Effect of Normal Range Serum Thyrotrophin Levels on Bone Mineral Density of post-menopausal women and older men

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Abstract

Objective: To analyze the effect of serum TSH levels within the normal range on bone mineral density (BMD) of post-menopausal women and older men. **Methods:** A total of 570 subjects (305 older men aged 50 years or older and 265 post-menopausal women) with normal thyroid function were enrolled. According to the tertiles of serum normal TSH levels, men (T1, T2, and T3), and post-menopausal women (N1, N2, and N3) were divided into three groups, respectively. The differences in blood calcium, phosphorus, 25(OH) vit D, right calcaneal and left forearm BMD levels between the groups with different TSH levels were compared. **Results:** The right calcaneus BMD in T1 or T2 group of men was significantly lower than those in T3 group (all $P < 0.05$). The right calcaneus and left forearm BMD in N1 or N2 group of post-menopausal women was significantly lower than those in N3 group (both $P < 0.05$). There was no significant difference in serum calcium and phosphorus levels, 25 (OH) vit D between the three groups with different TSH levels of men or post-menopausal women (all $P > 0.05$). The prevalence of right calcaneal osteoporosis of N1 or N2 group, and the prevalence of left forearm osteoporosis of N1 group in postmenopausal women was significantly higher than those of N3 group (all $P < 0.05$). The TSH levels were significantly positively correlated with right calcaneal BMD of men ($R = 0.116$, $P = 0.044$), and positively correlated with right calcaneal and left forearm BMD of post-menopausal women ($R = 0.198$ and $R = 0.135$, $P < 0.05$). BMD considered as the dependent variables, after adjusting for gender, age, BMI, waist circumference, serum calcium, phosphorus and 25 (OH) vit D levels, the risks of right calcaneal osteoporosis in N1 group of post-menopausal women were 2.278 times that of N3 group. The different TSH levels in men showed no association with the risks of osteoporosis (all $P > 0.05$). **Conclusions:** The normal serum TSH levels of men or post-menopausal women were related to BMD. The TSH levels within the lower normal range were associated with the risks of osteoporosis in post-menopausal women.

Background

With the development of society and progression in medical technology, people paid more and more attention to the increased metabolic osteopathy. Osteoporosis is a kind of metabolic diseases that seriously harmed the health of the public, which increased the risks of fracture and had a great impact on people's lives. According to the study by Abrahamsen *et al.*, hyperthyroidism may increase the risks of hip fractures [1]. In depth analysis on thyrotrophin (TSH) showed that the changes in TSH levels within the normal range may also affect bone metabolism. Leader [2] *et al.* reported that women over the age 65 were associated with significantly increased risks of hip fractures in normal or lower TSH levels, indicating that the fluctuation of TSH levels within the normal range may have an impact on bone mineral density (BMD), and this in turn increased the risks of fractures to some extent. Although several scholars paid attention regarding the relationship between normal TSH levels and bone metabolism, the conclusions were still inconsistent. Also there are few studies conducted on the relationship between normal TSH levels and bone density or osteoporosis in healthy people in China until now. Hence, this study aimed to investigate the effect of serum normal TSH levels on the BMD of post-menopausal women and elderly males in China.

Subjects And Methods

Subjects

A total of 2885 volunteers from some areas of Gansu province, China, who participated in the "Thyroid diseases and iodine nutrition status national survey (Tide)" were included. Finally, a total of 570 subjects with normal thyroid function were enrolled in this study, including 305 older men aged 50 years or older, and 265 post-menopausal women.

All subjects were from Chinese ethnic Han, had more than 5 years of living history in the community (or village) of the survey areas. These subjects did not accept iodine-containing contrast agents or ethamidone for nearly 3 months. Written and oral information of the protocol was explained to them before screening, and informed consents were obtained from each eligible participant.

Exclusion criteria were as follows: (1) patients with abnormal thyroid function in the past or at present, and whether or not drug therapy was adopted; (2) patients with diabetes in the past and with diabetes diagnosed during study participation; (3) patients with calcium supplements or vitamin D treatment within 1 year; (4) patients with kidney diseases, parathyroid gland dysfunction, myeloma, bone tumor or bone metastatic tumor; (5) patients with long-term use of corticosteroids; (6) pregnant women.

Methods

A questionnaire survey was conducted by uniformly trained investigators. The survey included basic data (such as age, sex, age of menopause, and so on), previous medical history and medication (ongoing or any previous history).

