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The association between testosterone deficiency and metabolic syndrome in middle-aged and elderly men in Korea: a comparative analytical cross-sectional study

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Abstract

Background: The number of elderly patients with metabolic syndrome is on the rise in Korea. A prevalent indication of aging in males is a decrease in testosterone levels. This study was conducted as a cross-sectional study to analyze the prevalence of metabolic syndrome due to testosterone deficiency in middle-aged and elderly individuals. **Methods**: The participants included 6118 middle-age men aged 40 to 59 and 1542 middle-aged men aged 60 to 79 (7660 participants). A testosterone level of 2.5 ng/mL or less was used as the diagnostic criterion for testosterone deficiency. The study used logistic regression to calculate the odds ratio and find the cut-off value of testosterone for metabolic syndrome. The results showed that 8.3% of middle-aged and 12.9% of elderly individuals had testosterone deficiency, and 39.3% of testosterone deficiency middle-aged and 52.8% of testosterone deficiency elderly individuals had metabolic syndrome. **Results**: Testosterone deficiency had a significantly increased risk of metabolic syndrome (middle-age odds ratio, 1.58; 95% confidence interval, 1.31–1.94 and elderly odds ratio 2.32; 95% confience interval, 1.71–3.13). The cut-off value of testosterone for metabolic syndrome was 4.2 ng/mL in middle-age and 3.9 ng/mL in older age. Engaging in regular physical activity has a posivive impact on metabolic syndrome, leading to a 36% decrease in the likelihood of developing metabolic syndrome in middle-aged individuals who engage in exercise and a 13% decrease in elderly. **Conclusions**: Middle-age and elderly individuals with testosterone deficiency had an increased risk of metabolic syndrome, and exercise had a preventive effect even if they had testosterone deficiency. High exercise and low alcohol consumption reduced metabolic syndrome prevalence even in the presence of testosterone deficiency. The results of this study will provide useful information for preventing metabolic syndrome in people with testosterone deficiency.

Keywords

Testosterone; Deficiency; Metabolic syndrome; Middle-age; Elderly; Cut-off value

Asociación entre la deficiencia de testosterona y el síndrome metabólico en hombres de mediana edad y mayores en Corea del Sur: un estudio transversal analítico comparativo

Resumen

Antecedentes: El síndrome metabólico está aumentando entre los ancianos en Corea del Sur y los niveles bajos de testosterona son uno de los fenómenos del envejecimiento. Una indicación frecuente del envejecimiento en los hombres es una disminución en los niveles de testosterona. Este estudio se realizó como un estudio transversal para analizar la prevalencia del síndrome metabólico debido a la deficiencia de testosterona en personas de mediana edad y mayores. **Métodos**: Los participantes incluyeron 6118 hombres de mediana edad de 40 a 59 años y 1542 hombres de mediana edad de 60 a 79 años (7660 participantes). Un nivel de testosterona de 2.5 ng/mL o menos se utilizó como criterio de diagnóstico para la deficiencia de testosterona. **Resultados**: La deficiencia de testosterona tuvo un riesgo significativamente mayor de síndrome metabólico (odds ratio de mediana edad, 1.58; confience interval del 95%, 1.31–1.94 y odds ratio de ancianos 2.32; confience interval del 95%, 1.71–3.13). El valor de corte de testosterona para el síndrome metabólico fue de 4.2 ng/mL en la mediana edad y de 3.9 ng/mL en la edad avanzada. Realizar actividad física de forma regular tiene un impacto positivo sobre el síndrome metabólico, dando lugar a una disminución del 36% en la probabilidad de desarrollar síndrome metabólico en personas de mediana edad que realizan ejercicio y una disminución del 13% en personas mayores. **Conclusiones**: Las personas de mediana edad y mayores con deficiencia de testosterona tenían un mayor riesgo de síndrome metabólico, y el ejercicio tenía un efecto preventivo incluso si tenían deficiencia de testosterona. El ejercicio intenso y el bajo consumo de alcohol redujeron la prevalencia del síndrome metabólico incluso en presencia de deficiencia de testosterona. Los resultados de este estudio proporcionarán información útil para prevenir el síndrome metabólico en personas con deficiencia de testosterona.

Palabras Clave

Testosterona; Deficiencia; Síndrome metabólico; Edad mediana; Ancianos; Valor de corte

1. Introduction

Cardiovascular disease is one of the leading causes of death worldwide, and metabolic syndrome (MS) is considered a precursor to it. In Korea men, the prevalence of MS increased significantly from 25.8% in 2001 to 40.0% in 2020 [1]. While multiple factors can lead to MS, such as insufficient physical activity and imbalanced dietary choices, aging stands out as a significant influencer. With advancing age, individuals experience various physiological transformations, including reduced cardiovascular and metabolic capabilities, as well as a decline in testosterone levels, all of which contribute to the development of MS [2, 3].

