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ORIGINAL RESEARCH

Low TSH Levels Within Euthyroid Range Could Play a Negative Role on Bone Mineral Density in Postmenopausal Women with Type 2 Diabetes

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Objective: We aimed to evaluate the relationship between thyroid-stimulating hormone (TSH) and bone mineral density (BMD) in euthyroid type 2 diabetes (T2D).

Methods: This retrospective analysis enrolled 439 T2D patients with normal thyroid function, including 226 males and 213 females. All the female patients were postmenopausal. Serum glycosylated hemoglobin A1c (HbA1c), TSH, free triiodothyronine (FT_3), and free thyroxine (FT_4) concentrations were analyzed. BMD of the lumbar spine (L_1–L_4), femoral neck, and hip joint was determined using dual-energy X-ray absorptiometry.

Results: The patients were grouped based on tri-sectional quantiles of the TSH levels: 0.55~1.70mIU/L (Group 1), 1.71~2.58mIU/L (Group 2), and 2.59~4.74mIU/L (Group 3). Our data showed that, in male patients, no difference in BMD was identified among groups. In postmenopausal women, unlike at the lumbar spine ($P = 0.459$), the mean BMD at the femoral neck ($P = 0.014$) and hip joint ($P = 0.014$) had a statistical difference among groups and increased with TSH level. In addition, our analysis demonstrated that TSH levels shown no correlation with BMD at all sites in males. However, in females, BMD at the femoral neck ($r = 0.156$, $P = 0.023$) and hip joint ($r = 0.172$, $P = 0.012$) had a positive correlation with TSH levels. After adjusting for age and BMI, multiple regression analysis showed that TSH levels influenced BMD at the femoral neck ($\beta = 0.188$, $P = 0.001$) and hip joint ($\beta = 0.204$, $P = 0.001$) in female patients.

Conclusion: In summary, our data demonstrates that low TSH levels are associated with decreased BMD at the femoral neck and hip joint in postmenopausal T2D women with euthyroidism.

Keywords: type 2 diabetes, thyroid-stimulating hormone, bone mineral density, menopause

Introduction

Type 2 diabetes (T2D) is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance, and accounts for more than 90% of all the diabetic subjects. Sustained hyperglycemia enhances the chances of developing of chronic complications in patients with T2D.[1] Indeed, studies have indicated that osteoporosis is a significant complication of T2D in addition to the other well-established complications.[2,3] Osteoporosis is a metabolic bone disease characterized by decreased bone mass and destruction of bone microstructure, leading to bone fragility and increased risk of fracture.[4] Chronic complications of diabetes can induce microvascular damage, resulting in systemic microcirculation disorders, accelerating formation of microthrombosis and abnormal blood supply to

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the bones, thus affecting bone metabolism.[5] T2D also can cause bone mass destruction and microstructural changes through a variety of other complex factors.[6]

On the other hand, thyroid function is closely related with bone health and an abnormal thyroid function significantly affects bone health.[7–9] Hyperthyroidism accelerates bone turnover and increases the frequency of bone remodeling. High bone turnover accelerates bone loss and increases susceptibility to osteoporosis and fracture.[10] Besides, subclinical hyperthyroidism is associated with reduced bone mineral density (BMD) and increased risk of fractures.[11–13] However, the impact of hypothyroidism and subclinical hypothyroidism on bone health remains unclear.[7–9,11] Despite slight controversy, recent researches show that thyroid function can affect BMD, even if it is within the normal reference range. Some studies have indicated that, within the normal range, low thyroid-stimulating hormone (TSH) or high thyroid hormone levels contribute to decreased BMD and increased risk of fractures,[14–21] while others have failed to define such a relationship.[22–24]

Patients with T2D are at a high risk for osteoporosis. However, whether thyroid status influences bone health in patients with T2D as observed in the general population remains unclear. Here, we interrogated the effect of normal thyroid function on BMD in men and postmenopausal women with T2D patients. This study presents a new approach for the clinical prevention of osteoporosis in patients with T2D using the thyroid function profile.