The height, weight and waist circumference of all the subjects were measured, and the height was recorded accurately to 0.1cm, and the weight accurate to 0.1kg. Body mass index (BMI) was calculated to determine the circumference of the midpoint between the lower margin of the lumbar rib and the upper margin of the iliac bone.

After fasting for 8 hours at night, the venous blood samples were collected in the morning. The blood calcium (Ca) and phosphorus (P) levels were measured by Bs-220 automatic biochemical analyzer (Mairui Biotechnology Co. LTD, China), and 25 - hydroxyl vitamin D [25 (OH) vit D] levels were detected by Rt-6000 enzyme standard analyzer (Rayto Life and Analytical Sciences Co., Ltd, Shenzhen, China). The thyroid stimulating hormone levels were measured by Chemiluminescence immunoassay (Cobas 601 analyzer, Roche diagnosis, Switaerland). The BMD levels were measured by Osteosys Exa-3000 dual-energy X-ray bone density meter (Gerry langbo technology development co., LTD, Beijing, China) in g/cm², and the T values were analyzed automatically by the software. According to the method recommended by WHO in 1994, i.e., the measurement of BMD was compared with the same gender's peak bone density, where the standard deviation of bone (T), if the subjects with T values of one or more than one sites, was

≤ -2.5 , then it was considered as osteoporosis; in the range of $-2.5 < T$ values ≤ -1 was considered as reduction of bone mass, and T values > -1 was considered as normal bone mass.

The normal reference range of serum TSH levels was 0.27–4.20 mIU/L. To evaluate the differences according to the tertiles of TSH levels in the normal range, the subjects were divided into three groups. (1) Men: T1 group: TSH 0.40–1.78 mIU/L; T2 group: TSH 1.79–2.73 mIU/L; T3 group: TSH 2.74–4.20 mIU/L; (2) Post-menopausal women: N1 group (0.28–2.01) mIU/L, N2 group (2.02–3.23) mIU/L and N3 group (3.24–4.20) mIU/L.

Statistical Analysis

All the data were analyzed using SPSS 23.0 software. The normal distribution data were described as. The comparison among multiple groups was performed by single factor analysis of variance (ANOVA) followed by LSD multiple comparison. Chi-square test was used to analyze the counting data between multiple groups. Spearman correlation analysis was used for ranked data. After bone density stratification, binary logistic regression analysis was performed. A P value < 0.05 was considered to be statistically significant.

Results

Effect of TSH levels within the normal range on bone metabolism of older men

Comparison of parameters between the three groups with different TSH levels

The total prevalence of left forearm osteoporosis in older men was 32.1% (98/305), and the total prevalence of right calcaneal osteoporosis in older men was 31.8% (97/305).

The right calcaneus BMD in the T1 or T2 group of older men was significantly lower than those in T3 group (both $P < 0.05$). The waist circumference levels in group T1 or T2 group, and BMI levels in T2 group were significantly lower than those in T3 group (all $P < 0.05$). There was no significant difference in age, serum calcium and phosphorus levels, 25 (OH) vit D and left forearm BMD levels between the three groups with different TSH levels of older men (all $P > 0.05$, Table 1).

Comparison of the prevalence of osteoporosis between the three groups with different TSH levels

There was no significant difference in the prevalence of left forearm and right calcaneal osteoporosis between the three groups with different TSH levels in older men (all $P > 0.05$, Table 2).

Correlation between TSH levels and BMD

Spearman correlation analysis showed the TSH levels of elderly males were significantly positively correlated with right calcaneal BMD ($R = 0.116$, $P = 0.044$), but no significant correlation with left forearm BMD ($R = 0.081$, $P = 0.168$).

Risks assessment of osteoporosis at different TSH levels

BMD considered as the dependent variables, after adjusting for gender, age, BMI, waist circumference, serum calcium, serum phosphorus and 25 (OH) vit D levels, the different TSH levels showed no association with the risks of osteoporosis (all $P > 0.05$, Table 3.).

Effect of TSH levels within the normal range on bone metabolism of post-menopausal women

Comparison of parameters between the three groups with different TSH levels

The total prevalence of left forearm osteoporosis in post-menopausal women was 32.5%, and the total prevalence of right calcaneal osteoporosis in post-menopausal women was 37.2%.

The left forearm BMD, and right calcaneal BMD of N1 or N2 group in post-menopausal women showed significantly lower than that of N3 group (both $P < 0.05$). The age of N1 group was significantly higher than that of N3 group ($P < 0.05$). The BMI, waist circumference, blood calcium and blood phosphorus, and 25(OH) vit D levels showed no significant difference between the three groups of different TSH levels in post-menopausal women (all $P > 0.05$, Table 4).