Testosterone is a hormone that is primarily produced in the testes and is associated with the development of male characteristics. These encompass a heightened libido, improved erectile capabilities, the emergence of facial and body hair, as well as the formation of secondary sexual characteristics and individual traits. Testosterone is also important for the growth of muscles and bones, as well as the maintenance of healthy skin and bone [4]. Healthy adults are advised to maintain a testosterone level of 2.5 ng/mL, with levels below this threshold classified as testosterone deficiency (TD). According to the Jäger study, TD was identified in 15.2% of men [5]. Although men with TD may experience symptoms such as difficulty with sexual desire or erections, fatigue, loss of muscle mass and irritability, many men have no symptoms at all. Hence, it is crucial to undergo testing for TD in order to detect possible cases, as there is a likelihood that numerous men are unaware of their condition [6].

Research shows that non-smokers tend to have 4–9% higher testosterone levels than smokers [7], and those who consume alcohol excessively have a 4.37-fold increased risk of developing TD compared to non-drinkers [8]. Despite the ongoing debate regarding the potential dangers of TD, research indicates that it may influence the development of cardiovascular disease or multiple sclerosis. A study conducted by Lopez *et al*. [9], found that individuals with low testosterone had a 1.72-fold increased risk of myocardial infarction and a 1.74-fold increased risk of heart failure. Meanwhile, individuals with elevated levels of testosterone exhibited a 31% lower likelihood of developing MS in comparison to those with low testosterone [10].

Despite its significance, there is still a lack of research related to TD. The majority of research distinguishes between testosterone levels that fall below TD or compares testosterone levels across various groups. Nonetheless, gathering adequate data on TD proves to be difficult because of its low prevalence and the necessity to contrast it with TD among MS patients [11]. Also, as Korea's elderly population is aging rapidly, and the prevalence of cardiovascular disease and MS is increasing, there is a need to continue research on TD and MS. Therefore, the purpose of this study is to explore the frequency of MS in relation to TD using a substantial amount of data. Additionally, the study attempts to suggest a threshold value of total testosterone for MS using a receiver operating characteristic (ROC) curve. We hypothesized that there would be a significant increase in MS prevalence in individuals with TD and that health behaviors would be positively affected.

2. Methods

2.1 Participant and study process

This study was conducted on individuals who visited a health screening center in Seoul Asan Medical Center from January to December 2022. The study was a cross-sectional single-center study. The center visitors did not suffer from severe illnesses. They voluntarily underwent various tests to proactively manage their health, bearing the costs themselves. The data analyzed in this study was collected only from the individuals who provided their consent for various tests, analysis and publication. The study objectives and benefits were explained to participants verbally as well as in written form. Initially, data from 10,996 people aged 40 to 79 years were collected, and data from 3336 people were excluded. Reasons for exclusion included failure to complete relevant medical tests or questionnaires, failure to consent to the study and publication, and history of urological or cardiovascular disease (Fig. 1). A total of 7660 people analyzed in the study, out of which 6118 individuals were middle-aged and 1542 were elderly. The data has been encoded and stored using random numbers to ensure confidentiality. Visitors to the health screening center did not have severe disease and were selected to undergo a clinical test set consisting of a series of tests. Some visitors were able to opt in or decline additional medical screening.

2.2 Metabolic syndrome

MS applied the guidelines of the Adult Treatment Panel III from National Cholesterol Education Program (NCEP-ATPIII) [12], and waist circumference followed Korean guidelines [13]. MS was characterized by the presence of 3 to 5 of the following five risk factors: (1) An elevated waist circumference (WC) of $\geq$90 cm; (2) Elevated serum triglyceride (TG) $\geq$150 mg/dL; (3) Low levels of high-density lipoprotein cholesterol (HDLc), defined as $<$40 mg/dL; (4) Elevated blood pressure (BP), defined as systolic blood pressure (SBP) $\geq$130 mmHg or diastolic blood pressure (DBP) $\geq$85 mmHg, or current use of antihypertensive medications; and (5) Elevated glucose (hyperglycemia), defined as $\geq$100 mg/dL, or current use of antidiabetic medications.

2.3 Blood sample collection

Blood collection was performed at a single location between 8:00 and 10:00 AM. All visitors were required to have an empty stomach for at least 8 hours, register at the center, change into light gowns and consult with a doctor before undergoing the planned examination. After checking the patient's basic vital signs and allowing them to rest for about 20 minutes, a nurse collected 15 mL of blood from the median cubital vein using a syringe. Serum was separated from the collected blood by centrifugation at 3000 rpm for 15 minutes, and then enzyme analysis was performed using an automated chemical analyzer (TBA-200FR; Toshiba, Tokyo, Japan). The serum total testosterone levels were measured using a radioimmunoassay kit (TESTO CT2; Cisbio Bioassays, Codolet, France). In this study, people with a TD of 2.5 ng/mL or less were included [5].

