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Study of the relationship between FT3, FT4, and TSH with bone resorption indices in men with hypothyroidism

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ABSTRACT

Aim: This study aimed to find the effect of hypothyroidism in men on metabolism and bone mineral density.

Method: The study included a patients group of 90 men suffering from hypothyroidism and 120 healthy subjects as a control group. The study comprised the estimation of the concentration of Blood free triiodothyronine (FT3), free thyroid hormone (FT4), thyroid stimulating hormone (TSH), bone resorption index type I collagen C-terminal peptide (CTX-1), the serum calcium (Ca2+), serum phosphorus (Pi3+), the bone mineral density of the lumbar spine and femoral neck.

Results: In the hypothyroidism men group: (1) the bone mass was lower than the control group with significant differences, (2) the bone resorption index CTX-1 was significantly higher than that in the control group and calcium and phosphorus were not different from those in healthy control subjects, and (3) TSH was positively correlated with CTX-1. Male TSH and CTX-1 levels were positively correlated.

Conclusions: There is bone loss in men with hypothyroidism, which may be related to increased bone resorption.

Keywords: *bone metabolism; bone mineral density; hypothyroidism*

INTRODUCTION

Recent studies have shown that the thyroid-stimulating hormone (TSH) has a major regulatory role in bone remodeling, independent of thyroid hormone.[1,2] Patients with subclinical hypothyroidism have elevated serum TSH and normal value of thyroid hormone, so it is a suitable model to study the role of TSH in regulating bone metabolism. At present, there is a controversy about the impact of TSH on bone mineral density and bone metabolism in both domestic and foreign studies. The study by Jin Yunyun et al.[3,4] showed that hypothyroidism may cause bone loss and decreased bone mineral density. An investigation pointed out that the bone mineral density of patients with hypothyroidism is affected by serum TSH. However, a multicenter study in the United States did not observe a significant correlation between TSH and bone mass.[5]. Therefore, in this study, by measuring the bone mineral density and bone metabolism indices of patients with hypothyroidism, and comparing them with the normal control group, this study explored the impact of TSH on bone metabolism indices and bone mineral density in men with hypothyroidism.

MATERIALS AND METHODS

A total of 210 cases who were examined in the Marjan Teaching Hospital between October 2020 and October 2021 were selected. Among them, 120 healthy men were in the control group with an average age of (52.97 ± 1.55) years, BMI (23.50 ± 1.05) kg/m^2 and 90 men with hypothyroidism with an age mean (51.66 ± 1.64) years, BMI (23.59 ± 1.12) kg/m^2. There was no significant change in the smoking, exercise, diabetes, and hypertension composition ratios between the two groups. The criteria of hypothyroidism diagnoses considered were TSH > 4.2 mIU/L, FT3 and FT4 within the normal range. Exclusion criteria include patients with thyroid disease after application of anti-thyroid drugs, levothyroxine tablets, surgical treatment, long-term drugs that affect bone metabolism, and liver and kidney dysfunction. The serum TSH level in the hypothyroidism group was elevated than in the control group, and the difference was statistically significant ($P < 0.05$). The concentrations of FT3 and FT4 in the hypothyroidism group were lower than in the control group ($P < 0.05$), Table 1.

Collection of Fasting Blood Samples

Approximately 5 mL of blood was collected for serum separation and then stored at −20°C for later use. A biochemical analyzer was used to reveal the serum levels of FT4, FT3, and TSH.

Detection of bone metabolism and resorption indices

The serum levels of calcium and phosphorus were measured by the colorimetric method, whereas CTX-1 levels were detected by ELISA.

TABLE 1. Basic data of control and hypothyroidism men groups.

Basic information	Control group. n = 120	Hypothyroidism men group, n = 90	P value
Age (year)	52.97 ± 1.55	51.66 ± 1.64	0.22
BMI (kg/m**2**)	23.50 ± 1.05	23.59 ± 1.12	0.29
Smoking, n/%	43/35.9	41/45.5	0.23
Exercise, n/%	32/26.6	30/33.3	0.25
Diabetes, n/%	20/16.6	26/28.9	0.70
Hypertension, n/%	55/45.9	74/82.2	0.63
FT3 pmol. L**-1**	4.82 ± 0.08	4.20 ± 0.06	0.04*
FT4 pmol. L**-1**	15.20 ± 0.05	13.54 ± 0.48	0.04*
TSH pmol. L**-1**	2.34 ± 0.45	5.14 ± 1.23	0.01*

** Signification at P value < 0.05*

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Detection of Bone Density

The Dual energy X-ray absorptiometry was used to estimate the bone density of the lumbar spine (L1-4) and left femoral neck and to calculate the T value. According to the diagnostic criteria of WHO for osteoporosis.[6]: T value ≥ −1.0 referred to normal bone mass, T value (−2.5 to −1.0) referred to osteopenia and T value ≤ −2.5 referred to bone mass. Note: As long as there is one decrease in T value in two parts, it is regarded as osteopenia or osteoporosis.