Comparison of the prevalence of osteoporosis in the three groups with different TSH levels

The prevalence of right calcaneal osteoporosis of N1 or N2 group in postmenopausal women was significantly higher than those of N3 group (both $P < 0.05$). The prevalence of left forearm osteoporosis of N1 group in postmenopausal women was significantly higher than that of N3 group ($P < 0.05$, Table 5).

Correlation between TSH levels and BMD

Spearman correlation analysis showed that the TSH levels of post-menopausal women were significantly positively correlated with right calcaneal BMD ($R = 0.198$ $P = 0.001$), and the left forearm BMD ($R = 0.135$ $P = 0.033$).

Risks assessment of osteoporosis at different TSH levels

BMD considered as the dependent variables, after adjusting for gender, age, BMI, waist circumference, serum calcium, serum phosphorus and 25 (OH) vit D levels, the risks of right calcaneal osteoporosis in N1 group of post-menopausal women were 2.278 times that of N3 group ($P < 0.05$). No differences were observed in the risks of left forearm osteoporosis in post-menopausal women with different TSH levels ($P > 0.05$, Table 6).

Discussion

Previous studies showed that abnormal thyroid function (hyperthyroidism or hypothyroidism) may affect BMD [3, 4]. However, in recent years, some studies showed that even fluctuations in thyroid function within the normal range directly affected the bone metabolism through TSH.

The present study showed a positive correlation between the normal TSH levels of men and right calcaneal BMD, showing a significant decrease in the right calcaneal BMD in the group with TSH levels within the lower normal range (0.40–1.78) mIU/L. Till now, there were very few studies on the relationship between the TSH levels within the normal range and bone metabolism of the men. Lee *et al.* [5] reported that even TSH levels (0.36–1.05 mIU/L) in the lower normal range would reduce the BMD of buttocks, showing a negative impact on the geometric structures of the proximal buttocks. In addition, the osteoporosis and serum TSH levels were directly correlated, and during hypothyroidism treatment, maintaining the TSH levels within the upper limit of normal range had an important preventive effect on osteoporosis [6].

This study showed that the left forearm and right calcaneal BMD levels of N1 or N2 group in postmenopausal women were significantly lower than those of N3 group. The prevalence of right calcaneal osteoporosis of N1 or N2 group in postmenopausal women was significantly higher than those of N3 group, and the prevalence of left forearm osteoporosis of N1 group in postmenopausal women was significantly higher than that of N3 group. The normal TSH levels in postmenopausal women was positively correlated with right calcaneal and left forearm BMD. According to a previous study, a positive correlation between the TSH levels within the normal reference range and BMD of the femoral neck, hip and ward's triangle area was found in China [7]. Leader *et al.* [2] reported that women with normal thyroid function, aged more than 65-years, and TSH levels within the lower normal range (0.35 to 1.60 mIU/L) led to decreased proximal femur BMD and alterations in the cortical bone geometry, which significantly increased the risk of hip fractures. Lee *et al.* [5] reported that the normal range lower TSH levels (0.36–1.17 mIU/L) also showed a negative impact on the BMD of the hip and the geometric structures of the proximal hip, resulting in decreased BMD of the femoral neck and total hip joints. All the above results suggested that TSH levels within the lower normal range may lead to decreased BMD and increased prevalence of osteoporosis in post-menopausal women.

The mechanism of correlation between the serum TSH levels and osteoporosis was still unclear. TSH receptor (TSHR) was mainly expressed in thyroid follicular cells [8], however, the studies showed that TSHR also existed in osteoblasts and osteoclasts [8–10]. TSH acts as a skeletal balance spinner, affecting bone reconstruction, bone formation of osteoblasts, and bone absorption of osteoclasts by TSHR on pre-osteoblasts and osteoblasts [11]. Studies in rodents showed that TSH may prevent bone loss and stimulate bone formation [8, 12–13]. TSHR knock-out in mice with normal free T4 and T3 levels showed severe osteoporosis and also focal osteoid sclerosis, indicating the regulatory effects of TSH on bone cell formation and osteoblast differentiation [8]. The bone formation of TSHR gene knock-out mice was lower than the normal control mice, and after thyroid hormone replacement, the bone formation was increased slightly, but was still below the levels of normal mice, which indicated that TSH may have an impact on bone i.e., independent of thyroid hormone [14]. The TSH may stimulate differentiation of mouse embryonic stem cells into osteoblasts [15]. Intermittent injection of recombinant TSH can restore the osteoporosis caused by ovariectomies in adult rats and improve the skeletal strength of the rats, and this may be related to the TSHR existence on osteoblasts or osteoclasts [12].