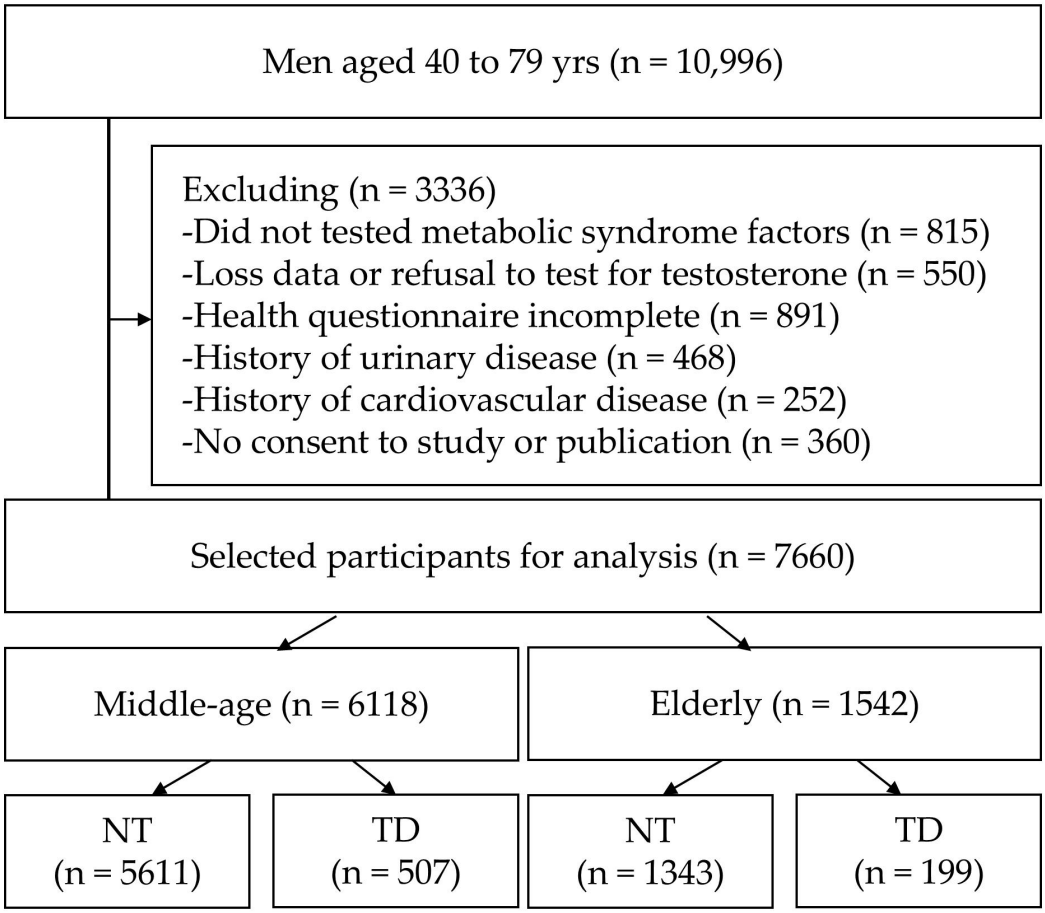

FIGURE 1. Participant's flow. Data were selected in the following order. Men data were first collected by age, and participants were excluded to reduce bias, finally, middle-aged and elderly were separated to NT and TD groups. Abbreviation: yrs, years; NT, normal testosterone; TD, testosterone deficiency.

2.4 Health-related questionnaire

To assess the status of active health management, a questionnaire was created and distributed by the credible World Health Organization [14–16]. The questionnaire examined the behaviors related to smoking, alcohol consumption and exercise habits. The most representative questions were extracted one by one and analyzed. For smoking, participants were asked to select one of the following: 1 = no experience at all, 2 = quitting smoking and 3 = currently smoking. For alcohol consumption, participants were asked to choose from 1 = less than once a week, 2 = 2–3 times a week, 3 = more than 4 times a week. For exercise, participants were asked to indicate how many days per week they exercised: 1 = 3–7 days a week, 2 = 1–2 days a week and 3 = 0 days a week.

2.5 Data analysis

The data analysis for this study was carried out using SPSS 23.0 (IBM Corporation, Armonk, NY, USA). Variables were analyzed separately, with individuals in their 40s and 50s defined as middle-age and those in their 60s and 70s defined as elderly. The first thing that was performed was the Kolmogorov-Smirnov test, which was used to test normality and was analyzed using a parametric statistical method. Mean and standard deviation were used to present MS variables and general information, and an independent *t*-test was used to compare groups. Information regarding alcohol consumption, smoking and exercise was obtained from a questionnaire and was categorized into 3 or 4 levels and analyzed using a chi-square test. Stepwise multiple regression analysis was used to identify the MS factors that affect testosterone. Health behavior variables that appeared significant were considered confounding factors and adjusted variables. Binary logistic regression analysis was used to calculate the adjusted odds ratio (OR). Finally, the Receiver Operating Characteristic (ROC) curve analysis method was used to present guidelines for TD prevention, using MedCalc 11.4. A (MedCalc, Ostend, Belgium). The area of under the curve (AUC), sensitivity and specificity were determined, with a confidence interval (CI) of 95% and a significance value of 0.05.

3. Results

3.1 General characteristics

The prevalence of TD was 8.3% in middle-aged patients and 12.9% in elderly patients. The study revealed that the TD group was of a more advanced age compared to the NTD group. In addition, the middle-aged and elderly individuals in the TD group exhibited lower levels of HDLc and notably higher diastolic blood pressure (DBP) in comparison to the

NT group. It was observed that height was significantly reduced only in elderly TD patients. With regards to health habits, such as drinking, smoking and exercise, there were significant differences between groups in all three categories in the middle-aged group. However, only drinking and exercise were significant in the elderly group (Table 1).

