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Association of serum thyroid-stimulating hormone and bone mineral density in Chinese adults with normal thyroid function

Jia Chen[1], Lidong Hu[2], Ning Li[3], Wei Deng[1], Xiaojie Xu[1], Ling Wang[4], Kaiping Zhao[5], Shuai Lu[3], Xuejiao Liu[5], Xiaoguang Cheng[4*] and Xieyuan Jiang[3*]

Abstract

Purpose This study aims to investigate the association of serum TSH with BMD in Chinese adults with normal thyroid function.

Methods These participants were divided into tertiles based on serum TSH levels. Linear regression model and multinomial logistic regression models were used to analyze the associations of continuous BMD and categorical BMD with serum TSH, respectively.

Results In women younger than 60 years, BMD decreased with the increase of TSH at normal level, while in women older than 60 years, BMD increased with the increase of TSH at normal level; besides, the BMD of women younger than 60 years old was significantly higher than that of women over 60 years old (156.05 ± 39.34 mg/cm^3 vs. 86.95 ± 29.51 mg/cm^3, $P < 0.001$). Linear regression results showed negative associations of BMD and normal TSH level in women with age younger than 60 years (β=-4.34, $P < 0.001$), but this inverse trend was observed in women over 60 years old (β = 2.04, $P = 0.041$). Both in men younger than 60 years and over 60 years old, BMD decreased with the increase of TSH at normal levels; besides, the BMD of men younger than 60 years was significantly higher than those over 60 years old (143.08 ± 32.76 mg/cm^3 vs. 108.13 ± 31.99 mg/cm^3, $P < 0.001$).

Conclusions The results demonstrated an opposite trend in BMD at normal TSH levels in younger and elder females, that is, in females younger than 60 years, BMD decreased with the increase of TSH, which indicated that TSH might play a different role in younger and elder females. However, this trend was not significant in males.

Summary

This study demonstrated an opposite trend in BMD at normal TSH levels in younger and elder females, that is, in females younger than 60 years, BMD decreased with the increase of TSH, which indicated that TSH might play a different role in younger and elder females.

Keywords Thyroid-stimulating hormone, Bone mineral density, Normal thyroid function

*Correspondence:
Xiaoguang Cheng
xiao65@263.net
Xieyuan Jiang
jxytrauma@163.com

Full list of author information is available at the end of the article

Introduction

Bones in healthy people are constantly undergoing a finely dynamic remodeling process, which will preserve the strength and integrity to perform their functions [1]. When this dynamic remolding process is unbalanced, bone mineral density (BMD) progressively reduces, which will ultimately resulting in osteopenia and even osteoporosis [2, 3]. Osteoporosis is known as a silent epidemic of 21st century, due to its profound impact on public health. As a serious, progressive and early asymptomatic, it will lead to disability and increased risk of fracture [4]. The evidence for the association of thyroid function with BMD has been increasing.

It was indicated that thyroid-stimulating hormone (TSH) exerted a direct effect on bone turnover mediated via its receptors on osteoblast and osteoclast precursors [5–7], even though this has not been well established in other studies [8]. Many studies investigating the association of TSH with bone disease have concentrated in the effects of thyroid disease and thyroid hormone replacement therapy, and most studies have only included women. A few studies assessed the correlation between serum TSH and BMD in healthy people, and few studies has included men. Two studies have demonstrated that hip BMD in postmenopausal women increased linearly with the increased serum TSH level, even within the normal reference range [9, 10]. After adjusting for body mass index, no correlation was found between serum TSH level and hip BMD in elderly men [11]. However, some studies have also reported discrepant results [12, 13].

Recently, studies shown that different serum TSH level within the normal reference range could affect the bone health status, and low TSH level might contribute to impaired BMD and increased risk of fracture [14, 15]. However, due to the small sample size, it failed to define such an association. In this study, we will explore the association of serum TSH level and BMD in Chinese adults with normal thyroid function through the China Biobank Study, a prospective, nationwide multicenter population cohort.

