Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Influence of Low Total Triiodothyronine Levels on Bone Turnover Markers in Type 2 Diabetes Mellitus

Zelin Li[1,2]
Xian Yu[2]
Luping Ren[2]
Zi Wang[3]
Fei Wang[1,2]
Yujiao Jia[1,2]
Shuchun Chen[1,2,4]

[1]Graduate School of Hebei Medical University, Shijiazhuang, Hebei, People's Republic of China; [2]Department of Endocrinology, Hebei General Hospital, Shijiazhuang, Hebei, People's Republic of China; [3]Department of Infectious Diseases, Shanghai Fourth People' s Hospital, Shanghai, People's Republic of China; [4]Hebei Key Laboratory of Metabolic Diseases, Shijiazhuang, Hebei, People's Republic of China

Purpose: The aim of this study was to investigate whether low total triiodothyronine (TT3) could affect bone turnover in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: This is a cross-sectional study that recruited 577 patients with T2DM, 141 patients formed the low TT3 group (TT3<1.30nmol/L) and 436 patients formed the control group (TT3≥1.30nmol/L), and the low TT3 group was further subdivided into four groups based on the TT3 level. To investigate whether TT3 level is associated with poor glycemic control, all participants were divided into high glycosylated hemoglobin (HbA1c) group and low HbA1c group using HbA1c 10.5% as the boundary.

Results: The levels of OC and PINP were significantly lower in the low TT3 group compared with the control group ($P < 0.05$). TT3 positively correlated with OC and PINP (r = 0.219, P = 0.009; r = 0.208, $P = 0.019$) in the low TT3 group, and this positive correlation still existed after adjusting for other factors in multilinear regression analysis. Next, we want to find a cut-off point to prevent osteoporosis, we divided the patients in the low TT3 group into four groups based on the TT3 level, the levels of OC and PINP were significantly lower in the TT3 < 1.00 nmol/L group than in the TT3 ≥ 1.00 nmol/L groups.

Conclusion: In patients with T2DM, low TT3 levels are associated with impaired bone formation. What's more, bone formation was significantly impaired when TT3 was <1.00 nmol/L.

Keywords: bone turnover markers, low TT3 level, thyroid hormones, type 2 diabetes mellitus

Introduction

Diabetes and thyroid dysfunction are the two most common endocrine diseases in clinical practice,[1] and they often co-occur. Insulin and thyroid hormones play an essential role in metabolism and interact with each other. Compared with the healthy population, patients with diabetes are more susceptible to thyroid dysfunction. A study found that the prevalence of type 2 diabetes mellitus (T2DM) with thyroid dysfunction in older adults in China was 23.9%.[2] As a metabolic disease, diabetes has gradually become a public health problem of global concern, it can cause a variety of complications, including osteoporosis. Similarly, osteoporotic is common, with an estimated 120 million osteoporosis patients in China in the year 2000.[3] Thyroid dysfunction is a risk factor for osteoporosis. In fact, untreated, hyperthyroidism, subclinical hyperthyroidism and hypothyroidism are established causes for secondary osteoporosis. In the absence of primary thyroid dysfunction,

Correspondence: Shuchun Chen
Department of Endocrinology, Hebei General Hospital, Shijiazhuang, Hebei, People's Republic of China
Tel +86 31185988406
Fax +86 31185988406
Email chenshuc2014@163.com

Received: 1 March 2021
Accepted: 11 May 2021
Published: 16 June 2021

changes in circulating thyroid hormone parameters are often observed in systemic non thyroid diseases, such as T2DM.[4] Patients with T2DM are more likely to suffer from low total triiodothyronine (TT3) levels compared with healthy people, this finding is more common in people with poor glycemic control.[5,6] It is not clear whether the low TT3 levels in patients without thyroid disease especially in T2DM patients. We evaluated whether low TT3 levels are associated with bone turnover markers (BTMS).

To date, no study explored whether low TT3 levels affected bone turnover in patients with T2DM. In our hospital, the low TT3 level is defined as TT3<1.3nmol/L. Considering the importance of thyroid hormones in the bone, the purpose of this study was to investigate: 1) The relationship between low TT3 levels and levels of bone turnover markers (BTMs) in patients with T2DM; 2) Stratified experiments were conducted in patients with low TT3 levels according to the TT3 levels to find the cutoff point; 3) Whether poor glycemic control can affect TT3 level. It provided a basis for the early intervention and prevention of the occurrence and development of osteoporosis in patients with T2DM.

Materials and Methods

Study Population

This was a hospital-based cross-sectional study, which was conducted in the Department of Endocrinology, Hebei General Hospital, from December 2018 to December 2019. Patients complying with the WHO diagnostic criteria for diabetes, 1999, were included. Patients with thyroid diseases, such as hyperthyroidism, hypothyroidism, subclinical hypothyroidism and subclinical hyperthyroidism, patients with acute and chronic diabetic complications, pregnant women, patients with hepatic or renal dysfunction or malignant tumor, and patients using agents that could affect bone metabolism were excluded. This study was approved by the medical ethics committee of Hebei General Hospital, and all patients signed the informed consent form before enrollment. This study was conducted in accordance with the Declaration of Helsinki.