3.2 Metabolic components and testosterone deficiency

Patients with TD who are middle-aged displayed a significant increase in MS across all areas except for HDLc. In contrast, elderly patients did not show any relationship between glucose and TD. In comparison to the NT group, the MS in the TD group rose by a factor of 1.58, and in the group of elderly participants, it surged by 2.32 times (95% CI, 1.71–3.13). Triglyceride had the highest OR value, and the TD group's OR increased in comparison to the NT group (middle-aged: OR, 1.57; 95% CI, 1.31–1.88 and elderly: OR, 2.00; 95% CI, 1.48–2.70) (Table 2).

3.3 Multi-regression about metabolic syndrome components for testosterone deficiency

Multiple regression analysis was performed to examine the effect of MS components on testosterone levels in middle-age and elderly individuals. The study findings indicated that waist size, systolic and diastolic blood pressure, as well as triglyceride levels, were important factors influencing testosterone levels ($p < 0.05$). However, excluded variables such as HDLc and glucose were not significant ($p > 0.05$) (Table 3).

3.4 Health behavior and metabolic syndrome prevalence in the testosterone deficiency group

Fig. 2 is a graph of the OR of MS according to health habits such as alcohol frequency, smoking experience, and exercise

TABLE 1. General characteristics of testosterone normal and deficiency.

Variables	Middle-age (n = 6118)		*p*	Elderly (n = 1542)		*p*
	NT n = 5611, 91.7%	TD n = 507, 8.3%		NT n = 1343, 87.1%	TD n = 199, 12.9%	
Age, yr	50.5 ± 4.9	51.3 ± 4.9	<0.001	64.7 ± 4.2	65.5 ± 4.9	0.032
Height, cm	170.2 ± 6.9	170.1 ± 5.7	0.662	168.4 ± 5.7	167.1 ± 6.2	0.027
Weight, kg	71.9 ± 9.2	73.9 ± 9.2	<0.001	69.7 ± 8.4	71.1 ± 12.2	0.039
Body mass index, kg/m^2	24.8 ± 2.7	25.5 ± 2.6	<0.001	24.5 ± 2.5	25.1 ± 4.1	0.004
Waistline, cm	86.2 ± 7.0	88.1 ± 6.9	<0.001	87.1 ± 7.1	89.2 ± 8.4	<0.001
Systolic BP, mmHg	119.8 ± 12.8	122.1 ± 13.5	<0.001	123.1 ± 14.4	126.9 ± 13.9	<0.001
Diastolic BP, mmHg	76.9 ± 9.2	77.6 ± 8.8	0.092	76.0 ± 8.6	76.6 ± 8.3	0.416
HDLc, mg/dL	51.8 ± 12.3	51.0 ± 11.3	0.153	52.6 ± 12.9	51.3 ± 13.7	0.201
Triglyceride, mg/dL	148.1 ± 94.0	158.7 ± 90.8	0.015	125.8 ± 65.1	147.9 ± 103.9	<0.001
Fast glucose, mg/dL	104.7 ± 21.7	106.8 ± 22.3	0.035	106.4 ± 20.3	111.9 ± 31.5	<0.001
MS, n (%)	1627 (29.0%)	199 (39.3%)		437 (32.5%)	105 (52.8%)	
Alcohol frequency						
Low	2306 (41.1%)	177 (35.0%)		741 (55.2%)	92 (46.2%)	
Medium	2222 (39.6%)	204 (40.2%)	0.005	391 (29.1%)	64 (32.0%)	0.014
High	1083 (19.3%)	126 (24.8%)		211 (15.7%)	43 (21.8%)	
Smoking experience						
Never	1156 (20.6%)	95 (18.7%)		344 (25.6%)	52 (26.1%)	
Quitting	2873 (51.2%)	234 (46.1%)	<0.001	741 (55.2%)	108 (54.3%)	0.872
Current	1582 (28.2%)	178 (35.2%)		258 (19.2%)	39 (19.6%)	
Exercise attendance						
High	685 (12.2%)	48 (9.5%)		381 (28.4%)	59 (29.6%)	
Medium	1969 (35.1%)	158 (31.1%)	0.041	488 (36.3%)	72 (36.2%)	0.922
Low	2957 (52.7%)	301 (59.4%)		474 (35.3%)	68 (34.2%)	

$p < 0.05$ indicates a statistically significant difference between NT and TD in independent t-test and chi-square test; abbreviation: NT, normal testosterone; TD, testosterone deficiency; MS, metabolic syndrome; yr, years; BP, blood pressure; HDLc, high density lipoprotein cholesterol.

TABLE 2. Odd ratio of metabolic syndrome risk factors for testosterone deficiency.