Materials and Methods
Participants
A total of 439 T2D patients, including 226 males and 213 females, hospitalized at the Department of Endocrinology of Shanghai Pudong Hospital from May 1, 2019, to July 31, 2020, were enrolled in this study. All the included women were postmenopausal. TSH, free triiodothyronine (FT_3), and free thyroxine (FT_4) values of the participants were within the reference range. Patients with secondary osteoporosis, such as thyroid or parathyroid diseases, drugs induced, or tumors, as well as those with bone metabolic diseases, anti-osteoporosis treatments or drugs use history affecting bone metabolism within the past 6 months were excluded from the study. In addition, patients with acute liver, kidney, heart or brain diseases, mental diseases were excluded.

Measurements
We recorded height and weight and then computed body mass index (BMI). Fasting veinal blood samples were obtained and analyzed within 2 hours. Glycosylated hemoglobin A1c (HbA1c) was measured and we tested serum TSH, FT_3, and FT_4 using immunoluminometric assay. The reference range for the TSH was 0.55mIU/L~4.78mIU/L. BMD at the lumbar spine (L_1–L_4), femur neck, as well as hip joint was evaluated by dual-energy X-ray absorptiometry (DXA).

Statistical Analysis
Statistical analyses were performed using SPSS 22.0 version and GraphPad Prism v.8. Kolmogorov–Smirnov test was used to evaluate the normal distribution of the data. The normal distribution data was described by $\bar{X} \pm S$. In addition, the Student's *t*-test was used to compare the two groups while one-way *ANOVA* was used to assess variances among the three groups. We then performed post hoc comparison using $LSD - t$, while Pearson correlation analysis was used to analyze the correlation among variables. On the other hand, non-normal distribution data was represented by $M(Q25, Q75)$. Mann–Whitney *U*-test was used to compare between two groups, while Kruskal–Wallis *H*-test was used for comparison among three groups. Spearman correlation analysis was used to evaluate the correlation among variables. In addition, multivariate regression analysis was performed to explore the relationship between the TSH and BMD after adjusting for age and BMI. A *P* value<0.05 was considered statistically significant.

Results
Clinical Baseline Characteristics
The baseline characteristics for the T2D patients with normal thyroid function were shown in Table 1. Compared with males, female patients were older, had a longer diabetic duration, and their BMD was dramatically reduced at the lumbar spine, femoral neck, and hip joint.

BMD in Different TSH Concentration Groups
The patients were grouped based on tri-sectional quantiles of the TSH levels: 0.55~1.70mIU/L (Group 1), 1.71~2.58mIU/L (Group 2), and 2.59~4.74mIU/L (Group 3). Our data showed that, in male patients, there was no difference in age, BMI, duration of diabetes, HbA1c as well as BMD

Table 1 Baseline Characteristics of the Study Participants

Variables	Male	Female	P
N	226	213	
Age (year)	64.10±10.50	67.38±10.37	0.001**
BMI (kg/m^2)	25.33±3.33	25.48±3.78	0.674
HbA1c (%)	9.37±2.07	9.38±2.30	0.988
Diabetic Duration (year)	10(3,15)	10(6,18)	0.017*
FT$_3$ (pmol/L)	4.66±0.54	4.33±0.48	<0.001**
FT$_4$ (pmol/L)	15.76±2.11	15.38±2.01	0.053
TSH (mIU/L)	2.06±0.96	2.41±0.98	<0.001**
BMD L$_1$ (g/cm^2)	0.97±0.17	0.81±0.15	<0.001**
BMD L$_2$ (g/cm^2)	1.01±0.18	0.84±0.15	<0.001**
BMD L$_3$ (g/cm^2)	1.05±0.20	0.88±0.16	<0.001**
BMD L$_4$ (g/cm^2)	1.04±0.20	0.88±0.17	<0.001**
BMD Lumbar spine (g/cm^2)	1.03±0.19	0.86±0.16	<0.001**
BMD Femur neck (g/cm^2)	0.78±0.13	0.66±0.12	<0.001**
BMD Hip joint (g/cm^2)	0.92±0.14	0.80±0.17	<0.001**

Notes: *$P<0.05$; **$P<0.01$.
Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; FT$_3$, free triiodothyronine; FT$_4$, free thyroxine; TSH, thyroid-stimulating hormone; BMD, bone mineral density.