TSH may directly affect bone reconstruction in a part of subclinical hyperthyroidism patients with lower bone health [16], and so it was considered that in addition to the traditional influence of thyroid hormone on bone, TSH may have direct effects on bone health status [17–19]. Hueston *et al*/thought that TSH may be more sensitive to reflect the special relationships between thyroid function and bone metabolic indexes than thyroid hormone, which may be attributed to hypothalamus-pituitary-thyroid axis, and whether it was a positive or a negative feedback [20]. The short-term stimulation with recombinant TSH by post-menopausal women undergoing thyroidectomy can inhibit type I collagen-terminal peptide and bone alkaline phosphatase, indicating that TSH can inhibit bone absorption [16]. Acar *et al*. [6] believed that during the treatment of hypothyroidism, maintaining TSH levels within the upper limit of reference range showed an important preventive effect on post-menopausal women's osteoporosis. In addition, the BMD was decreased with decreasing TSH levels, while the serum free thyroxine was not correlated with BMD in elderly women with normal thyroid function [5]. Therefore, TSH may have an effect on bone that was independent of thyroid hormone, and TSH levels within the higher normal range may have a protective effect on bone.

TSH can inhibit the formation, differentiation and function of osteoclasts by regulating certain cytokines [8, 13]. Abe *et al* [8] found that TSH regulated absorption and formation of bone through low abundance G protein coupled TSHR on the osteoclast precursor, activated c-Jun amino terminal kinase (JNK) and nuclear factor kappa B (NF- κ B) signaling pathway, abating the RANKL and tumor necrosis factor- α expression, and directly inhibited osteoclast formation. In addition, this inhibited the expression of collagen type I and osteoblasts differentiation by down-regulating low-density lipoprotein related protein 5 (LRP5) and fetal liver kinase 1 (FLK-1) expression, and inhibiting the effect of Wnt and vascular endothelial growth factor signaling pathway.

Conclusions

In conclusion, the present study indicated that the normal TSH levels of men and post-menopausal women were related to BMD. The TSH levels within the lower normal range in postmenopausal women were more likely to have osteoporosis. Therefore, the TSH levels in higher normal range may be more beneficial to prevent osteoporosis in healthy people, especially in post-menopausal women.

Abbreviations

BMD: Bone mineral density; TSH: Thyrotrophin; Ca: Calcium; P: Phosphorus; 25 (OH) vit D: 25 - hydroxyl vitamin D; JNK: Jun amino terminal kinase; NF- κ B: Nuclear factor kappa B; LRP5: Low-density lipoprotein related protein; FLK-1: Fetal liver kinase 1.

Declarations

Ethics approval and consent to participate

The study was approved by the First Affiliated Hospital of China Medical University Medical Science Research Ethics Board (Ethics reference numbers AF-SOP–07–1.0–01). Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used during this study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

LJF, FSB, JGJ, MLH, SWM and NY contributed to data collection. WBL, LYJ and WD measured the data. LJF and QLP analyzed the data. LJF and QLP interpreted the data and wrote the manuscript. LJF and TXL discussed the data and revised the manuscript. All authors have read and approved the final version.

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Tables

Table 1. Parameters of the three groups with different TSH levels in older men

Parameters	T1 group (102)	T2 group (103)	T3 group (100)
Age (year)	61.04±8.29	61.10±8.60	61.66±8.69
BMI(Kg/m2)	24.34±2.72	23.92±2.85#	25.11±3.07
Waist circumference (cm)	86.84±9.61#	87.40±9.70#	90.30±7.85
Ca (mmol/L)	2.19±0.08	2.15±0.21	2.16±0.19
P (mmol/L)	0.96±0.21	0.92±0.13	0.93±0.18
25 (OH) vit D (ng/mL)	14.86±6.61	13.92±5.54	15.04±5.70
Left forearm BMD (g/cm2)	0.45±0.08	0.44±0.07	0.46±0.09
Right calcaneal BMD (g/cm2) (g/cm2) (g/cm2)	0.48±0.12#	0.48±0.11#	0.52±0.12

BMIBody mass index; 25 (OH) vit D: 25 - hydroxyl vitamin D; BMD: Bone mineral density; Ca: blood calcium; P: blood phosphorus. T1 group: TSH0.40-1.78mIU/LT2 group: TSH1.79-2.73mIU/L; T3 group: TSH2.74-4.20mIU/L. #P<0.05: compared with T3 group.