Data statistical analysis

Data analysis using SPSS 23.0 software. Continuous quantitative data are represented by M ± S. The *t*-test was used to compare the means among independent samples, the χ test was used to compare the rate and frequency, and the Mann–Whitney U test was used to contrast the rank data. The correlation between bone metabolism indices and thyroid function were analyzed by Pearson correlation. The test level for overall comparison was α = 0.05, and the test level after adjustment for subgroup comparison was α = 0.0167.

RESULTS

Comparison of bone mass distribution in each group

The bone mass in the hypothyroidism group was significantly decreased compared to that of the control group with significant changes (P < 0.05), Table 2.

Comparison of bone metabolism indices in each group

The bone resorption index CTX-1 in men with hypothyroidism was significantly elevated than in the control group, Table 3. According to the correlation analysis, male TSH and CTX-1 levels were positively correlated (r = 0.17, P = 0.01), Table 4.

TABLE 2. Distribution of bone mass in each group.

Study groups	Total Number	Normal	Bone mass reduce	Bone loss	Z	P value
Control	120	86	33	1	2.28	0.01*
Hypothyroidism	90	53	36	2		

** Signification at P value < 0.05, the corrected inspection level α/3=0.0167*

TABLE 3. Comparison of bone metabolism indices in each group.

Indices	Control subjects (M ± S.D.)	Men with hypothyroidism (M ± S.D.)	*t* value	P Value
Ca^{2+} (mmol. L-**1**)	2.45 ± 0.13	2.41 ± 0.14	0.033	0.87
Pi^{3+} (mmol. L-**1**)	1.24 ± 0.26	1.29 ± 0.20	1.002	0.29
CTX-1(pg.ml-**1**)	1.41 ± 1.01	2.43 ± 1.90	7.80	0.00*

TABLE 4. Correlation analysis of bone metabolism and hypothyroidism indices.

Indices	FT3		FT4		TSH	
	r	P	R	P	r	P
Ca^{2+}	0.20	0.15	0.15	0.19	−0.11	0.35
Pi^{3+}	−0.01	0.52	−0.16	0.39	0.04	0.85
CTX-1	0.05	0.61	−0.06	0.58	0.17	0.01*

** Signification at P value < 0.05*

DISCUSSION

The dynamic balance between bone formation and bone resorption is important for normal bone metabolism, regulated by various factors. In recent years, endocrine osteoporosis has been increasing day by day, and thyroid disease is an important cause of secondary osteoporosis. In the past, it was believed that osteoporosis caused by abnormal thyroid function was mainly due to thyroid hormones accelerating bone turnover and bone resorption was greater than bone formation, thus manifesting osteoporosis, which had nothing to do with thyroid-stimulating hormone.[7,8] Other studies have shown that TSH itself has regulation ability in bone metabolism, independent of thyroid hormones.[9,10] TSH is regulated by the thyroid-stimulating hormone receptor (TSHR) acting on the cell surface.[11,12] TSHR is not only expressed on the thyroid follicular cell membrane but in recent years, scientists have also detected the RNA and protein expression of TSHR in many extrathyroid tissues, such as thymocytes, cardiomyocytes, hematopoietic stem cells, lymphocytes, testicular cells, kidney, brain. Rat osteosarcoma cells, mouse osteoblasts, etc.[13,14] Animal experiments have shown that TSH prevents bone remodeling by binding to TSHR on the membrane of osteoblasts and osteoclasts, resulting in decreased osteogenesis and osteoclast effects, resulting in bone loss in mice. Studies on animal models showed that the bone mineral density of TSHR knockout mice was notably lower than that of wild-type mice.[5,16] When the expression of TSHR is reduced by 50%, it can lead to large areas of osteoporosis and focal bone sclerosis in knockout mice.[17] Regarding the mechanism of TSH regulating bone metabolism, in vitro studies have shown that TSH acts on TSHR and mainly regulates the expression of bone metabolism markers such as IL-11, OPN, and ALP through the Gs-cAMP pathway.[18]

A small molecule ligand of TSHR, D3-βArr, can enhance the TSHR-mediated β-arrestin1 molecular pathway to promote osteoblast differentiation.[19,20] Therefore, the TSH-TSHR pathway plays a major role in regulating bone metabolism.