Methods

Participants

The participants were from the China Biobank Study that was registered with the U.S. clinical trials database (clinicaltrials.gov: NCT03699228). In the current study, low-dose computed tomography (LDCT) chest scan data obtained primarily for lung cancer screening were used to retrospectively assess lumbar spine trabecular volumetric BMD. In this study, all participants underwent the measurement of thyroid function. The participants with hormone levels beyond the normal range of fT3 (3.1 ~ 6.8 pmol/I), fT4 (12 ~ 22 pmol/I), and TSH (0.27 ~ 4.2 mIU/I) were excluded (Fig. 1). This program was reviewed and approved by the Ethics Committee of Beijing Jishuitan Hospital, and informed consents for participation in this program were obtained from all participants.

Lumbar vertebra scanning by LDCT

LDCT is now widely used for lung cancer screening, and the subsequent analysis of these CT scans allowed the assessment of volumetric BMD at lumbar 1 and 2 through the Mindways QCT Pro software calibrated to the QCT phantom (Mindways, Austin, TX, USA) [16]. The region of interest was defined as the oval-shaped areas containing the largest area of trabecular bone in the middle plane of each vertebral body, excluding the cortical bone and basal vertebral plexus.

Definitions of osteoporosis and osteopenia

According to recommendations of the China guideline for the diagnosis criteria of osteoporosis with QCT (2018) [16], osteoporosis was defined as average volumetric

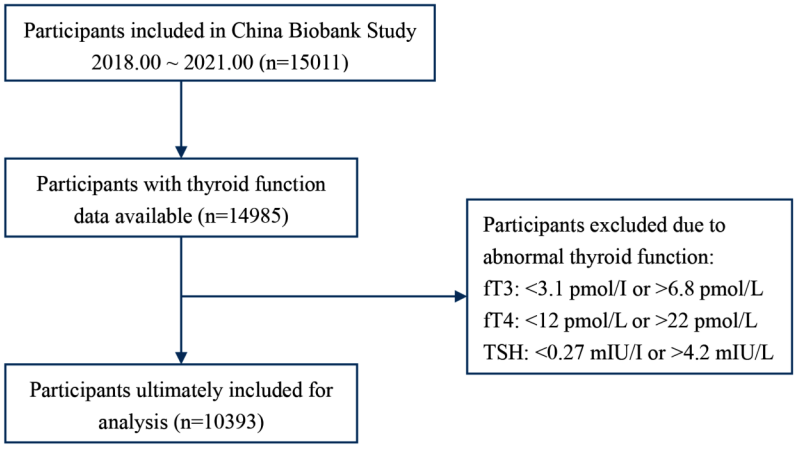

Fig. 1 The flow chart of this study subjects

BMD at L1 and L2 less than 80 mg/cm^3; osteopenia was defined as average BMD between 80 ~ 120 mg/cm^3.

Evaluation criteria

To investigate the difference of BMD at different serum TSH levels, the participants were equally divided into three groups based on tertiles of serum TSH level in normal range, i.e., the 1st (0.27 mIU/L < TSH_low < 1.58 mIU/L), 2nd (1.58 mIU/L ≤ TSH_mid < 2.89 mIU/L), and 3rd (2.89 mIU/L ≤ TSH_high < 4.20 mIU/L) tertile groups.

Statistical analysis

All analyses were performed with the Stata MP 16.0 (StataCorp, College Station, TX, USA) software. Value of categorical variable was expressed as number (percentage). Value of continuous variable with positive distribution was expressed as mean ± SD. The primary outcome was continuous BMD measured with LDCT. The secondary outcome was the risk of osteopenia and osteoporosis (BMD < 80 mg/cm^3 vs. 80 mg/cm^3 ≤ BMD < 120 mg/cm^3 vs. BMD ≥ 120 mg/cm^3). The ANOVA or Kruskal-Wallis test were used to determine whether there was statistically significant difference among TSH tertile groups for continuous variables. The Pearson's χ^2 or Fisher's exact test was used to analyze differences among TSH tertile groups for categorical variables. The coefficient (β) with 95% CI for BMD in relation to gender and age was analyzed with general linear regression. Relative risk ratio (RRR) with 95% CI for osteopenia and osteoporosis risk in relation to gender and age was analyzed with multinomial logistic regression. In addition, subgroup analysis stratified by gender and age was also performed. P-value < 0.05 was considered to be statistically significant.