Table 2. Prevalence of older men osteoporosis between the three groups with different TSH levels

Parameters	Normal/reduced bone	osteoporosis	χ^2	<i>P</i>
Right calcaneal				
T1 group	63 (61.8%)	39 (38.2%)		
T2 group	72 (69.9%)	31 (30.1%)		
T3 group	72 (72.0%)	28 (28.0%)		
T1 group: T2 group			1.509	0.219
T1 group: T3 group			2.386	0.122
T2 group: T3group			0.108	0.742
Left forearm				
T1 group	72 (70.6%)	30 (29.4%)		
T2 group	66 (64.1%)	37 (35.9%)		
T3 group	70 (70.0%)	30 (30.0%)		
T1 group: T2 group			0.987	0.320
T1 group: T3 group			0.008	0.927
T2 group: T3 group			0.805	0.370

T1 group: TSH 0.40-1.78 mIU/L; T2 group: TSH 1.79-2.73 mIU/L; T3 group: TSH 2.74-4.20 mIU/L.

Table 3. Risk assessment of osteoporosis at different TSH levels in older men

Parameters	B	OR	<i>P</i>	95%CI
Right Calcaneal				
T1 group	0.093	1.098	0.777	0.575-2.095
T2 group	0.319	1.376	0.326	0.728-2.598
T3 group	0a			
Left Forearm				
T1 group	0.370	1.448	0.276	0.744-2.816
T2 group	-0.070	0.932	0.838	0.476-1.826
T3 group	0a			

T1 group: TSH 0.40-1.78 mIU/L; T2 group: TSH 1.79-2.73 mIU/L; T3 group: TSH 2.74-4.20 mIU/L

Table 4. Parameters of the three groups with different TSH levels in post-menopausal women

Parameters	N1 group (88)	N2 group (89)	N3 group (88)
Age (year)	59.65±10.86#	56.99±9.29	54.25±7.52
BMI (Kg/m ²)	23.57±3.11	24.19±3.26	23.44±2.84
Waist circumference (cm)	81.66±8.67	82.01±8.32	80.85±7.88
Ca (mmol/L)	2.19±0.12	2.20±0.05	2.18±0.14
P (mmol/L)	1.08±1.32	1.07±0.12	1.07±0.14
25 (OH) vit D (ng/mL)	12.30±6.63	12.00±4.94	12.13±4.61
Left forearm BMD (g/cm ²)	0.35±0.10#	0.35±0.09#	0.38±0.80
Right calcaneal BMD (g/cm ²)	0.33±0.11#	0.35±0.12#	0.39±0.11

BMI: Body mass index; 25 (OH) vit D: 25 - hydroxyl vitamin D; BMD: Bone mineral density; Ca: blood calcium; P: blood phosphorus. N1 group: TSH 0.28-2.01 mIU/L, N2 group: TSH 2.02-3.23 mIU/L, N3 group: TSH 3.24-4.20 mIU/L. #*P*<0.05: Compared with N3 group.

Table 5. Prevalence of osteoporosis in post-menopausal women with different TSH levels

Parameters	Normal/Reduced bone	osteoporosis	χ^2	<i>P</i>
Right Calcaneal				
N1 group	43(50%)	43(50%)		
N2 group	54(61.4%)	34(38.6%)		
N3 group	67(77%)	20(23%)		
N1 group: N2 group			2.277	0.131
N1 group: N3 group			13.628	0.000
N2 group: N3 group			5.021	0.025
Left Forearm				
N1 group	50(60.2%)	33(39.8%)		
N2 group	53(65.4%)	28(34.6%)		
N3 group	63(76.8%)	19(23.2%)		
N1 group: N2 group			0.473	0.492
N1 group: N3 group			5.259	0.022
N2 group: N3 group			2.579	0.108

post-menopausal women: N1 group: TSH 0.28-2.01 mIU/L, N2 group: TSH 2.02-3.23 mIU/L, N3 group: TSH 3.24-4.20 mIU/L.

Table 6. Risk assessment of osteoporosis at post-menopausal women with different TSH levels

Parameters	B	OR	<i>P</i>	95%CI
Right Calcaneal				
N1 group	0.823	2.278	0.047	1.011-5.132
N2 group	0.425	1.530	0.306	0.678-3.451
N3 group	0a			
Left Forearm				
N1 group	-0.091	0.913	0.858	0.338-1.462
N2 group	0.156	1.169	0.742	2.468-2.955
N3 group	0a			

N1 group: TSH 0.28-2.01 mIU/L; N2 group: TSH 2.02-3.23 mIU/L; N3 group: TSH 3.24-4.20 mIU/L.