± 7.7	71.9 ± 11.5
BMI, kg/m^2	24.7 ± 2.4	25.9 ± 2.7*	24.9 ± 2.4	25.6 ± 2.8
SBP, mmHg	123.9 ± 13.7	124.0 ± 12.6	128.8 ± 15.8	136.0 ± 13.3*
DBP, mmHg	77.8 ± 9.1	77.0 ± 8.5	77.5 ± 8.4	77.8 ± 11.5
Glucose, mg/dL	102.3 ± 19.8	110.4 ± 31.8*	105.8 ± 23.2	113.6 ± 27.3*
TC, mg/dL	196.3 ± 31.8	199.9 ± 35.9	185.8 ± 31.2	193.1 ± 31.3
HDLC, mg/dL	52.6 ± 14.8	48.3 ± 11.7*	50.3 ± 11.5	50.8 ± 11.7
LDLC, mg/dL	128.0 ± 28.4	129.8 ± 30.2	118.1 ± 26.0	125.6 ± 26.8
TG, mg/dL	154.3 ± 87.7	186.5 ± 111.1*	124.9 ± 57.8	140.1 ± 81.0*
Testosterone, ng/mL	8.33 ± 2.88	2.92 ± 0.62*	7.45 ± 2.62	2.46 ± 0.76*

**p<0.05; BMI, body mass index; DBP, diastolic blood pressure; ELD, elderly; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; MA, middle-aged men; NTD, nontestosterone deficiency; SBP, systolic blood pressure; TC, total cholesterol; TD, testosterone deficiency; TG, triglyceride.*

The incidence rates of hypertension in middle-aged participants were 12.8 and 13.5% in the NTD and TD groups, respectively; this difference was not found to be significant. Among all the participants, diabetes occurred in 5.7 and 11.7% of men in the NTD and TD groups, respectively. Furthermore, the RR of diabetes increased by 1.771 times (95% confidence interval [CI], 1.252–2.506; p<0.001) in the TD group, compared to the NTD group. Among the elderly men, the RR of hypertension increased by 1.573 times (95% CI, 1.150–2.152; p=0.005) and that of diabetes increased by 1.649 times (95% CI, 1.043–2.607; p=0.032) in the TD group, compared to the NTD group.

RR of TD in People with PHTN and IFG Levels

Table 4 shows the results of follow-up of 1308 middle-aged and 626 elderly people with normal

TABLE 3 Relative Risks of Diabetes and Hypertension according to the Testosterone Level (n = 2242).

	DG	NDG	χ^2, p	RR (95% CI)	p
MA, Hypertension					
NTD	167 (12.8%)	1141 (87.2%)	0.542	Reference	–
TD	25 (13.5%)	157 (86.5%)		1.026 (0.789–1.335)	0.845
MA, Diabetes					
NTD	75 (5.7%)	1233 (94.3%)	0.002*	Reference	–
TD	21 (11.7%)	161 (88.3%)		1.771 (1.252–2.506)	<0.001*
ELD, Hypertension					
NTD	119 (19.0%)	507 (81.0%)	0.005*	Reference	–
TD	40 (31.7%)	86 (68.3%)		1.573 (1.150–2.152)	0.005*
ELD, Diabetes					
NTD	65 (10.4%)	561 (89.6%)	0.012*	Reference	–
TD	23 (18.3%)	103 (81.7%)		1.649 (1.043–2.607)	0.032*

**p<0.05; CI, confidence interval; DG, disease group; ELD, elderly; MA, middle-aged men; NDG, nondisease group; NTD, nontestosterone deficiency; RR, relative risk; TD, testosterone deficiency.*
Note. The adjusted variables are body mass index, high-density lipoprotein cholesterol, triglyceride, and age.

TABLE 4 RR of TD according to Blood Pressure and Glucose Levels (n = 1934).

		NTD	TD	χ^2, p	RR (95% CI)	p
MA, n (%)		1225 (93.7%)	83 (6.3%)			
BP	NBP	961 (95.5%)	45 (4.5%)	<0.001*	Reference	–
	PHTN	264 (87.4%)	38 (12.6%)		2.421 (1.275–5.782)	0.002*
Glucose	NGL	858 (96.1%)	35 (3.9%)	0.018*	Reference	–
	IFG	366 (88.2%)	49 (11.8%)		1.710 (1.138–2.569)	0.010*
EDL, n (%)		561 (89.6%)	65 (10.4%)			
BP	NBP	399 (95.2%)	20 (4.8%)	<0.001*	Reference	–
	PHTN	162 (78.3%)	45 (21.7%)		3.091 (1.775–5.386)	<0.001*
Glucose	NBP	363 (93.1%)	27 (6.9%)	0.035*	Reference	–
	IFG	198 (83.9%)	38 (16.1%)		2.187 (1.012–5.312)	0.044*