(Table 2). On the other hand, whereas there were no statistically differences in age, BMI, duration of diabetes, and HbA1c, the female patients showed differences in BMD (femoral neck: $P = 0.014$, hip joint: $P = 0.014$), and increased with TSH level (Table 3). In addition, there was a significant decline in the BMD at the femoral neck ($P = 0.004$) and hip joint ($P = 0.004$) in females in Group 1 compared to Group 3 (Figure 1).

Correlation Between BMD and TSH Concentration

For the correlation analysis, BMD was used as a dependent variable, while age, BMI, diabetic duration, HbA1c, and TSH were used as independent variables. The results showed that, in males, BMD at the lumbar spine was positively correlated with

Table 2 BMD in Different TSH Concentration Groups (Male)

Variables	Group 1	Group 2	Group 3	P
N	96	69	61	
Age (year)	62.73±9.89	64.45±11.35	65.87±10.32	0.179
BMI (kg/m^2)	25.22±3.19	25.19±3.35	25.68±3.55	0.631
HbA1c (%)	9.72±2.08	9.23±2.11	8.99±1.93	0.079
Diabetic Duration (year)	7.5(2,14.75)	10(3.5,16)	10(4.5,18.5)	0.153
BMD Lumbar spine (g/cm^2)	1.01±0.19	1.03±0.17	1.06±0.20	0.277
BMD Femur neck (g/cm^2)	0.78±0.15	0.77±0.12	0.78±0.12	0.939
BMD Hip joint (g/cm^2)	0.92±0.14	0.93±0.14	0.93±0.13	0.909

Abbreviations: Group 1, TSH 0.55~1.70mIU/L; Group 2, TSH 1.71~2.58mIU/L; Group 3, TSH 2.59~4.74mIU/L; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; BMD, bone mineral density; TSH, thyroid-stimulating hormone.

Table 3 BMD in Different TSH Concentration Groups (Female)

Variables	Group 1	Group 2	Group 3	P
N	52	77	84	
Age (year)	68.87±10.25	65.61±9.56	68.10±10.04	0.157
BMI (kg/m^2)	26.01±4.29	25.35±3.75	25.26±3.47	0.502
HbA1c (%)	9.32±2.44	9.65±2.19	9.16±2.31	0.397
Diabetic Duration (year)	10(8,19.75)	10(5,18)	10(4.25,16.50)	0.471
BMD Lumbar spine (g/cm^2)	0.85±0.14	0.86±0.16	0.88±0.16	0.459
BMD Femur neck (g/cm^2)	0.63±0.12	0.66±0.12	0.69±0.12	0.014*
BMD Hip joint (g/cm^2)	0.76±0.13	0.79±0.16	0.85±0.19	0.014*

Note: *$P<0.05$.
Abbreviations: Group 1, TSH 0.55~1.70mIU/L; Group 2, TSH 1.71~2.58mIU/L; Group 3, TSH 2.59~4.74mIU/L; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; BMD, bone mineral density; TSH, thyroid-stimulating hormone.

age and BMI. Besides, BMD at the femoral neck and hip joint was negatively associated with age but positively related to BMI. BMD at all sites had no relationship with TSH (Table 4). In postmenopausal women, BMD at the lumbar spine had a positive relationship with BMI but negatively correlated with age. In addition, BMD at the femoral neck and hip joint exhibited a positive association with BMI and TSH, but a negative relationship with age and diabetic duration (Table 5).

Factors Influencing BMD at the Femoral Neck and Hip Joint in Postmenopausal T2D Women

For stepwise regression analysis, BMD at the femoral neck and hip joint were considered to be dependent variables, while age, BMI, diabetic duration, HbA1c, and TSH were independent variables. At the femoral neck, age, BMI and TSH influenced BMD (the adjusted R^2 =0.288, F =29.599, $P<0.001$), with age making the strongest contribution ($\beta = -0.468$, $P<0.001$), followed by BMI ($\beta = 0.192$, $P = 0.001$), and TSH ($\beta = 0.188$, $P = 0.001$) (Table 6). On the other hand, at the hip joint, the data showed that age, BMI, and TSH were the influencing factors of hip joint (the adjusted R^2 =0.257, $F = 25.381$, $P <0.001$), and age had the greatest influence ($\beta = -0.345$, $P < 0.001$), followed by BMI ($\beta = 0.310$, $P < 0.001$), and TSH ($\beta = 0.204$, $P = 0.001$) (Table 7).