Variables	Group	Middle-age			Elderly		
		MS, no risk	MS, risk	Odds ratio (95% CI)	MS, no risk	MS, risk	Odds ratio (95% CI)
Waistline and TD							
	NT	3974 (70.8%)	1637 (29.2%)	1.00	877 (65.3%)	466 (34.7%)	1.00
	TD	324 (63.9%)	183 (36.1%)	1.37 (1.13–1.66)	109 (54.8%)	90 (45.2%)	1.55 (1.15–2.10)
Blood pressure and TD							
	NT	3276 (58.4%)	2335 (41.6%)	1.00	565 (42.1%)	778 (57.9%)	1.00
	TD	269 (53.1%)	238 (46.9%)	1.24 (1.03–1.49)	59 (29.6%)	140 (70.4%)	1.72 (1.25–2.38)
HDLc and TD							
	NT	4841 (86.3%)	770 (13.7%)	1.00	1172 (87.3%)	171 (12.7%)	1.00
	TD	436 (86.0%)	71 (14.0%)	1.02 (0.79–1.33)	158 (79.4%)	41 (20.6%)	1.78 (1.22–2.60)
Triglyceride and TD							
	NT	3175 (56.6%)	2436 (43.4%)	1.00	855 (63.7%)	488 (36.3%)	1.00
	TD	230 (45.4%)	277 (54.6%)	1.57 (1.31–1.88)	93 (46.7%)	106 (53.3%)	2.00 (1.48–2.70)
Glucose and TD							
	NT	2696 (48.0%)	2915 (52.0%)	1.00	569 (42.4%)	774 (57.6%)	1.00
	TD	199 (39.3%)	308 (60.7%)	1.43 (1.19–1.72)	82 (41.2%)	117 (58.8%)	1.05 (0.78–1.42)
MS and TD							
	NT	3984 (71.0%)	1627 (29.0%)	1.00	906 (67.5%)	437 (32.5%)	1.00
	TD	308 (60.7%)	199 (39.3%)	1.58 (1.31–1.91)	94 (47.2%)	105 (52.8%)	2.32 (1.71–3.13)

$p < 0.05$ indicates a statistically significant difference between NT and TD in Chi-square test and logistic regression; adjusted variables: middle-age: age, alcohol, smoking, exercise; elderly: age alcohol, exercise; abbreviation: NT, normal testosterone; TD, testosterone deficiency; HDLc, high density lipoprotein cholesterol; CI, confidence interval; MS, metabolic syndrome.

TABLE 3. Multi regression of metabolic syndrome components for testosterone deficiency.

Variables	Middle-aged				Elderly			
	Un-standardized coefficients B	Standardized coefficients B	*t*	*p*	Un-standardized coefficients B	Standardized coefficients B	*t*	*p*
Waistline	−0.027	−0.101	−7.394	<0.001	−0.023	−0.088	−3.334	<0.001
Systolic BP	−0.025	−0.169	−7.341	<0.001	−0.025	−0.193	−5.037	<0.001
Diastolic BP	0.026	0.124	5.373	<0.001	0.033	0.150	3.935	<0.001
Triglyceride	−0.001	−0.039	−2.826	0.005	−0.002	−0.088	−3.176	0.002
HDLc	0.003	0.017	1.243	0.214	0.002	0.012	0.424	0.672
Glucose	−0.001	−0.013	−0.998	0.318	−0.002	−0.020	−0.768	0.443

$p < 0.05$ indicates a statistically significant variables in multiple regression; Abbreviation: BP, blood pressure; HDLc, high density lipoprotein cholesterol.

frequency, including only those with TD. In the middle-aged group, there was a 25% (OR, 0.75; 95% CI, 0.56–0.92) reduction in low alcohol frequency, a 14% (OR, 0.86; 95% CI, 0.72–0.98) reduction in those who never smoked, and a 36% (OR, 0.64; 95% CI, 0.41–0.86) reduction in the group that exercised frequently. Conversely, among elderly individuals, there was a 17% (OR, 0.83; 95% CI, 0.70–0.95) reduction in low alcohol consumption frequency, a 13% (OR, 0.87; 95% CI, 0.67–0.94) decrease in high exercise frequency, and smoking showed no significant impact.

3.5 Receiver operating characteristic curve of testosterone for metabolic syndrome

The ROC identified the testosterone cut-off value that can be used to identify MS and its risk factors. In middle-aged people, the testosterone cut-off value for MS ranged from 3.9 to 4.4 ng/mL, while for MS it was 4.2 ng/mL. Above the cut-off value, MS was found to decrease by 31%. For elderly people, the testosterone cut-off value was found to be 3.7 to 4.0 ng/mL, and MS decreased by 29% above 3.9 ng/mL (Table 4).

