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ORIGINAL RESEARCH

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Prevalence of osteopenia and osteoporosis in middle-aged and older Korean men with testosterone deficiency syndrome: a cross-sectional study

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Abstract

Testosterone plays an important role in regulating fertility, muscle mass and bone density. Low bone mineral density has been reported in men with testosterone deficiency syndrome (TDS); however, there is limited research available on the prevalence of TDS. In this study, we aimed to determine the prevalence of osteoporosis and osteopenia in middle-aged and older men (n = 4707, age: 40–79 years) with TDS. Their total serum testosterone levels were measured, and TDS was defined as a testosterone level of $\leq$3.5 ng/mL. To assess bone mineral density, we used dual-energy X-ray absorptiometry to measure the density at the lumbar spine (L1–L4) and femoral neck (T-score: osteopenia ≤ -1.0; osteoporosis ≤ -2.5). We performed logistic regression analysis to calculate adjusted odds ratios (AORs) after adjusting for age, body mass index, physical activity and VO_{2peak} (Volume oxygen peak). The results showed a significant difference in physical activity between men with TDS and those without TDS (NTDS) in both middle-aged and older age groups ($p < 0.05$). Among middle-aged men, the AOR for osteopenia in the lumbar spine was 1.2-fold higher (Confience interval, CI (Confidence interval), 1.017–2.698), and in the femoral neck, it was 1.3-fold higher (CI, 1.012–3.013) for individuals with TDS compared to those without TDS. In older men, the AOR for osteopenia in the femoral neck increased by 1.4-fold (CI, 1.029–2.530). In conclusion, our findings suggest that middle-aged men with TDS have a higher likelihood of experiencing osteopenia in both the lumbar spine and femoral neck, while older men are more likely to have osteopenia, specifically in the femoral neck, but not osteoporosis.

Keywords

Testosterone deficiency syndrome; Bone mineral density; Osteoporosis; Osteopenia

1. Introduction

In diseases characterized by low bone mineral density (BMD), such as osteopenia and osteoporosis, there is an imbalance between bone mineral loss and bone remodeling, where the rate of bone mineral loss exceeds the rate of bone remodeling [1]. Although reduced bone density may not be a direct risk factor for mortality in older adults, it can contribute to increased mortality as a secondary cause. Fragility fractures, especially those occurring in the hip, can result in long-term limitations in independent mobility and have been linked to a mortality rate of 25% within one year following the fracture. In addition, vertebral fractures are associated with a 2.7-fold higher risk of mortality [2]. Osteoporosis is more prevalent in women than men, while osteopenia is more frequently observed in men. The global aging of populations has led to an increased incidence of bone density disorders in both genders. According to a study by Kaushal *et al.* [3], the prevalence of osteoporosis was observed to be 11.1% in women and 4.2% in men, while the prevalence of osteopenia was 40.3% in women and 29.9% in men.

The primary cause of BMD in men is the natural process of aging. However, there are also secondary factors that contribute to this decline, including inadequate nutrition, low levels of vitamin D, low body mass index (BMI), high alcohol consumption, low physical activity (PA) and muscle strength, as well as decreased testosterone levels [4]. Testosterone is a key male sex hormone primarily produced by the testicles and plays a significant role in regulating fertility, muscle mass, personality traits and bone density. As men age, testosterone levels gradually decrease at a rate of approximately 1–2% per year. When testosterone levels consistently fall below 3.5 ng/mL, it is referred to as testosterone deficiency syndrome (TDS), which requires hormone therapy and careful monitoring [5, 6]. While the incidence of osteoporosis is lower in men compared to women, the decline in testosterone levels is not as drastic as the decline in estrogen levels observed in postmenopausal women. As a result, TDS incidence in men ranges from 10–40% [7, 8]. Decreased testosterone levels are associated with increased bone density loss and fracture

risk. Kacker *et al.* [9] reported that men with TDS or sexual dysfunction had a 3.79-fold higher risk of osteoporosis, and an increase in spinal bone density was observed in 43 men following testosterone treatment.