Discussion

This study included T2D patients with normal thyroid function. Our correlation analysis demonstrated that age and BMI were strongly correlated with BMD at all sites. We showed that only the BMD at the lumbar spine was positively related with age in males, while the others were negatively correlated.
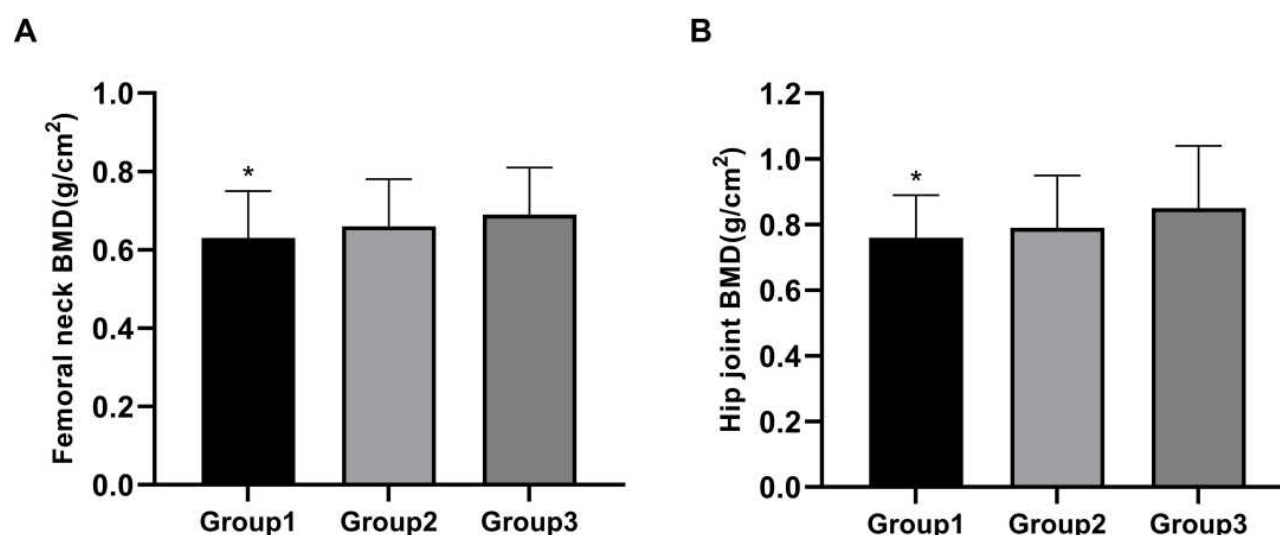
Figure 1 Comparison of femoral neck BMD (**A**) and hip joint BMD (**B**) among the different TSH concentration groups in T2D female patients. The BMD at the femoral neck and hip joint increased with TSH level. *$P<0.05$ compared with Group 3.
Abbreviations: T2D, type 2 diabetes; BMD, bone mineral density; Group 1, TSH 0.55~1.70mIU/L; Group 2, TSH 1.71~2.58mIU/L; Group 3, TSH 2.59~4.74mIU/L.

In agreement with previous studies, our data showed that BMD at all sites had a positive correlation with BMI.[25,26] We could, however, not demonstrate and correlation between TSH and BMD at all sites in male patients.[27] On the other hand, in postmenopausal women, high levels of TSH within the normal range were associated with high BMD at the femoral neck and hip joint, but not with BMD at the lumbar spine. Multiple regression analysis showed that the positive correlation between TSH levels and BMD for the two sites did not change after adjustment for age and BMI. This is consistent with the results in many previous studies involving healthy subjects without T2D.[16,20,21]

Table 4 Correlation Between BMD at Different Sites and TSH Concentration (Male)