In this study, the bone mass loss in the two groups was compared by measuring the dual-energy X-ray bone mineral density of the research subjects, and it was observed that the bone mass in men with hypothyroidism group was significantly lower than that in the control group, suggesting decreased bone amounts in men with hypothyroidism. Hao Xiaoyun.[21,22] conducted a study on men with hypothyroidism in Taiyuan and found that their lumbar spine and hip bone mineral densities were decreased than in the control group.

The study of 22 patients with hypothyroidism by Liang Libo et al.[23] showed that the serum calcium and bone mineral density concentration of men and women in the hypothyroidism group were lower than that in the control group, and the serum phosphorus level of men with hypothyroidism increased. Another study found that the blood phosphorus and iPTH of participants in the subclinical hypothyroidism group were higher than that in the control group, and 25(OH)D was decreased compared to that in the control group. There was no significant difference in serum calcium between the two groups.[24] However, there was no significant difference in calcium and phosphorus between the study groups. It is generally believed that in hypothyroidism, due to the decrease in thyroid hormone levels, the blood calcium level decreases, and the blood phosphorus level increases. However, the thyroid hormone levels in patients with hypothyroidism are in the normal range, only the TSH level is elevated, and there is no epidemiological data on the changes in calcium and phosphorus levels.

CTX-1 is a group of specific peptides at the carboxyl terminus of type I collagen, and is the most widely used markers of collagen degradation, and it is the commonly used indicator to assess the level of bone turnover. In this paper, by measuring the levels of CTX-1 in the research subjects,

the results suggest that the level of bone resorption index CTX-1 is increased in men with hypothyroidism, and the difference is statistically significant. Histomorphological studies of adult bone remodeling by some scholars[25,26] showed that the rate of bone remodeling slowed down in hypothyroidism, the time of osteoblast-mediated bone formation was extended by 2 times, and the osteoclast-mediated bone resorption was extended by 4 times. The overall performance of bone mass and bone mineralization increased. In hyperthyroidism, both bone formation and bone resorption are accelerated, and the level of bone resorption is higher than the level of bone formation, showing high-transformation osteoporosis.[27]

In this research, we further analyzed the correlation between TSH, FT3, FT4, and bone metabolism indices and found that TSH was positively correlated with CTX-1, suggesting that in men with hypothyroidism, the level of bone turnover may be accelerated, and the level of bone resorption is higher than the level of bone formation. This can lead to osteopenia or even osteoporosis. However, the analysis of FT3, FT4, and bone metabolism indices did not find a significant correlation. This may be because the levels of T3 and T4 in our observed participants are in the normal range, which is insufficient to cause changes in the biochemical indices of bone metabolism. This research did not measure the levels of osteocalcin, vitamin D3, parathyroid hormone, and other indicators, therefore the results have certain limitations. As a next step, we can increase the detection indicators to comprehensively evaluate the bone metabolism status of patients with hypothyroidism, and further explore the metabolism status of men with hypothyroidism and the downstream mechanisms for increased absorption. In addition, this study focused only on analyzing the correlation between the research factors and this cannot explain its causal relationship. The results of the study have certain limitations. Larger sample size cross-sectional studies or cohort studies are required to explore the correlation between bone metabolism and related mechanisms of the thyroid function system.

ETHICAL APPROVAL:

The manuscript is original and all the data, results pertaining to this manuscript are original based on the research performed. The authors have followed academic integrity and have not copied any content/results from another source.

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The authors of the study do not have any conflicts of interest

INFORMED CONSENT:

The authors of the manuscript agree to publish this research in the journal if it is considerable by the editors of the journal. The authors provide full consent for reviewing and publishing this manuscript.

V. All the authors of this study contributed equally in terms of performing the research as well as in preparing the manuscript. All the authors of the study followed the guidelines of the corresponding author. Any query/suggestion related to the manuscript can be reached to the corresponding author.

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