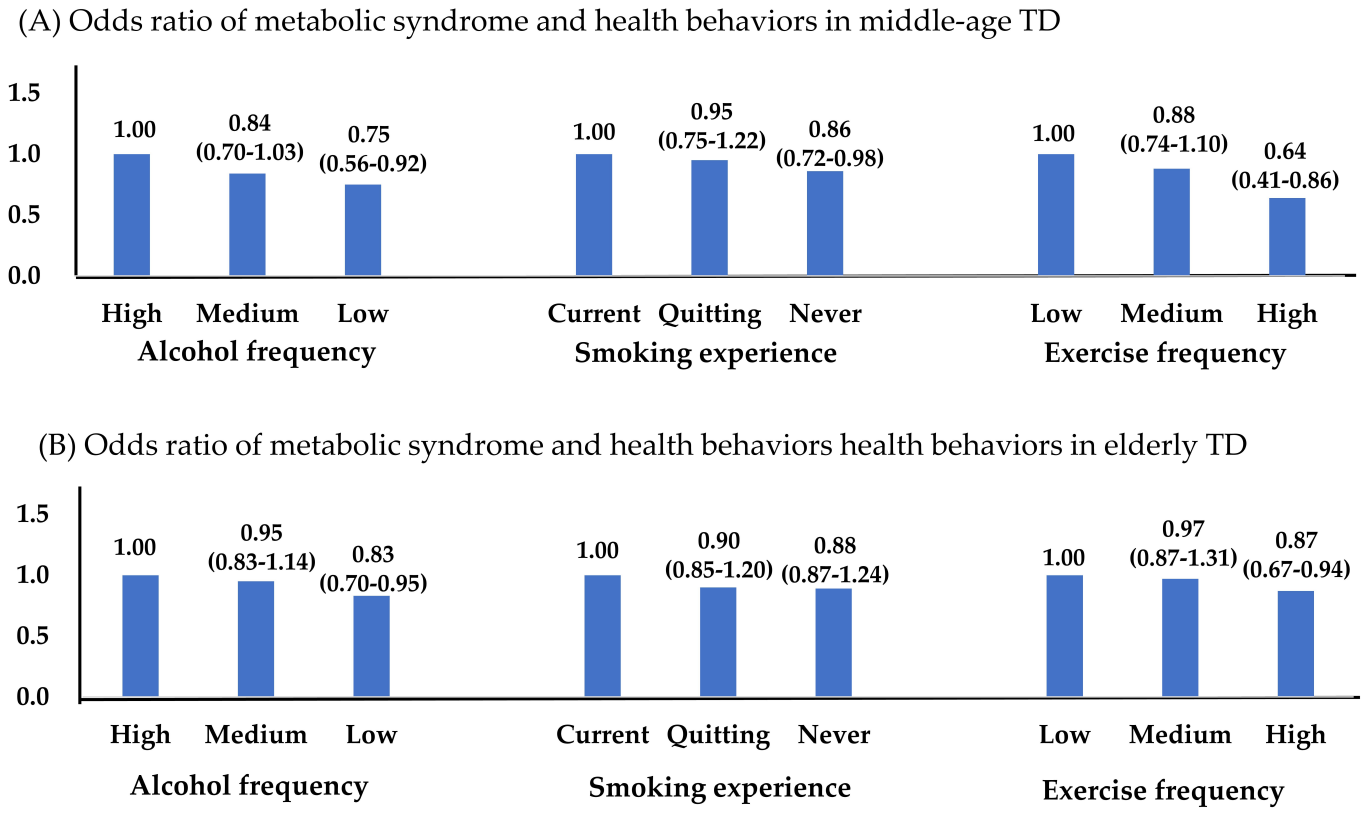

FIGURE 2. Health behavior and metabolic syndrome prevalence in testosterone deficiency. (A) middle-age, (B) elderly. Only participants with TD were included, and the odds ratios for alcohol frequency, smoking experience and exercise frequency were calculated. $p < 0.05$ indicates a statistically significant odds ratio in logistic regression; Adjusted variables: middle-age: age, alcohol, smoking, exercise; elderly: age alcohol, exercise; abbreviation: TD, testosterone deficiency.

TABLE 4. Receiver operating characteristic curve of testosterone for metabolic syndrome.

Variables	Cut-off Testosterone, ng/mL	AUC	Sensitivity	Specificity	*p*	Odd ratio (95% CI)
Middle-aged						
Waistline	4.0	0.550	43.5	63.0	0.008	0.76 (0.68–0.85)
Blood pressure	3.9	0.536	51.3	55.1	0.007	0.77 (0.70–0.86)
HDLc	4.3	0.519	60.3	42.2	0.031	0.91 (0.79–1.06)
Triglyceride	4.4	0.558	66.1	43.1	0.007	0.69 (0.62–0.76)
Glucose	4.2	0.513	57.0	46.4	0.037	0.89 (0.81–0.99)
MS	4.2	0.557	62.0	47.4	0.008	0.69 (0.62–0.78)
Elderly						
Waistline	3.9	0.535	54.1	50.2	0.015	0.82 (0.66–0.99)
Blood pressure	4.1	0.519	60.3	42.2	0.011	0.82 (0.67–0.99)
HDLc	3.7	0.540	68.1	44.3	0.021	0.80 (0.59–1.07)
Triglyceride	4.0	0.576	68.5	43.0	0.013	0.65 (0.53–0.81)
Glucose	3.9	0.528	63.7	41.4	0.011	1.07 (0.87–1.31)
MS	3.9	0.563	60.0	49.4	0.010	0.71 (0.57–0.88)

$p < 0.05$ indicates a statistically significant cut-off in receiver operating characteristic curve; abbreviation: AUC, area of under curve; HDLc, high density lipoprotein cholesterol; CI, confidence interval; MS, metabolic syndrome; Adjusted variables: middle-age: age, alcohol, smoking, exercise; elderly: age, alcohol, exercise.

4. Discussion

Multiple studies have revealed that MS is a condition that is closely related to cardiovascular disease and is often caused by aging. The decrease in testosterone levels is considered as a factor that contributes to the occurrence of MS in males. Due to the rapid increase in the elderly population in Korea and the need for cardiovascular disease prevention, further research is necessary to understand the connection between these factors.