Variables	Lumbar Spine		Femoral Neck		Hip Joint	
	r/r_s	P	r/r_s	P	r/r_s	P
Age (year)	0.140	0.035*	−0.181	0.006*	−0.135	0.042*
BMI (kg/m^2)	0.286	<0.001**	0.332	<0.001**	0.329	<0.001**
HbA1c (%)	−0.002	0.971	0.126	0.059	0.059	0.376
Diabetic Duration (year)	0.106	0.114	−0.001	0.988	0.029	0.665
TSH (mIU/L)	0.101	0.130	0.020	0.761	0.039	0.562

Notes: *$P<0.05$; **$P<0.01$.
Abbreviations: BMD, bone mineral density; HbA1c, glycosylated hemoglobin A1c; TSH, thyroid-stimulating hormone; BMI, body mass index.

Table 5 Correlation Between BMD at Different Sites and TSH Concentration (Female)

Variables	Lumbar Spine		Femoral Neck		Hip Joint	
	r/r_s	P	r/r_s	P	r/r_s	P
Age (year)	−0.260	<0.001**	−0.479	<0.001**	−0.368	<0.001**
BMI (kg/m^2)	0.268	<0.001**	0.234	0.001**	0.338	<0.001**
HbA1c (%)	−0.015	0.825	0.079	0.250	0.076	0.269
Diabetic Duration (year)	−0.001	0.987	−0.204	0.003**	−0.168	0.014*
TSH (mIU/L)	0.080	0.243	0.156	0.023*	0.172	0.012*

Notes: *$P<0.05$; **$P<0.01$.
Abbreviations: BMD, bone mineral density; HbA1c, glycosylated hemoglobin A1c; TSH, thyroid-stimulating hormone; BMI, body mass index.

Table 6 Multiple Regression Analysis of the Factors Influencing BMD at the Femoral Neck in Postmenopausal Female T2D Patients

Variables	Femoral Neck R^2=0.288 P<0.001				
	B	SE	β	t	P
Age (year)	−0.006	0.001	−0.468	8.014	<0.001**
BMI (kg/m^2)	0.006	0.002	0.192	3.286	0.001**
TSH (mIU/L)	0.023	0.007	0.188	3.244	0.001**

Note: **P<0.01.
Abbreviations: BMD, bone mineral density; T2D, type 2 diabetes; BMI, body mass index; TSH, thyroid-stimulating hormone; B, unstandardized coefficient; β, standardized coefficient.

Table 7 Multiple Regression Analysis of the Factors Influencing BMD at the Hip Joint in Postmenopausal Female T2D Patients

Variables	Hip joint R^2=0.257 P<0.001				
	B	SE	β	t	P
Age (year)	−0.006	0.001	−0.345	5.782	<0.001**
BMI (kg/m^2)	0.014	0.003	0.310	5.205	<0.001**
TSH (mIU/L)	0.035	0.010	0.204	3.439	0.001**

Note: **P<0.01.
Abbreviations: BMD, bone mineral density; T2D, type 2 diabetes; BMI, body mass index; TSH, thyroid-stimulating hormone; B, unstandardized coefficient; β, standardized coefficient.

Serum thyroid hormone and TSH are the basic indicators of thyroid function. Since TSH is more sensitive to changes in the thyroid status, it is considered the mainstay indicator to distinguish between normal and abnormal thyroid function. Besides, it has been demonstrated that hyperthyroidism and subclinical hyperthyroidism are associated with decreased BMD and increased fracture risk. In this study, low levels TSH within the normal range were associated with decreased BMD in the femoral neck and hip joint in postmenopausal women with T2D. We hypothesized that mild subclinical hyperthyroidism might also be present in patients with TSH at the low levels of the normal range. The TSH reference range only includes 95% of the reference population, and the lower limit of the reference is relatively normal. Moreover, endocrine and metabolic disorders in T2D patients might also influence the reference range of TSH.[28,29] Therefore, TSH levels at the low normal range may also affect the BMD.