Androgens, including testosterone, play a crucial role in maintaining bone density by promoting bone mass anabolism and stimulating periosteal apposition, which increases bone size and strength [4]. Despite ongoing research, the exact physiological effects of testosterone on BMD remain partially understood. The incidence of both TDS and low BMD increases with age, and these conditions are influenced by various health behaviors, making their relationship complex. According to a study by Ko *et al.* [10], TDS prevalence was 1.6 times higher in smokers and decreased by 7.7% with high-intensity exercise. Additionally, the frequencies of alcohol consumption and strength training differed significantly between individuals with healthy BMD and those with low BMD [11].

However, despite some studies highlighting low BMD in men with TDS, research focusing on the prevalence of osteoporosis and osteopenia in this population remains scarce. Therefore, we designed this study to assess the prevalence of osteoporosis and osteopenia in Korean men with and without TDS and explore the relationship between TDS and health behaviors such as physical fitness, PA, alcohol consumption and smoking.

2. Materials and methods

2.1 Research process and participants

The present study involved the analysis of data from a total of 4707 men who voluntarily visited the healthcare center of a hospital in Korea. Only data from participants who provided consent for analysis and publication were included. The age range of the participants was between 40 and 79 years, with 2769 individuals classified as middle-aged men (40–59 years) and 1938 individuals as older men (60–79 years). This study followed a cross-sectional design.

The inclusion and exclusion criteria for participant selection are detailed in Fig. 1. Initially, we had a pool of 5936 patients. Among them, 1229 patients were excluded for various reasons: 125 were receiving medication for diseases related to our study, 1003 did not undergo the necessary tests or had missing data, and 101 either declined to participate, underwent surgery due to severe illness, or displayed psychological instability.

The healthcare center examination was conducted as follows: Participants arrived at the hospital before 9 AM for identification, examination guidance and protocol explanations. On the examination day, they had consultations with physicians regarding their health conditions and their consent for the examination was reconfirmed. They were instructed to fast for 8 hours before undergoing blood tests and also completed a questionnaire about their medical history and health behaviors, including physical activity, alcohol consumption and smoking. Body measurements (height, weight and body composition), electrocardiography and blood pressure assessments were conducted, followed by blood sampling, BMD and physical fitness measurements. Ethics approval and consent from the participants were obtained for this study.

2.2 BMD and testosterone

Dual-energy X-ray absorptiometry (Lunar Prodigy iDXA; General Electric Healthcare, Waukesha, WI, USA) was used to measure BMD. Measurements were taken at the lumbar spine (L1–L4) and femoral neck with participants in the supine position (Fig. 2). The T-score was calculated, with values of ≤ -1.0 indicating osteopenia and ≤ -2.5 indicating osteoporosis [12].

For blood collection, the participants were required to fast for >8 h and instructed to avoid excessive exercise and overexertion for 7 days prior to the collection. A radioimmunoassay kit (TESTO CT2; Cisbio Bioassays, Codolet, France) was used to determine total serum testosterone levels. Blood samples were collected at 8 AM by a trained nurse and analyzed using an automated analyzer (TBA-200FR; Toshiba, Tokyo, Japan) employing the enzymatic method. Based on previous literature, patients with total serum testosterone levels of ≤ 3.5 ng/mL were classified as TDS, while those with levels >3.5 ng/mL were classified as non-TDS (NTDS) [6].

2.3 Body composition and health behavior questionnaire

Body composition was analyzed using impedance equipment (Inbody 720; Inbody Co., Seoul, Korea), and data on variables such as body fat percentage and skeletal muscle percentage were recorded. Smoking, drinking and physical activity (PA) habits were assessed through questionnaires administered prior to the health examinations. Smoking status was categorized as "smoker", "former smoker" or "never smoker". To evaluate the risk associated with alcohol consumption, the amount of pure alcohol consumed was calculated based on the type, quantity and frequency of alcohol intake. Consumption of 1–40 g/day was classified as "low", 41–60 g/day as "medium" and over 61 g/day as "high" [13, 14]. For assessing PA, the International Physical Activity Questionnaire of the World Health Organization was used [15]. According to the guidelines provided by the American College of Sports Medicine (ACSM), physical activity of at least 30 minutes per day, 3–5 days per week, is recommended, based on which the patients' PA levels were classified as "low" (below the recommended amount), "medium" (meeting the recommendations) and "high" (exceeding the recommendations) [16].