Results

Baseline characteristics of participants

A total of 10,393 euthyroid Chinese adults, including 4,171 females and 6,222 males, were ultimately included for analysis, and their baseline characteristics by gender and TSH level were showed in Table 1. In female, there was a significantly difference in terms of age among the TSH tertile groups, however, no difference was observed in male. BMI was the lowest in the TSH_low group in both female and male, and there was significant difference between any group. BMD in both female and male was the highest in the TSH_low group, however, statistical difference was only observed in female. In female, there was a significantly difference in terms of osteoporosis and osteopenia among the TSH tertile groups, however, no difference was observed in male. TSH level was the lowest in the TSH_low group in both female and male, and there was significant difference between any group. fT3 and fT4 levels were the lowest in the TSH_low group in both female and male, however, statistical difference was only observed in male.

Distribution of BMD in normal TSH level

Due to the significant negative association between BMD and age, age was stratified by 60 years old (Supplemental Fig. 1). Fitting curves of BMD across normal TSH levels stratified by gender and age were illustrated in Fig. 2. In women aged less than 60 years, BMD decreased with the increase of TSH at normal level, while in women aged 60 years and older, BMD increased with the increase of TSH at normal level (Fig. 2A); besides, the BMD of women aged less than 60 years was higher than that of women aged 60 years and older (156.05 ± 39.34 mg/cm^3 vs. 86.95 ± 29.51 mg/cm^3, $P < 0.001$) (Fig. 2A). Both in men aged less than 60 years and aged 60 years and older, BMD decreased with the increase of TSH at normal levels (Fig. 2B); besides, the BMD of men aged less than 60 years was higher than that of men aged 60 years and older (143.08 ± 32.76 mg/cm^3 vs. 108.13 ± 31.99 mg/cm^3, $P < 0.001$).

To further investigate the difference of BMD based on different serum TSH levels, these participants were equally divided into three groups according to

Table 1 Clinical characteristics of participants based on gender and TSH tertile groups

	Female				Male			
TSH tertile groups	**TSH_low**	**TSH_mid**	**TSH_high**	***P***	**TSH_low**	**TSH_mid**	**TSH_high**	***P***
	***n* = 1133**	***n* = 1944**	***n* = 1094**		***n* = 2119**	***n* = 2945**	***n* = 1158**	
Age, year	48.73 ± 13.57	49.11 ± 13.18	50.90 ± 12.46	< 0.001	48.43 ± 13.13	48.22 ± 13.00	48.35 ± 12.88	0.851
BMI, kg/m^2	22.64 ± 3.04	23.04 ± 3.19	23.38 ± 3.08	< 0.001	24.61 ± 3.02	24.91 ± 3.09	25.34 ± 3.15	< 0.001
BMD, mg/cm^3	143.63 ± 51.46	141.19 ± 45.75	134.24 ± 45.14	< 0.001	136.48 ± 35.98	136.76 ± 35.58	134.40 ± 34.01	0.146
Osteoporosis, n (%)	145 (12.80)	198 (10.19)	144 (13.16)	0.019	123 (5.80)	141 (4.79)	59 (5.09)	0.270
Osteopenia, n (%)	228 (23.08)	463 (26.51)	287 (30.21)	0.002	585 (29.31)	817 (29.14)	344 (31.30)	0.387
TSH, mIU/L	1.14 ± 0.30	2.21 ± 0.37	3.48 ± 0.38	< 0.001	1.13 ± 0.30	2.16 ± 0.36	3.46 ± 0.38	< 0.001
fT3, pmol/L	4.53 ± 0.57	4.57 ± 0.55	4.57 ± 0.52	0.136	4.88 ± 0.63	5.02 ± 0.61	5.10 ± 0.58	< 0.001
fT4, pmol/L	15.66 ± 2.34	15.77 ± 2.17	15.70 ± 2.04	0.408	15.64 ± 2.56	16.17 ± 2.42	16.58 ± 2.15	< 0.001

TSH_low: 0.27 ~ 1.58 mIU/L; TSH_mid: 1.58 ~ 2.89 mIU/L; TSH_high: 2.89 ~ 4.20 mIU/L; BMI: body mass index; BMD: bone mineral density; TSH: thyroid-stimulating hormone; fT3: free triiodothyronine; fT4: free thyroxine