It has been thought that bone abnormalities caused by hyperthyroidism are due to thyroid hormones rather than TSH. Recent exploration has shown that TSH may play a direct role in bone protection. In 1998, Inoue et al first reported that TSH receptor could be expressed in osteoblast-like rat osteosarcoma cells.[30] Subsequently, studies in TSH receptor knockout mice demonstrated that osteoblasts and osteoclasts expressed TSH receptor, and TSH receptor-deficient mice was more prone to develop high bone turnover osteoporosis.[31] Hase et al showed that TSH could inhibit the production of TNF-α and thus adversely regulate osteoclast differentiation.[32] In addition, Sun et al showed that an injection of recombinant TSH had a strong anti-bone resorption effect on bones in rats.[33] Besides, bone phenotypes were compared between wild-type and TSH receptor knockout mice and showed that both thyroid hormone and TSH can affect the bone.[34]

In addition, gender has been closely associated with BMD. In this study, compared with men, BMD decreased significantly at all sites in postmenopausal female patients, suggesting that gender influences bone metabolism. Data has shown that postmenopausal females have higher bone turnover. It has been established that postmenopausal osteoporosis occurs mainly of the decreased estrogen level, which reduces the inhibitory effect of estrogen on osteoclasts, and increases the number of osteoclasts, reduces apoptosis, and prolongs life span, as well as enhances bone resorption function. Although there was an increase in osteoblasts that contributed to bone formation, it was not sufficient to compensate for excessive bone resorption. The active and unbalanced bone remodeling results in thinness or fracture of trabecular bones, increased cortical bone porosity, and reduced bone strength.[35] Our study showed that low normal TSH levels could lead to decreased BMD at the femoral neck and hip joint in women, but not in men. Siru et al showed that TSH within the euthyroid range had no correlation with fracture risk in men compared to women.[27] In addition, the risk of fracture of thyroxine replacement therapy was also dependent on sex.[36] These studies may indicate that postmenopausal women are more susceptible to thyroid status than men.

In postmenopausal female patients, low normal levels of TSH may lead to decreased BMD at the femoral neck and hip joint but not at the lumbar spine. Similarly, Van der Deure and Murphy et al showed that low normal TSH levels or high thyroid hormone levels were only associated with BMD at the femoral neck, but not at the lumbar spine.[16,19] This might define the selectivity of the thyroid action to the lumbar spine and the femur. Thyroid hormones affect the cortex more than trabeculae, examining areas rich in cortical bone, such as the forearm and femoral neck, may have a greater impact than measuring only areas containing trabeculae.[37] In a series of

animal experiments, Suwanwalaikorn et al reported that TSH inhibitor L-thyroxine reduced BMD in the femur of rats, but not in the spine.[38–40] And gene expression markers in osteoblasts and osteoclasts were significantly increased in femur, but not in the lumbar spine. Long-term overdose of L-thyroxine in adult rats selectively affected the femoral bone over the vertebrae.[39] Therefore, we hypothesized that TSH may exert differential effects on the lumbar spine, femoral neck, and hip joint due to the specificity of the bone site. In addition, this could also be due to extrapyramidal calcification, especially osteophytes.[41–43] Orwoll et al demonstrated that subjects with osteophytes had higher spinal BMD, but not at the femoral site.[42] And osteophytes have a greater influence in men.[44] The results may also explain the positive correlation between lumbar spine BMD and age in males. Extra vertebral calcification interferes with the measurement of lumbar BMD. Besides, this measurement error might also interfere with the observation of the effect of TSH on lumbar spine BMD.

This study was conducted retrospectively and collected data from a single center. We did not fully consider other factors such as diet, lifestyle and labor intensity. The influence of sex hormones and menopausal years in postmenopausal women was not analyzed. However, our study supplemented the effect of normal thyroid function on bone health in patients with T2D, and separately investigated the effects in men and postmenopausal women. There is need for further exploration involving large prospective cohort studies.

In summary, our data demonstrates that low TSH levels are associated with decreased BMD at the femoral neck and hip joint in postmenopausal T2D women with euthyroidism. However, we could not find any association between serum TSH and BMD in T2D men within euthyroid range.

Ethical Statement

This study was approved by Shanghai Pudong Hospital affiliated with Fudan University (Shanghai, China), and followed the guidelines outlined in the Declaration of Helsinki. Informed written consent was obtained from the patients for the review of the medical data and publication of this study.

Funding

Disclosure

The authors claim that there is no conflict of interest.

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