2.4 VO_{2peak} and grip strength

VO_{2peak}, representing maximum aerobic exercise capacity, was assessed using a graded exercise test performed on a Quark CPET treadmill (Quark CPET, Cosmed Co., Rome, Italy) following the Bruce protocol, as outlined in the ACSM guidelines [16]. Before the test, the participants were asked about their familiarity with treadmills. Those who were unfamiliar underwent sufficient practice to become acquainted with treadmill usage. During the test, the speed and inclination of the treadmill were increased every 3 minutes to progressively challenge the participants and determine their maximum capacity. Heart rate, blood pressure, and rated perceived exertion (RPE) were recorded at each stage, and the electrocardiogram was monitored by a cardiologist. Participants wore a mask

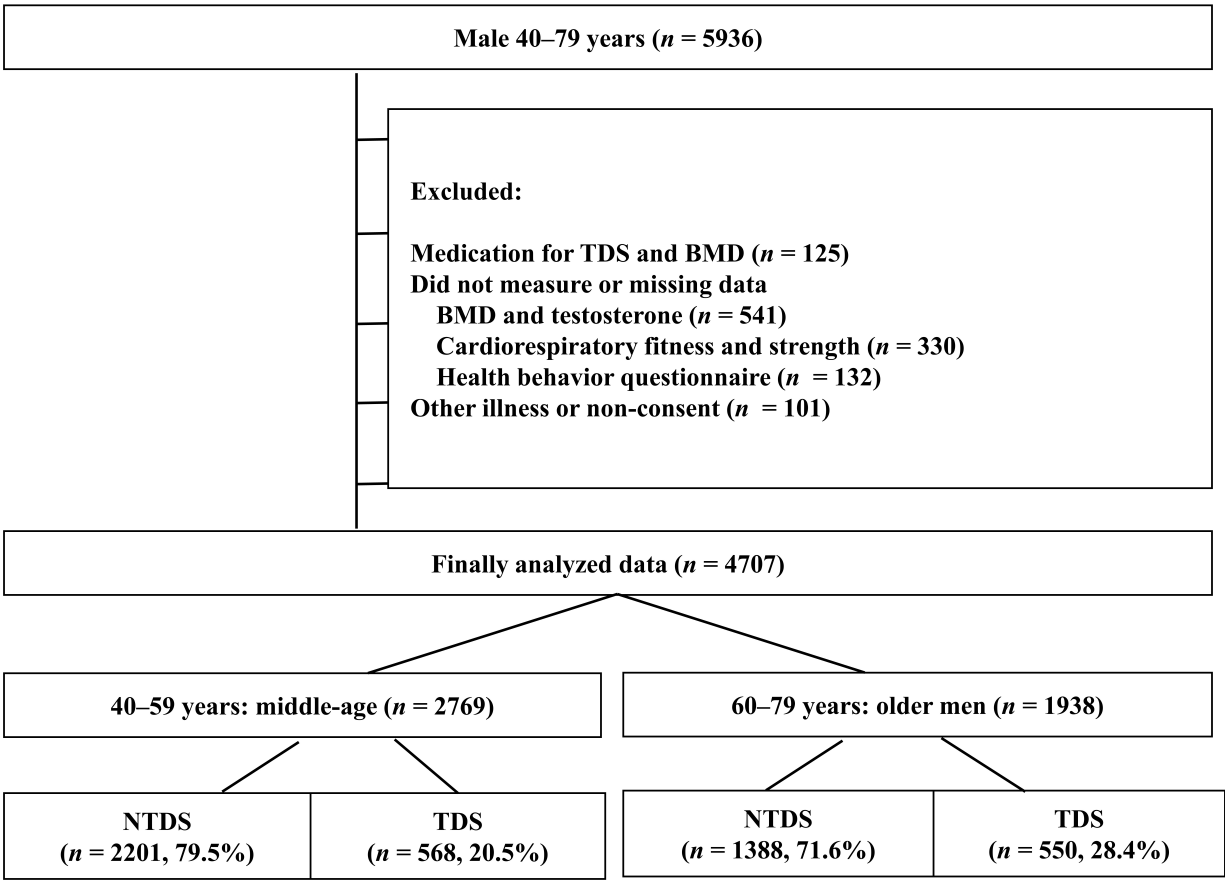

FIGURE 1. Flowchart illustrating the study inclusion and exclusion criteria for participant selection. BMD: bone mineral density; TDS: testosterone deficiency syndrome.