This study found that certain factors like waist circumference, BP, TG and glucose had a significant impact on the decline in testosterone levels. Previous research has established a robust connection between these variables and testosterone levels. In previous research, data on blood pressure, body mass index and various body circumferences (waist, hip, thigh and neck) were collected from 108 participants aged 21 and above. The findings revealed an inverse relationship among testosterone levels, body mass index, body circumferences, and glucose metabolism [11]. To investigate the relationship between testosterone and MS, a case-control study was conducted on 88 MS patients and 88 healthy controls. The study found that the ratio of testosterone and estradiol was significantly lower in MS patients compared to healthy controls. This ratio has been recognized as a predictive factor for determining the chances of developing MS. Intriguingly, the research also revealed a robust association between this ratio and waist circumference [17]. The results of data analysis from the United States conducted by Liu *et al*. [18] showed a negative correlation between testosterone and MS. When the prevalence was examined after grouping testosterone into quartiles, the prevalence of MS decreased by 40–50% in the highest group compared to the lowest group [18]. These results are consistent with the results of this study.

Testosterone is an androgen hormone that has been studied to see if it affects MS or cardiovascular disease. The effects of testosterone have been examined in a study of prostate cancer patients who received androgen deprivation therapy for a long period of time. Androgen deprivation therapy is employed to inhibit the proliferation of cancer cells, resulting in a reduction in testosterone levels [19]. In meta-analysis of 9 cross-sectional studies by Jung *et al*. [20] compared 1762 patients and 5001 controls, and found that prostate cancer survivors have a 1.84-fold increased risk of MS.

The physiological mechanism by which testosterone affects cardiovascular risk factors is still not entirely clear. Despite the constraints in elucidating the exact trajectory, it has demonstrated a significant level of comprehension. The principle is that sex hormone binding globulin (SHBG) phosphorylates Jun N-terminal kinase and "extracellular signal-regulated kinase", which inhibits inflammatory cytokines such as "monocyte chemotactic protein-1", "tumor necros factor alpha" and "interleukin-6" [21].

Testosterone and insulin resistance exhibit a strong reverse correlation. In a study conducted in Korea by Kim *et al*. [22], it was confirmed that fasting glucose and glycated hemoglobin in people with TD were significantly higher than those in the normal testosterone group, showed a significant negative correlation with serum testosterone levels in men with diabetes. The correlation coefficients with testosterone were glucose $r = -0.142$ ($p = 0.002$) and hemoglobin A1C values $r = -0.097$ ($p = 0.040$) [22]. Androgen encompasses sex hormones, with testosterone serving as the principal male hormone and estrogen as the predominant female hormone. Sex hormones are present in free form, bound to albumin, and bound to SHBG. SHBG is responsible for the largest portion of sex hormones, which is 60–80%. A reduction in SHBG results in a decline in sex hormones. Studies have shown that individuals with reduced SHBG levels experience an elevation in insulin resistance and a higher incidence of type II diabetes, irrespective of their body mass [23]. SHBG can also regulate the activity of the "extracellular signal-regulated kinase" pathway, which is related to insulin resistance. *In vitro* studies have shown that SHBG was found to affect insulin resistance and gestational diabetes mellitus by regulating the expression of "glucose transporter-1" through the "cyclic adenosine monophosphate" and "protein kinase-A" pathways [24]. Fasting glucose and insulin levels were investigated in a testosterone therapy experimental study. While there was no change in the placebo group, fasting glucose and insulin in the treatment group decreased by −2.1% and −10.5% at 30 weeks and −4.9% and −35.5% after 138 weeks [25].

Testosterone has a significant impact on muscle growth, and its relationship with insulin sensitivity is very close. Testosterone plays a crucial role in managing the generation of fat tissue in muscles by overseeing the behavior of pluripotent stem cells and inhibiting the growth of preadipocytes. Consequently, it stimulates the formation of muscle cells with enhanced mitochondrial production capacity and improved insulin sensitivity, through the stimulation of oxidative phosphorylation gene expression [26].

It's worth noting that studies on testosterone and MS are not exclusively limited to men. A study conducted by Liu *et al*. [18] focused on adult women aged 20 years or older from the US National Health and Nutrition Examination Survey. The study discovered that women with high testosterone levels have a 20–65% lower risk of MS compared to those with low testosterone levels, and the correlation between testosterone and MS was significantly negative [18]. In research conducted in the United States, individuals were categorized based on their testosterone levels into four quartiles. The results revealed that the group with the highest testosterone levels exhibited a 61% decreased likelihood of developing MS in comparison to the group with the lowest testosterone levels. Interestingly, even post-menopause, there was still a potential 54% risk reduction in developing MS [27].