**p<0.05; BP, blood pressure; CI, confidence interval; ELD, elderly; IFG, impaired fasting glucose; MA, middle-aged men; NBP, normal blood pressure; NGL, normal glucose; NTD, nontestosterone deficiency; PHTN, prehypertension; RR, relative risk; TD, testosterone deficiency.*
Note. The adjusted variables are body mass index, high-density lipoprotein cholesterol, triglyceride, and age.

testosterone in the initial test. The incidence of TD in people with high blood pressure and glucose was analyzed. Groups were divided into normal blood pressure (NBP) and PHTN or NGL and IFG.

Among the middle-aged men, TD occurred in 4.5% of the participants with NBP and 12.6% of those with PHTN; thus, the RR of TD in PHTN increased by 2.421 times (95% CI, 1.275–5.782; p=0.002), compared with the NBP group. In addition, 3.9% of the middle-aged men with NGL and 11.8% of the men with IFG had TD; the RR of TD in the IFG group significantly increased by 1.710

times (95% CI, 1.138–2.569; p=0.010), compared to the NGL group.

Among the elderly men, TD occurred in 4.8% men with NBP and 21.7% men with PHTN; furthermore, the RR of TD increased by 3.091 times (95% CI, 1.775–5.386; p<0.001). In addition, TD occurred in 6.9 and 16.1% of the individuals in the NGL and IFG groups, respectively, and the RR of TD increased by 2.187 times (95% CI, 1.012–5.312; p=0.044) in the IFG group, compared to the NGL group.

DISCUSSION

Testosterone is a representative male sex hormone that diminishes with age. TD has been reported to increase the risk for cardiovascular disease.[18] However, some studies have reported the occurrence of TD in people with obesity, high blood pressure, or diabetes.[10,11] Another study revealed the inverse relationship between metabolic syndrome and testosterone and associated triglycerides and elevated blood pressure with low testosterone.[19] Hence, the causal relationship between testosterone and obesity, hypertension, or diabetes is not clear due to the complex relationship among age, obesity, and other cardiovascular risk factors.[18,20] Therefore, we examined these relationships by conducting a longitudinal study. Our results reveal that the RR of disease is higher in men with TD than in those without TD. These results are similar to those of Torkler et al.,[21] who performed a 5-year follow-up of 1484 patients aged 20–79 years and showed that the incidence of hypertension was 1.19 times higher in patients with TD, compared to those with high testosterone levels. In addition, Svartberg et al.[22] studied the relationship between testosterone and carotid atherosclerosis, in which an intima-media thickness greater than 1.04 mm was considered a significant criterion. Their results showed that carotid atherosclerosis was 1.51 times more prevalent in individuals with the lowest versus the highest quartile of testosterone levels. However, not all studies revealed a relationship between blood pressure and testosterone. For instance, a study by Yang et al.[23] found no significant difference in the testosterone level between hypertensive patients (12.0 ± 4.8 nmol/L) and healthy individuals (13.0 ± 4.5 nmol/L). The physiological mechanisms of testosterone on blood pressure are still debated. Some of the information obtained through animal experiments is as follows. The study suggested that testosterone or 5α-dihydrotestosterone had vasodilating effects on vascular and nonvascular smooth muscle. These effects might be mediated through the inhibition of L-type calcium channels.[24,25]

Our analysis on TD and diabetes revealed that the incidence of diabetes was significantly high in the TD group for both middle-aged (1.7 times) and elderly (1.6 times) men. An earlier study that followed 702 people for 11 years similarly found that men with testosterone levels in the lowest quartile had a 2.3 times higher prevalence of diabetes than those in the highest quartile.[26] Furthermore, people with TD have high insulin resistance[27]; in such people, the ability of the tissues to metabolize glucose and free fatty acids is low. This low metabolic capacity of the tissues increases the blood glucose level and, thereby, the likelihood of diabetes.[27,28] The physiological probability of one study explained as follows. Testosterone function stimulates myogenesis and block adipogenesis in pluripotent cells (C3H 10T1/2) through the androgen receptor-mediated pathway.[29]