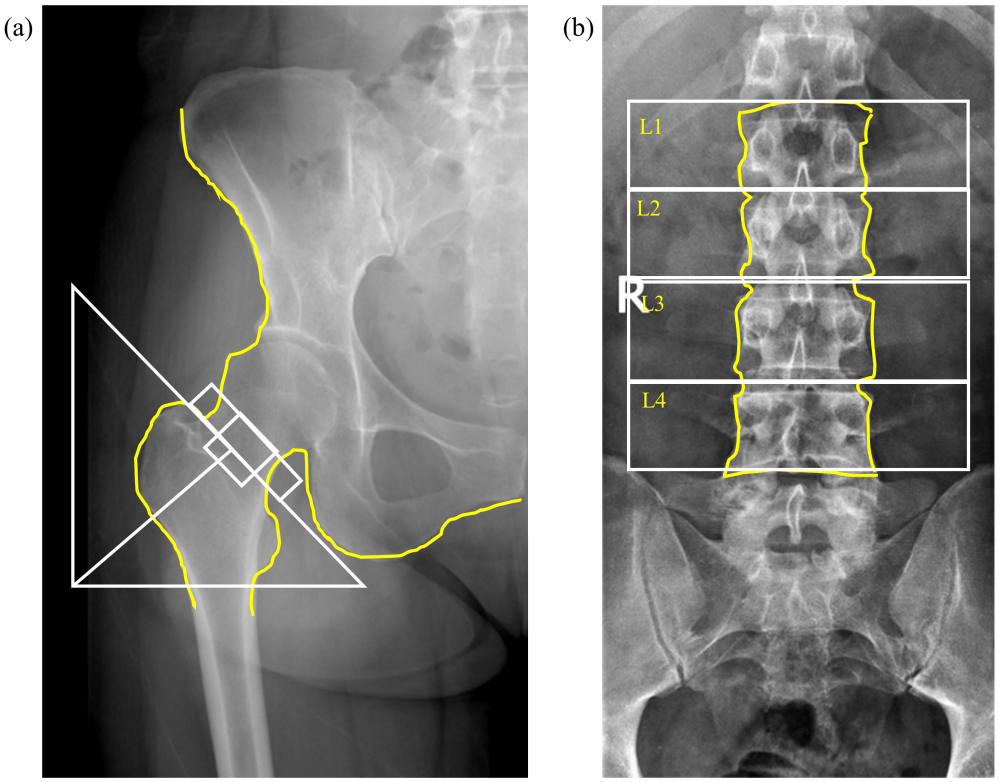

FIGURE 2. Bone mineral density location at X-ray at the (a) femoral neck and (b) lumbar spine 1–4.

equipped with sensors to analyze the amount of oxygen inhaled and carbon dioxide exhaled. Values meeting the absolute or relative end criteria were utilized. A participant's RPE scale score of $\geq$17 and a respiratory exchange rate of 1.15 were considered indicators of reaching maximum effort.

Grip strength was assessed using a dynamometer (Takei 5401; Takei Co., Tokyo, Japan) with a standardized testing method. Prior to the test, participants received explanations, demonstrations and practice sessions to ensure familiarity with the procedure. The dynamometer was adjusted to fit the participants' hands at the second knuckle. Participants stood with their waist, chest and knees extended while maintaining a forward gaze. Their arms were slightly apart, not touching the thighs, and their elbows were kept straight. Following the tester's signal, participants exerted maximum grip force for 2 seconds while maintaining the specified posture. The measurement was performed three times on each side, and the average of the highest values from both sides was recorded [17].

2.5 Data analyses

Data analysis was conducted using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of continuous variables, and it was determined that the main variables displayed a normal distribution. Mean and standard deviation values are presented, and an independent *t*-test was employed to compare variables between the NTDS and TDS groups. Categorical variables are reported as numbers and percentages, and chi-square tests were utilized for comparison.

For prevalence, logistic regression analysis was performed to calculate the adjusted odds ratio (AOR). Variables obtained through multiple regression analysis were used and adjusted, along with BMI, PA and VO_{2peak}. A 95% confidence interval (CI) was used, and statistical significance was set at $p < 0.05$.