The importance of maintaining healthy testosterone levels through smoking, drinking and exercising to maintain healthy testosterone remains unchanged. In this study, all three factors were related to the middle-age group. Additionally, drinking alcohol and exercise, except smoking, were also significant in the elderly group. These findings are consistent with previous studies. Tawfiq conducted a study that found smokers had notably reduced testosterone levels in comparison to non-smokers [28]. A large-scale meta-analysis also confirmed these results, and the phenomenon was observed in both men and women [18, 29]. A study analyzing the relationship between low testosterone and MS also showed that non-smokers had a 41% reduced incidence of MS compared to smokers,

which is consistent with the results of this study [18]. Despite numerous potential explanations, there is still ongoing disagreement, and investigations into the mechanisms of smoking have not resulted in a definitive comprehension. Additionally, this research revealed that smoking had a notable impact on the middle-aged cohort but not on the elderly cohort.

Regular exercise or physical activity is one of the most important things to keep your testosterone healthy. There are multiple advantages to this practice, including the regulation and enhancement of circulation, reduction of insulin resistance, enhancement of insulin sensitivity, and regulation of metabolism for fats and carbohydrates. Additionally, exercise directly suppresses fatty acid accumulation by burning calories [30]. Furthermore, engaging in physical activity aids in the preservation and enhancement of muscle cells, facilitating optimal testosterone function in both muscles and the body. This results in the ongoing release of the hormone, promoting overall health [31].

Meanwhile, one of the studies on testosterone and cardiovascular disease risk is to determine whether testosterone replacement therapy is safe for cardiovascular disease in TD patients [32–34]. A meta-analysis study showed that there was no significant difference in the incidence of myocardial infarction and stroke between the control group and the therapy group after 10 years of follow-up [32]. In another study, 182 people in the hormone treatment group were followed for 33 months to compare with 190 people in the placebo group. The incidence of cardiovascular disease was 7.0% in the treatment group and 7.3% in the placebo group, and no difference in the risk of cardiovascular disease was found between the two groups [33]. Analysis of 26 randomized trials also showed that hormone therapy did not significantly increase cardiovascular disease risk or mortality [34]. Overall, many studies have consistently shown that testosterone replacement therapy is safe for cardiovascular disease.

Expert opinions on TD diagnosis vary. In general, the normal value for testosterone is 2.5 ng/mL or higher, so this value should be applied [5]. However, other studies apply 3.5 ng/mL and 300 ng/dL in the sense of providing a proactive prevention signal [35, 36]. The background for applying these various standards is diverse, but the characteristics of TD may be the cause. TD is not life-threatening, is not as common as cardiovascular disease, and rarely causes symptoms that cause inconvenience in daily life, so various perspectives may have played a role in reaching consensus among experts.

This study has a limitation of cross-sectional design, which may lead to controversy about the causality of TD and MS. People with MS may experience TD due to obesity, inactivity, unhealthy diet, cardiovascular problems or long-term medications. The study participants were volunteers who visited a health screening center that incurred high costs, and the population sample may be biased toward people with high income levels who are interested in maintaining good health. It is also challenging to assert that data collected solely from one institution can accurately reflect an entire population. Existing literature mentions that there are many possibilities that affect testosterone. The study focused on a limited scope of factors that can impact testosterone levels, including dietary habits, physical activity, alcohol consumption and tobacco use. It is important to note that these confounding variables are implicated in the development of various conditions beyond just hypogonadism and metabolic disorders. Consequently, the covariate procedure has inherent limitations due to the broader implications of these factors. The study showed that testosterone deficiency increases the prevalence of MS, but it is unclear whether testosterone ultimately causes cardiovascular disease. It is expected that future long-term follow-up studies will be able to solve this problem.

Despite these limitations, this study has the following strengths: Our study once again confirmed the relationship between TD and MS. Additionally, even in the presence of TD, low frequency of drinking, non-smoking and high frequency of exercise could lower the risk of MS. Lastly, because the cutoff value was presented, it can be used as a specific guideline for MS prevention in TD patients for public health purposes.

The following points will need to be considered in future research. First of all, there is a need to further clarify the causality between TD and MS through large-scale, long-term longitudinal studies. Additionally, as a clinical experiment, analyzing the effect of changes in testosterone on MS variables through diet and exercise intervention could provide more reliable information.

5. Conclusions

This study analyzed the relationship between TD and MS using data collected from health screening centers at medical institutions in south Korea. The prevalence of TD was observed to be elevated in the elderly population in comparison to the middle-aged population. In the TD group, there was a 1.58-fold increase in middle-aged individuals and a 2.32-fold increase in elderly individuals, as opposed to the NT group. In people with TD, waist circumference, blood pressure and TG were identified as the most significant metabolic syndrome factors. Even in individuals with TD, lower a lower frequency of alcohol and a higher frequency of exercise were found to lower the prevalence of MS. In middle-aged, a cut-off value of testosterone 4.2 was identified for the prevention of MS, while in elderly, the cut-off value was 3.9. Beyond cut-off, the risk of developing MS decreased by 31% in middle-aged and 29% in the elderly. This study presented a testosterone cutoff value for MS that was not implemented in previous studies. Future research will need to further clarify the causality of the results shown in this study through longitudinal analysis and intervention studies.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

NNZ and YFL—designed the research study. NNZ, XH and YFL—performed the research. NNZ and YK—analyzed the data. NNZ, XH and YK—wrote the manuscript. All authors

read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Prior informed consent was obtained from all participants. This study was approved by the Institutional Review Board of Seoul Asan medical center (Number 160084).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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