Information and Biomarkers Collection

All participants completed a questionnaire to collect basic information, including gender, age, duration of disease. Height, weight were measured twice by professional, and the average value was recorded. Blood samples were collected from the patients after 8 h of fasting. The levels of total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), total triiodothyronine (TT3), total thyroid hormone (TT4), TSH, OC, β-CTX, and PNIP were measured.

Statistical Analysis

All analyses were conducted using Statistical Product and Service Solutions 25.0 (SPSS 25.0). The normality of the distribution was tested using the Kolmogorov–Smirnov test. Continuous variables are presented as median (25th, 75th interquartile range) and mean ± standard deviation values. For categorical variables, data were expressed as numbers (percentages). The biochemical parameters between two groups were compared using the Student *t*-test or Mann–Whitney test. $\chi 2$ test was employed to compare categorical variables. The biochemical parameters in the four subgroups of the low TT3 group were compared using analysis of variance or Kruskal–Wallis *H*-test. The correlations between BTMs and TT3, TT4, TSH, and other biochemical parameters were analyzed using Pearson and Spearman correlation tests. Multiple linear regression analysis was used to study the independent correlation between TT3 and BTMs. A P value less than 0.05 was considered statistically significant.

Results

Clinical Characteristics of All Participants

A total of 577 patients with T2DM (208 female and 369 male) were included in this study. The mean age was 58.00 years, the mean BMI was 25.83 kg/m^2 and the mean diabetes duration were 10 years. In the cohort of all participants, the mean FBG level was 8.52mmol/L and the mean HbA1c level was 8.90% (Table 1). The mean TT3 level was 1.45 noml/L, and the 141 patients had low TT3 levels (TT3<1.30nmol/L).

Comparison of Basic Parameters Between the Low TT3 Group and Control Group

The levels of OC, PINP were significantly lower in the low TT3 group than in the control group ($P < 0.001$, $P < 0.001$, respectively). However, the levels of bone resorption marker β-CTX showed no significant difference

Table 1 Clinical Characteristics of All Participants

	Subjects (n=577)
Gender	Male (369, 63.95%)
Age	58.00 (49.00, 67.00)
DM duration (years)	10.00 (3.00, 15.00)
BMI (kg/m^2)	25.83 (23.44, 27.94)
TC (mmol/L)	4.68 (3.93, 5.54)
TG (mmol/L)	1.43 (1.01, 2.08)
LDL-C (mmol/L)	2.94 (2.16, 3.56)
HDL-C (mmol/L)	1.10 (0.93, 1.36)
FBG (mmol/L)	8.52 (6.70, 11.74)
TT3 (nmol/L)	1.45 (1.30, 1.68)
TT4 (nmol/L)	91.95 (82.20, 103.20)
TSH (μIU/mL)	1.84 (1.26, 2.59)
HbA1c (%)	8.90 (7.60, 10.80)
OC (ng/mL)	11.59 (9.15, 14.20)
B-CTX (ng/mL)	0.34 (0.22, 0.45)
PINP (ng/mL)	35.66 (27.65, 45.64)

Abbreviations: BMI, Body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; TT3, total triiodothyronine; TT4, total thyroid hormone; TSH, thyroid-stimulating hormone; HbA1c, glycated hemoglobin; OC, osteocalcin; β-CTX, type I collagen carboxyterminal peptide beta special sequence; PINP, N-terminal propeptide of type I collagen.

between the two groups. The difference in BTMs between low TT3 group and control group is shown in Figure 1.

The serum HbA1c levels significantly increased in patients with low TT3 levels compared with patients with normal thyroid hormone levels (P < 0.001). The baseline anthropometric and biochemical characteristics of the low TT3 group and control group are shown in Table 2.

Comparison of the Prevalence of Low TT3 Between the High HbA1c Group and Low HbA1c Group

The prevalence of low TT3 was significantly higher in high HbA1c group than in low HbA1c group (χ^2 = 20.493, P < 0.001). The levels of TT3 were significantly lower in the high HbA1c group than in the low HbA1c group (P < 0.001).

Correlations Between BTMs and TT3 Levels in Low TT3 Group

OC was found to positively correlate with TT3 (r = 0.219, *P* = 0.009). Also, a significant positive correlation was observed between PINP and TT3 (r = 0.206, *P* = 0.019). However, there were no correlation between β-CTX and TT3 (r = −0.168, *P* = 0.057) (Figure 2) (Table 3).