3. Results

3.1 General characteristics

Table 1 presents the comparison of the general characteristics between the middle-aged and older groups. Height, weight and BMI were found to be significantly higher in middle-aged men than in older men. In addition, the BMD of the lumbar spine and femoral neck, as well as testosterone levels, the main indicators in this study, were also higher in the middle-aged group compared to the older group.

3.2 Body composition, health behavior and physical fitness

Table 2 presents the differences in body composition, health behaviors, and physical fitness between participants with and without TDS. The results indicated that BMD and T-scores of the lumbar spine and femoral neck were significantly higher in the NTDS group compared to the TDS group, both in older and middle-aged men. However, there were no significant differences between the two groups regarding muscle mass, body fat percentage, grip strength or household income. In terms of health behaviors, alcohol consumption and smoking were only significantly different in the older group, while no significant differences were observed in the middle-aged group.

3.3 Multiple regression analysis of testosterone and variables

Table 3 shows the relationship between testosterone levels and the variables determined through multiple regression analysis with stepwise selection. The variables entered into the analysis were age, BMI, PA and VO_{2peak}, while variables such as muscle mass, body fat, smoking, alcohol consumption, grip strength, household income and smoking were removed from the analysis.

3.4 Adjusted odds ratio of osteopenia and osteoporosis according to TDS

Tables 4 and 5 present the incidence of BMD diseases according to TDS, the results of chi-square analysis, and the AOR obtained through logistic regression analysis. In the middle-aged group, the chi-square test results showed significant associations between TDS and osteopenia in the lumbar spine and femoral neck, as well as osteoporosis in the lumbar spine (excluding femoral neck osteoporosis). The AOR results indicated that compared to NTDS individuals, the AOR for osteopenia was 1.2-fold higher in the lumbar spine and 1.3-fold higher in the femoral neck for individuals with TDS. However, no significant AOR was observed for osteoporosis.

In older men, the chi-square analysis revealed significant associations between TDS and osteopenia in the femoral neck, as well as osteoporosis in the lumbar spine and femoral neck. However, the AOR analysis indicated a significant result only for femoral neck osteopenia. Compared to individuals without TDS, the AOR for femoral neck osteopenia was 1.4-fold higher in individuals with TDS (Table 5).

4. Discussion

Testosterone, being primarily produced in the Leydig cells of the testicles, is widely recognized as a key male sex hormone and an androgen steroid hormone. It circulates throughout the body *via* the bloodstream and plays an important role in promoting sexual characteristics such as the growth and maturation of reproductive organs, the stimulation of body hair growth, and an increase in musculoskeletal size [8].

The findings of this study indicate an increased risk of osteopenia in men with TDS, which is consistent with previous research. Numerous studies have consistently emphasized that hypogonadism, or low testosterone levels, is a secondary contributor to bone loss in men, accounting for 16–30% of cases of osteoporosis development and up to 50% of osteoporotic fractures [9, 18]. A Korean study examining the association between testosterone and bone density in 144 male identical twins and 1070 family members found a positive correlation between testosterone levels and BMD and also identified a significant genetic influence on testosterone levels and BMD [19]. However, it should be noted that a few studies have reported either no association or a negative relationship

TABLE 1. General characteristics of participants.

Variables	Total (n = 4707)	Middle-aged men (n = 2769)	Older men (n = 1938)	*p*
Age, yr	56.73 ± 8.54	50.81 ± 4.72	65.25 ± 4.74	<0.001
Height, cm	169.9 ± 6.25	171.03 ± 5.52	168.48 ± 6.90	<0.001
Weight, kg	72.32 ± 9.12	73.68 ± 9.00	70.33 ± 8.81	<0.001
BMI, kg/m^2	25.01 ± 2.66	25.20 ± 2.62	24.75 ± 2.63	<0.001
Testosterone, ng/mL	5.27 ± 2.48	5.45 ± 2.66	4.89 ± 2.14	<0.001
Lumbar spine BMD, g/cm^2	1.16 ± 0.25	1.23 ± 0.26	1.04 ± 0.19	<0.001
Femoral neck BMD, g/cm^2	0.99 ± 0.22	1.07 ± 0.24	0.89 ± 0.14	<0.001

p-value represents the comparison between middle-aged and older men; BMI: body mass index; BMD: bone mineral density.