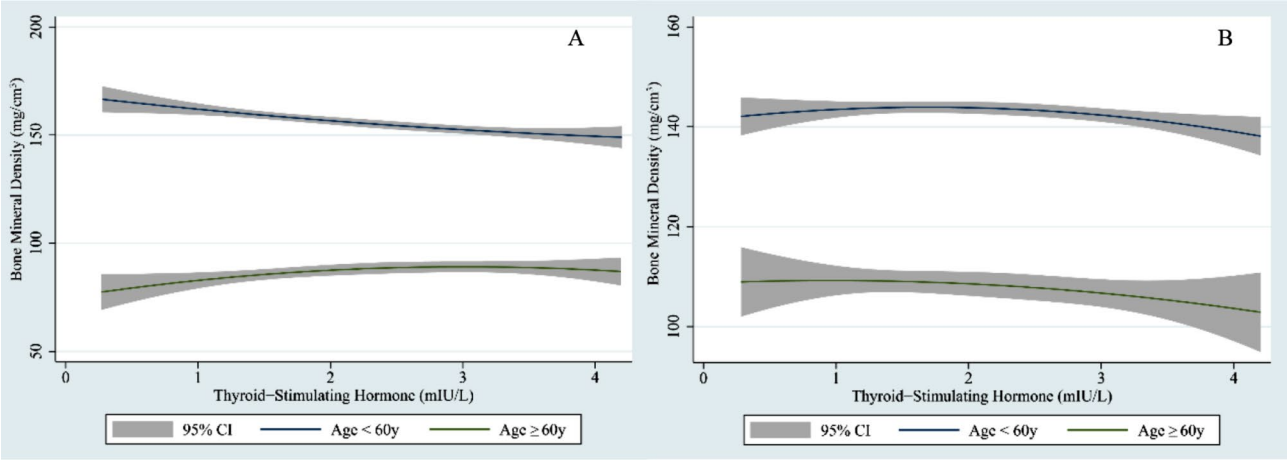

Fig. 2 Fitting curves of BMD with normal TSH level stratified by age (**A**: female; **B**: male)

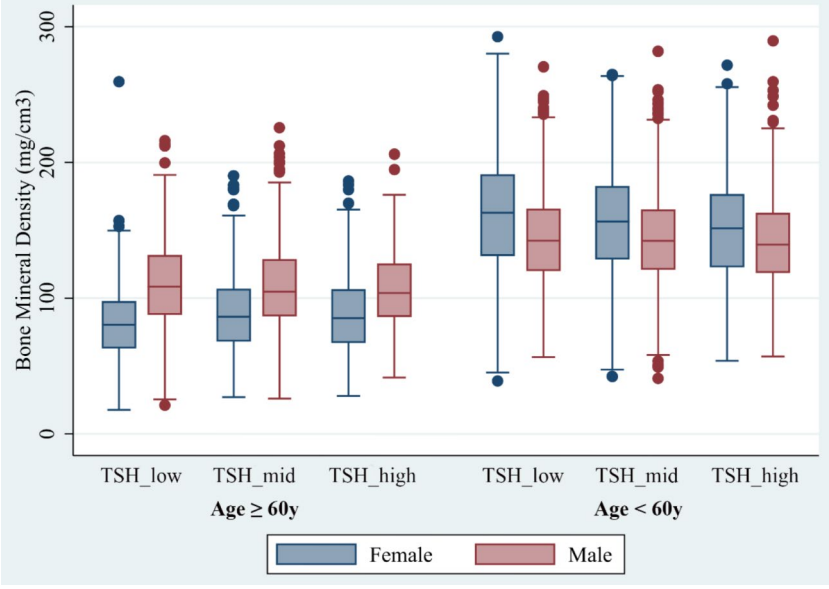

Fig. 3 Bone mineral density of three regions according to the TSH tertiles in female and male stratified by age

tertiles of serum TSH levels. In women aged less than 60 years, the BMD of participants in TSH_low group was higher than that of participants in TSH_high group (161.55±41.80 mg/cm^3 vs. 150.86±37.65 mg/cm^3, $P<0.001$). However, in women aged 60 years and older, these participants in the TSH_low group had lower BMD than those in the TSH_high group, but it did not reach statistically significant difference (82.52±29.81 mg/cm^3 vs. 87.73±28.94 mg/cm^3, $P=0.117$) (Fig. 3).