However, low testosterone reduces this function, thereby increasing insulin resistance with changes in body composition. Consistent with this concept, a 10-year longitudinal study reported that people with the lowest testosterone levels had the highest insulin resistance.[30] However, the causality of diabetes remains controversial. Since TD is also found in people with diabetes, it is debated whether TD is a cause or an outcome of diabetes.[31–33] In one study, 36.5% of patients with type 2 diabetes had TD, and a higher incidence of TD (below 3.0 ng/mL) was found to be associated with age, obesity,

smoking, a low socioeconomic status, and blood pressure.[33] People with normal weight had a TD of 0.73, and the incidence of TD increased by 2.57 times for those in their 60s, compared to those in their 30s.[33] Yet another study revealed that TD occurred in 21% of people with diabetes and 13% of people without diabetes.[34] It is challenging to elucidate the causal relationships between testosterone and diseases because the factors affecting TD, as well as diabetes, hypertension, and cardiovascular disease, are diverse and complex. Moreover, testosterone levels gradually decline with age. In a study of 1382 patients with a mean age of 54 years, the testosterone level diminishes decreased from 16.2±1.4 nmol/L to 15.6±1.4 nmol/L over a 5-year follow-up period.[35] Similarly, we found that elderly men had a significantly lower testosterone level than middle-aged men. Moreover, the incidence of TD increased from 12.2% for middle-aged men to 16.8% for elderly men. Using the same criteria, another study reported that the TD occurrence rates in Korean men were 11.3% in their 40s, 13.7% in their 50s, 12.9% in their 60s, and 21.6% in their 70s.[9] Although the criteria for TD varied slightly from one study to another, most studies used a range of 2.0–3.5 ng/mL testosterone; most researchers often used a quartile method as well.[6,9,13,33] Since our study was conducted on Korean men, a testosterone level of 2.5 ng/mL was used as the TD threshold, as indicated in an earlier Korean study.[9]

Several earlier studies have reported the negative effects of TD on cardiovascular disease and risk factors, and the beneficial effects of hormone therapy.[36–38] However, in one study, testosterone replacement therapy did not seem to improve cardiovascular risk factors.[39] Although some studies report that increasing testosterone levels through testosterone replacement therapy induces cardiovascular disease and emphasize the risks of testosterone replacement therapy,[40] the majority of the studies on the topic and the general overall opinions support the positive effects of testosterone replacement therapy on cardiovascular disease and erectile dysfunction, and express minimal concern regarding side effects.[39,41,42]

This study's significance is that it longitudinally analyzes TD's effect on the incidence of diabetes and hypertension by dividing participants into two groups based on age. Furthermore, the investigation included a relatively long-term follow-up study, which was conducted separately for the middle-aged and the elderly participants. In addition, we examined the effect of high blood pressure and glucose levels on testosterone. Nevertheless, this study has some limitations. Our study considered serum total testosterone, rather than free testosterone. It is currently known that up to 98% of testosterone is bound to sex hormone–binding globulin or albumin in the body, and only 2–3%, which is a very small amount, is present as free testosterone. Free testosterone is believed to be the metabolically active fraction and is considered important in androgen deficiency diagnosis.[43] However, since this study did not isolate and test free testosterone, it is limited in its representation of TD.

Furthermore, hypogonadism is measured using biochemical tests and questionnaires. Earlier studies have reported that the incidence of late-onset hypogonadism measured using questionnaires was lower than that of hypogonadism measured using biochemical tests.[17] This is because the symptoms of hypogonadism are not only present in low testosterone. Another study examined the influence of hypercholesterolemia, depression, obesity, and diabetes on hypogonadism symptoms, including erectile dysfunction.[44–46] Therefore, rather than performing biochemical tests alone, studies should use questionnaires such as the Aging Male Symptoms (AMS) since the latter are very useful in treating hypogonadism and examine various clinical symptoms.[47] However, our study did not use AMS to examine TD.

In this study, the TD incidence rates were only 12.2 and 16.8% for middle-aged and elderly men, respectively. Due to this low disease incidence, only a low proportion of people were affected and, hence,

considered in the analysis; therefore, future studies should include more participants. Since testosterone levels diminishes slowly in middle-aged men but more rapidly in the elderly, long-term studies may yield different results.

CONCLUSIONS

TD increased the risk of diabetes by 1.7 times for middle-aged men and the risk of diabetes and hypertension by 1.5 and 1.6 times, respectively, for elderly men. In contrast, prehypertension or impaired glucose tolerance increased TD by 2.4 and 1.7 times in middle-aged men and 3.0 times and 2.1 times in elderly men, respectively.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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