TABLE 2. Relationship between BMD, body composition, health behavior and fitness between TDS and NTDS.

Variables	Middle-aged men		*p*	Older men		*p*
	NTDS (n = 2201)	TDS (n = 568)		NTDS (n = 1388)	TDS (n = 550)	
Testosterone	6.1 ± 2.42	2.93 ± 0.54	<0.001	5.91 ± 2.25	2.70 ± 0.62	<0.001
BMI, kg/m^2	24.7 ± 2.73	25.61 ± 2.89	<0.001	24.43 ± 2.36	25.11 ± 2.56	<0.001
Lumbar spine BMD, g/cm^2	1.30 ± 0.18	1.18 ± 0.19	0.012	1.10 ± 0.19	0.99 ± 0.17	0.027
Femoral neck BMD, g/cm^2	1.15 ± 0.14	1.01 ± 0.13	0.005	0.94 ± 0.15	0.81 ± 0.14	0.019
Fat, %	20.14 ± 4.30	21.65 ± 4.62	<0.001	21.06 ± 4.94	22.21 ± 4.84	<0.001
Muscle mass, %	43.43 ± 3.71	42.98 ± 3.86	0.368	43.19 ± 3.40	41.79 ± 3.21	0.425
VO_{2peak}, mL/kg/min	27.30 ± 10.86	20.02 ± 10.83	<0.001	24.51 ± 11.28	16.91 ± 11.54	<0.001
Grip strength, kg	39.22 ±7.73	38.31 ± 8.32	0.209	35.06 ± 7.63	34.75 ± 7.48	0.704
Smoking status, n (%)						
Never	319 (14.5)	76 (13.4)		265 (19.1)	85 (15.5)	
Previous	960 (43.6)	259 (45.6)	0.645	774 (55.8)	292 (53.0)	0.010
Smoker	922 (41.9)	233 (41.0)		349 (25.1)	173 (31.5)	
Alcohol, n (%)						
Low	682 (31.0)	180 (31.7)		685 (49.3)	239 (43.4)	
Medium	1203 (54.7)	325 (57.2)	0.127	574 (41.4)	243 (44.2)	0.026
High	316 (14.3)	63 (11.1)		129 (9.3)	68 (12.4)	
Household income, n (%)						
High	584 (26.5)	169 (29.7)		375 (27.0)	161 (29.3)	
Medium	1052 (47.8)	261 (46.0)	0.877	759 (54.7)	290 (52.7)	0.791
Low	565 (25.7)	138 (24.3)		254 (18.3)	99 (18.0)	
PA, n (%)						
6–7 days/week	277 (12.6)	14 (2.5)		257 (18.5)	70 (12.7)	
3–5 days/week	734 (33.3)	239 (42.1)	<0.001	589 (42.4)	232 (42.2)	0.003
0–2 days/week	1190 (54.1)	315 (55.4)		542 (39.1)	248 (45.1)	

BMI: body mass index; PA: physical activity; NTDS: non-testosterone deficiency syndrome; TDS: testosterone deficiency syndrome; BMD: bone mineral density.

TABLE 3. Multiple regression analysis of testosterone and variables.

Variables	Unstandardized coefficients		Standardized coefficients	*t*	*p*	Lower Bound	Upper Bound
	B	Std. Error	Beta				
(Constant)	12.808	0.756		16.940	0.001	11.325	14.291
Age	−0.048	0.007	−0.174	−6.684	0.001	−0.062	−0.034
BMI	−0.160	0.024	−0.165	−6.570	0.001	−0.207	−0.112
PA	−0.165	0.054	−0.077	−3.046	0.002	−0.271	−0.059
VO_{2peak}	−0.011	0.004	−0.069	−2.677	0.008	−0.019	−0.003

BMI: body mass index; PA: physical activity; std.: standard.

TABLE 4. Osteopenia and osteoporosis odds ratio of middle-aged men with TDS.