In men aged less than 60 years, the BMD of participants in TSH_low group was higher than that of participants in TSH_high group, but it did not reach statistically significant difference (143.77±33.33 mg/cm^3 vs. 140.80±31.62 mg/cm^3, $P=0.077$). Similarly, in men aged 60 years and older, participants in the TSH_low group had higher BMD than those in the TSH_high group, but it did not reach statistically significant difference (109.57±33.29 mg/cm^3 vs. 105.49±29.09 mg/cm^3, $P=0.381$) (Fig. 3).

Linear regression results

Table 2 showed the results of linear regression analysis for BMD and normal TSH level by gender and age. Negative associations of BMD and normal TSH level was indicated among total women (β=-4.01, 95% CI: -5.55 ~ -2.45, $P<0.001$) and women with aged less than 60 years (β=-4.34, 95% CI: -5.82 ~ -2.86, $P<0.001$), however, this inverse trend was found in women aged 60 years and older (β=2.04, 95% CI: 0.08 ~ 3.99, $P=0.041$). Besides, there was a significant negative association between BMD and normal TSH level in women aged 60 years and

Table 2 Linear regression for BMD and normal TSH level by gender and age

	Female				Male			
	Crude Model		Adjusted Model*		Crude Model		Adjusted Model*	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
All population								
TSH (mIU/L)	-4.01 (-5.55, -2.45)	< 0.001	-1.30 (-2.32, -0.28)	0.013	-0.53 (-1.53, 0.47)	0.297	-0.83 (-1.64, -0.02)	0.045
Age < 60y								
TSH (mIU/L)	-4.34 (-5.82, -2.86)	< 0.001	-2.02 (-3.21, -0.84)	0.001	-1.05 (-2.08, -0.02)	0.047	-0.71 (-1.58, 0.17)	0.116
Age ≥ 60y								
TSH (mIU/L)	2.04 (0.08, 3.99)	0.041	1.47 (-0.41, 3.34)	0.125	-1.51 (-3.54, 0.52)	0.145	-1.17 (-3.18, 0.83)	0.250

BMD: bone mineral density; TSH: thyroid-stimulating hormone; *Adjusting for age

older after adjusting age (β=-2.02, 95% CI: -3.21 ~ -0.84, *P*=0.001).

In male, BMD had a significant negative association with normal TSH level in men younger than 60 years (β=-1.05, 95% CI: -2.08 ~ -0.02, *P*=0.047), but this association was not kept while adjusting for age (β=-0.71, 95% CI: -1.58 ~ 0.17, *P*=0.116).

Multinomial logistic regression results

While transferring BMD to three categories (normal BMD, osteopenia and osteoporosis), the association of osteoporosis and osteopenia with TSH tertile groups by gender and age was showed in Table 3. In female, whatever total participants or participants younger than 60 years, osteopenia was significantly higher in participants with TSH_high and TSH_mid groups than those with TSH_low group, but this significance was not observed after adjusting for age. Besides, it was only found that in women over 60 years old, women with TSH_mid group had a lower incidence of osteoporosis than those with TSH_low group.

In male with osteopenia, no significance among TSH tertile group was found, whatever total participants or participants aged less than 60 years, except for men aged 60 years and older. In men aged 60 years and older, osteopenia was higher in participants with TSH_high group than those with TSH_low group, and this significance was kept after adjusting for age. In male with osteoporosis, no significance among TSH tertile groups was found, whatever total participants, participants aged less than 60 years, or participants aged 60 years and older.

Discussion

Our study included these participants with euthyroidism. These results indicated an opposite trend in BMD at normal TSH levels in younger and elder females, that is, in females younger than 60 years, BMD decreased with the increase of TSH, and the BMD of participants in low normal TSH levels (TSH_low group) was higher than those in high normal TSH levels (TSH_high group), while in females older than 60 years, BMD increased with the increase of TSH. However, this trend was not significant in males.

According to epidemiological findings released by National Health Commission of the People's Republic of China in 2018, population with osteoporosis accounted for 51.6% and 10.7% among women and men aged 65 years and older, respectively (https://ncncd.chinacdc.cn/). The incidence of osteoporotic fractures is inevitably increasing with the aging Chinese population, and it has been an important public health issue in China. There are many factors that increases the risk of osteoporotic fractures, such as longer duration of thyrotoxicosis and lower serum TSH level [17].