Group	Normal BMD	Low BMD	*p*	AOR
Lumbar spine osteopenia (excluded 76 osteoporosis), n (%)				
NTDS	1809 (84.2)	339 (15.8)	0.031	Reference
TDS	438 (80.4)	107 (19.6)		1.264 (1.017–2.698)
Femoral neck osteopenia (excluded 76 osteoporosis), n (%)				
NTDS	1931 (89.9)	217 (10.1)	<0.001	Reference
TDS	461 (84.6)	84 (15.4)		1.380 (1.012–3.013)
Lumbar spine osteoporosis, n (%)				
NTDS	2148 (97.6)	53 (2.4)	0.033	Reference
TDS	545 (96.0)	23 (4.0)		1.161 (0.704–6.631)
Femoral neck osteoporosis, n (%)				
NTDS	2199 (99.9)	2 (0.1)	0.144	Reference
TDS	566 (99.6)	2 (0.4)		No results

AOR: adjusted odds ratio; NTDS: non-testosterone deficiency syndrome; TDS: testosterone deficiency syndrome; BMD: bone mineral density.
Adjustment variables: age, body mass index, physical activity and VO_{2peak}.

TABLE 5. Osteopenia and osteoporosis odds ratio of older men with TDS.

Group	Normal BMD	Low BMD	*p*	AOR
Lumbar spine osteopenia (excluded 90 osteoporosis), n (%)				
NTDS	1059 (79.6)	271 (20.4)	0.300	Reference
TDS	398 (77.4)	116 (22.6)		1.166 (0.669–2.034)
Femoral neck osteopenia (excluded 90 osteoporosis), n (%)				
NTDS	1142 (85.9)	188 (14.1)	<0.001	Reference
TDS	395 (76.8)	119 (23.2)		1.448 (1.029–2.530)
Lumbar spine osteoporosis, n (%)				
NTDS	1335 (96.2)	53 (3.8)	0.023	Reference
TDS	516 (93.8)	34 (6.2)		1.488 (0.577–3.835)
Femoral neck osteoporosis, n (%)				
NTDS	1381 (99.5)	7 (0.5)	0.005	Reference
TDS	540 (98.2)	10 (1.8)		2.850 (0.806–6.661)

AOR: adjusted odds ratio; NTDS: non-testosterone deficiency syndrome; TDS: testosterone deficiency syndrome; BMD: bone mineral density.
Adjustment variables: age, body mass index, physical activity and VO_{2peak}.

between testosterone levels and BMD. For instance, in the US multiracial National Health and Nutrition Examination Survey, there was no negative association between BMD and total testosterone levels when they were <500 ng/dL in men aged 40–60 years. However, among non-Hispanic White, non-Hispanic Black, and Mexican American populations, total testosterone levels >500 ng/dL exhibited a negative association with BMD [20].

Given the potential impact of testosterone on BMD, numerous studies have examined the effects of hormone therapy to further investigate this relationship. One randomized trial conducted at six centers in Australia administered testosterone or a placebo for 2 years on men aged ≥50 years and investigated the difference in BMD between them. The results showed that compared with the control group, the experimental group had significantly increased tibial and radial cortex and total tibial and radial BMD [21]. However, these effects of testosterone therapy were reported to be obvious in middle-aged men while only partially present in older men. In a meta-analysis of seven randomized controlled trials comprising 800 patients, it was found that testosterone therapy did not significantly change the BMD of the whole body but induced significant changes in that of the spine, femoral neck and total hip [22].

The findings of our present study align with previous research, showing significant associations between TDS and BMD in the middle-aged group, while only the femoral neck exhibited significant associations in the older men group. These observations might be attributed to multiple factors influencing bone density beyond those considered in this study. Hence, while primary osteoporosis is related to senescence, secondary osteoporosis is influenced by various risk factors and causes [12, 23], suggesting that factors such as nutritional status and other underlying diseases could significantly impact bone density, particularly in older men. For instance, people with diabetes were reported to have a 4–5 times higher risk of osteoporosis than those without diabetes [24].

Testosterone therapy is not widely recommended as a primary treatment for low BMD. Testosterone therapy is recommended if low testosterone levels are the obvious cause of osteoporosis but not if the testosterone level is normal [25]. Testosterone and androgens have a complex relationship with bone-related cells. Androgen receptors are expressed in bone-associated osteoblasts, osteoclasts and osteocytes. Thus, loss of androgen receptors in osteoblasts can decrease trabeculae and trabecular bone mass [26], resulting in the low bone density observed in patients with androgen insensitivity syndrome and androgen receptor deficiency [27, 28]. Therefore, testosterone can potentially affect osteoblasts by promoting trabecular bone and osteocyte formation via androgen receptors [18]. However, while there is some understanding of the role of androgens in osteoblasts, there is a lack of studies exploring the relationship between androgens and osteoclasts. Further research is needed to investigate the pathophysiological mechanisms involved.

The present study observed a significant increase in the prevalence of osteopenia but not osteoporosis among the participants. It is worth noting that the incidence of osteoporosis in men is generally low, and severe complications such as osteoporotic fractures are rare, making it challenging to conduct comprehensive studies on such topics. As a result, guidelines for the treatment of osteoporosis in young men often recommend regular follow-ups rather than immediate active treatment in the absence of osteoporotic fractures [25].

In the present study, significant differences were observed in exercise-related variables such as VO_{2peak}, grip strength and PA between the NTDS and TDS groups in both age ranges. These findings align with a study conducted by Ko *et al.* [10], which focused on older men and found that the OR for TDS increased by 1.7-fold in the group with low muscle mass, while the risk of TDS decreased by 7.7% in the group engaging in frequent strength training. Numerous studies have demonstrated a correlation between testosterone levels and muscle mass and strength. For instance, in a study involving older men receiving hormone therapy, the experimental group exhibited improvements in muscle mass and strength compared to the placebo [29]. Moreover, testosterone levels were reported to be increased after 8 weeks of weight training [30]. These findings highlight the potential impact of testosterone on muscle-related variables and suggest that testosterone therapy and strength training may have beneficial effects on muscle mass and strength in older individuals.

Health experts commonly highlight the detrimental effects of smoking and alcohol consumption on both bone and sexual health. In the present study, although smoking and alcohol consumption did not show significant associations with TDS in the middle-aged groups, they were significant in the older groups. However, previous studies have yielded inconsistent results regarding the relationship between smoking, alcohol consumption and testosterone levels. For instance, one study reported a 1.6-fold increased OR for low testosterone in smokers, but the OR did not reach significance for smoking alone. Additionally, heavy drinkers were found to have a 4.37-fold increased risk of testosterone deficiency than non-drinkers [10, 31]. However, another study by Haik *et al.* [32] found no significant differences in testosterone and sex hormone-binding globulin levels between smokers and non-smokers. Although further research is needed to better understand the underlying physiological pathways and mechanisms involved, it is important to note that smoking and excessive alcohol consumption are recognized as risk factors for various health issues beyond their potential effects on testosterone levels.

In our present study, we observed that the TDS group had higher BMI and body fat percentage than the NTDS group, consistent with previous studies that reported similar associations. One possible physiological mechanism for this association could be that obesity can inhibit testosterone production and hypothalamic-pituitary-gonadal function by activating aromatase [33]. Further investigations could explore the relationship between TDS and cardiovascular risks, including obesity.

Our study also had several limitations. First, the participants were volunteers, so it cannot be determined whether individuals with limited access to healthcare facilities and lower health awareness would yield similar results. Additionally, considering the cross-sectional design of this study, we could not establish causality between low BMD and TDS. Furthermore, the pathophysiological mechanisms or pathways

underlying the observed associations could not be elucidated, and the use of memory-dependent test methods, such as questionnaires, might have introduced the possibility of over- or under-estimation in the data. Future studies should consider employing various methods, such as measuring free testosterone and BMD at different skeletal sites like the wrist, total hip and trochanter, and increasing the sample size to enhance the generalizability of the findings.

5. Conclusions

The present study revealed that middle-aged and older men with TDS had lower BMD than NTDS individuals. Age, BMI, PA and VO_{2peak} were identified as significant factors affecting testosterone levels. Compared to the NTDS group, the TDS group had an increased risk of osteopenia in the lumbar spine and femoral neck among middle-aged men and an increased risk of femoral neck osteopenia in older men, highlighting the importance of managing BMD-related health in men with TDS.

AVAILABILITY OF DATA AND MATERIALS

The subject institution of the data prohibits external export to protect patient information.

AUTHOR CONTRIBUTIONS

ZBW and YK—Conceptualization; YK and YC—methodology, writing–review and editing; YK—formal analysis, investigation; ZBW and YC—writing—original draft preparation, supervision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki with the approval of the Institutional Review Board of Asan medical center (approval number: S2015-2252). Participants submitted a handwritten consent form.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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