Recently, many studies demonstrated that low serum TSH level was significantly associated with low BMD in elderly women, which was consistent with our study [10, 17, 18]. Morris showed that BMD of postmenopausal women in USA increased as serum TSH level increased within the normal reference range, and women with low-normal serum TSH level were 3.4 and 2.2 times as likely to develop osteoporosis and osteopenia, as those with high-normal serum TSH level, respectively [10]. In addition, there was a study examining the association between low serum TSH level and fracture in older women, which included 600 women older than 65 years old [19]. TSH- suppressed women had an increased risk of hip and vertebral fractures during a 3.7-year follow-up, and low serum TSH concentration was an independent risk factor of fracture, which was also verified by another study [20]. Furthermore, the results adjusting for baseline BMD indicated that the increased risk of fracture in those with low serum TSH level was mediated through reducing bone mass. Another study included 13 prospective cohorts demonstrated that lower TSH and higher FT4 among euthyroid adults were associated with the increased risk of hip fracture and decreased BMD [21].

Many questions related to the role of low serum TSH level in bone loss aroused. So far, it was believed that this was solely caused by high thyroid hormones. Independent role of TSH has been examined through genetically modified mouse models that disrupted the reciprocal association between TSH and thyroid hormone [5, 7],

Table 3 Multinomial logistic regression for osteopenia/osteoporosis and TSH tertile groups by gender and age

		Female				Male			
		Crude Model		Adjusted Model*		Crude Model		Adjusted Model*	
		RRR (95% CI)	P	RRR (95% CI)	P	RRR (95% CI)	P	RRR (95% CI)	P
Osteopenia#	All population								
	TSH_mid vs. TSH_low	1.20 (1.00, 1.44)	0.047	1.16 (0.92, 1.45)	0.208	0.99 (0.87, 1.13)	0.897	1.01 (0.88, 1.17)	0.860
	TSH_high vs. TSH_low	1.44 (1.18, 1.77)	< 0.001	1.20 (0.93, 1.54)	0.168	1.10 (0.94, 1.29)	0.247	1.16 (0.97, 1.38)	0.106
	Age < 60y								
	TSH_mid vs. TSH_low	1.32 (1.04, 1.66)	0.020	1.24 (0.95, 1.62)	0.113	0.97 (0.83, 1.12)	0.670	0.93 (0.79, 1.09)	0.373
	TSH_high vs. TSH_low	1.59 (1.23, 2.06)	< 0.001	1.32 (0.98, 1.78)	0.069	1.10 (0.91, 1.33)	0.314	1.06 (0.86, 1.30)	0.590
	Age ≥ 60y								
	TSH_mid vs. TSH_low	0.79 (0.47, 1.34)	0.387	0.80 (0.47, 1.35)	0.398	1.25 (0.95, 1.65)	0.116	1.24 (0.94, 1.64)	0.124
	TSH_high vs. TSH_low	0.74 (0.42, 1.30)	0.292	0.75 (0.43, 1.33)	0.325	1.48 (1.01, 2.15)	0.043	1.46 (1.01, 2.14)	0.048
Osteoporosis#	All population								
	TSH_mid vs. TSH_low	0.81 (0.64, 1.02)	0.074	0.79 (0.57, 1.10)	0.166	0.81 (0.63, 1.05)	0.109	0.82 (0.62, 1.09)	0.174
	TSH_high vs. TSH_low	1.14 (0.88, 1.47)	0.315	1.02 (0.72, 1.46)	0.897	0.90 (0.65, 1.24)	0.507	0.95 (0.66, 1.37)	0.793
	Age < 60y								
	TSH_mid vs. TSH_low	0.92 (0.51, 1.65)	0.768	0.87 (0.46, 1.61)	0.649	0.86 (0.55, 1.33)	0.499	0.82 (0.52, 1.30)	0.403
	TSH_high vs. TSH_low	1.05 (0.54, 2.05)	0.877	0.85 (0.43, 1.69)	0.637	0.92 (0.53, 1.62)	0.777	0.91 (0.51, 1.62)	0.739
	Age ≥ 60y								
	TSH_mid vs. TSH_low	0.58 (0.34, 0.98)	0.040	0.58 (0.34, 0.98)	0.043	0.99 (0.69, 1.43)	0.972	0.92 (0.63, 1.33)	0.638
	TSH_high vs. TSH_low	0.65 (0.37, 1.13)	0.126	0.72 (0.41, 1.27)	0.257	1.27 (0.79, 2.05)	0.330	1.12 (0.38, 1.84)	0.664

TSH_low: 0.27 ~ 1.58 mIU/L; TSH_mid: 1.58 ~ 2.89 mIU/L; TSH_high: 2.89 ~ 4.20 mIU/L; BMI: body mass index; BMD: bone mineral density; TSH: thyroid-stimulating hormone; RRR: relative risk ratios; # Normal BMD as a reference; *Adjusting for age

that is, independently regulated bone resorption and formation of thyroid hormone, as opposed to being secondary to reduced thyroid hormone levels. Therefore, the authors concluded that TSH directly promoted skeletal conservation in adults. Some studies suggested that the effects of TSH on bone remodeling might be related to its inhibition of bone turnover, but the lack of this response in premenopausal women suggested that estrogen status has an effect on bone reactivity to TSH [22]. Low serum TSH level observed in thyroidectomized patients treated with levothyroxine was associated increased bone turnover in postmenopausal women and men, which was associated with increased osteoprotegerin and decreased serum receptor activator of NF-κB ligand levels.

Another finding of this study was that BMD in women younger than 60 years of age decreased as TSH increased within the normal reference range, although not reaching osteopenia status, but to statistically significant. This requires our vigilance and us to further explore the relevant mechanisms.

In addition, there was a gender difference in the change of BMD with advancing TSH. In our study, BMD in males decreased slightly as serum TSH level increased within the reference range. However, this trend was not significant in males. This could be explained by greater periosteal apposition in males, which would result in a greater cross-sectional bone diameter and biochemical advantage [23]. In males, loss of trabecular bone was usually related to the thinning of trabecular bars but maintaining their connectivity. However, in females, there were loss of connectivity and destruction of trabecular structure, which would further reduce bone strength [24]. It has also been confirmed that the occurrence of postmenopausal osteoporosis was mainly due to the reduction of estrogen level. The reduced estrogen level would decrease the suppressive effect of estrogen on osteoclasts, increase the quantity of osteoclasts, decrease cell apoptosis, and enhance bone resorption. In addition, study indicated that only lumbar BMD in men was associated with TSH [25], and there was no association of TSH levels in the euthyroid range with fracture risk in men compared to women [26].

There were a few limitations in this study. Some factors, such as the use of medications and medical history, were adjusted in regression analysis. The inclusion of these factors might help to elucidate the independent relationship between the BMD and TSH levels. Besides, there might be a small percentage of patients with euthyroid due to treatment, which might introduce some bias.

In summary, the results demonstrated an opposite trend in BMD at normal TSH levels in younger and elder females, that is, in females younger than 60 years, BMD decreased with the increase of serum TSH levels, which indicated that TSH might play a different role in younger and elder females. However, these trends were not significant in males. Therefore, focusing on how TSH in female and male interact with bone metabolism may help manage people to reduce the risk of osteoporosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12986-024-00841-9.

Supplementary Material 1

Author contributions

J.C., X.C. and X.J. conceived and designed the study. J.C. and L.H. drafted the manuscript. N.L., W.D., X.X., L.W., K.Z., S.L. and X.L. acquired the data. J.C. and L.H. interpreted and analyzed the data. X.C. and X.J. reviewed the manuscript for important intellectual content critically. All authors contributed to the article and approved the submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the research ethics committee of Beijing Jishuitan Hospital.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Endocrinology, Beijing Jishuitan Hospital, Capital Medical University, Beijing 100035, China
[2]Department of Rheumatology and Immunology, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China
[3]Department of Orthopedic Trauma, Beijing Jishuitan Hospital, Capital Medical University, Beijing 100035, China
[4]Department of Radiology, Beijing Jishuitan Hospital, Capital Medical University, Beijing 100035, China
[5]Department of Medical Record Management and Statistics, Beijing Jishuitan Hospital, Capital Medical University, Beijing 100035, China

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