Multivariate Linear Correlation Analysis of BTMs and TT3 Levels in Patients with T2DM

For participants with low TT3 levels, TT3 levels were positively correlated with OC in the crude model 1 (β=6.803, P<0.001), model 2 (adjusted for age, BMI, and duration of diabetes) (β=7.948, P<0.001), model 3 (adjusted for age, BMI, duration of diabetes, TC, TG, HDL and LDL) (β=9.135, P<0.001), model 4 (adjusted for age, BMI, duration of diabetes, TC, TG, HDL, LDL,

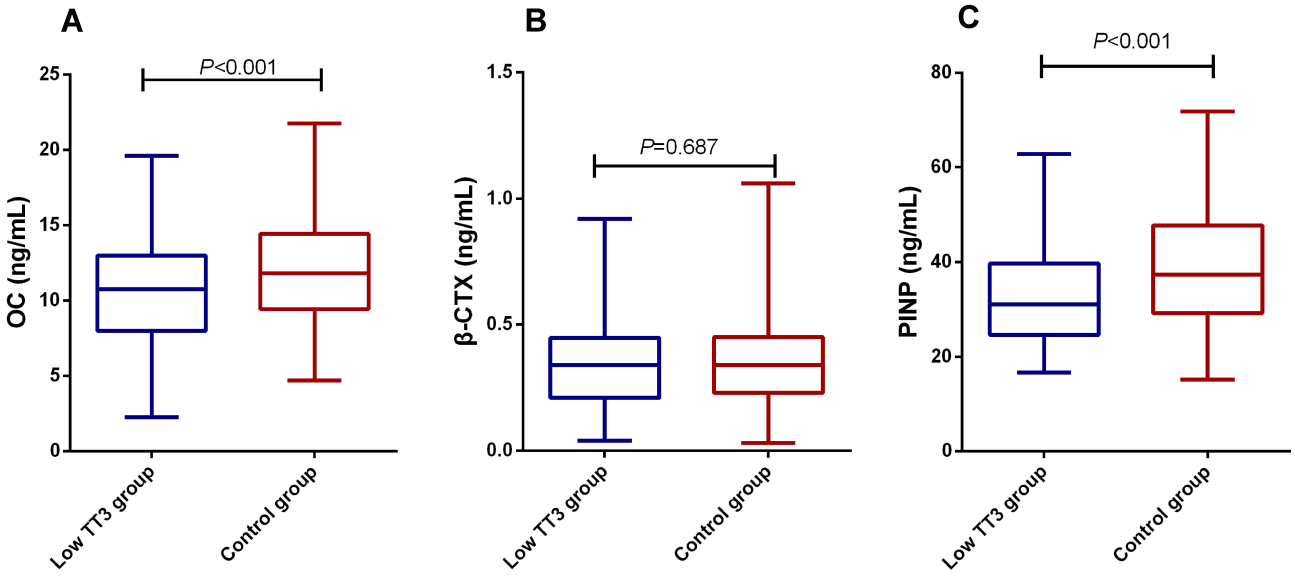

Figure 1 Comparisons of bone turnover markers levels in low TT3 group and control group in patients with type 2 diabetes mellitus. (**A**) Comparisons of OC levels in low TT3 group and control group in patients with type 2 diabetes mellitus. (**B**) Comparisons of β-CTX levels in low TT3 group and control group in patients with type 2 diabetes mellitus. (**C**) Comparisons of PINP levels in low TT3 group and control group in patients with type 2 diabetes mellitus.

Table 2 Clinical Characteristics of All Patients with T2DM with and without Low TT3 Levels

	Low TT3 Group (n=141)	Control Group (n=436)	P
Age (years)	59.33 ± 12.82	58.00 (49.00, 66.75)	<0.001
DM duration (years)	10.00 (3.00, 17.00)	10.00 (3.00, 15.00)	0.731
BMI (kg/m^2)	25.01 ± 3.44	26.03 (23.72, 28.33)	0.001*
TC (mmol/L)	4.76 (3.92, 5.71)	4.67 (3.93, 5.49)	0.481
TG (mmol/L)	1.31 (0.93, 1.92)	1.45 (1.04, 2.13)	0.062
LDL-C (mmol/L)	2.98 (2.17, 3.75)	2.92 (2.15, 3.53)	0.383
HDL-C (mmol/L)	1.14 (0.96, 1.42)	1.09 (0.92, 1.35)	0.450
FBG (mmol/L)	8.73 (6.42, 12.66)	8.44 (6.71, 11.01)	0.311
TT3 (nmol/L)	1.14 (1.00, 1.23)	1.54 (1.40, 1.74)	<0.001*
TT4 (nmol/L)	86.90 (76.19, 94.61)	94.24 (84.93, 104.68)	<0.001*
TSH (μIU/mL)	1.72 (1.08, 2.51)	1.87 (1.30, 2.62)	0.034*
HbA1c (%)	9.86 ± 2.26	8.70 (7.50, 10.40)	<0.001*
OC (ng/mL)	10.79 ± 3.62	11.81 (9.43, 14.44)	<0.001*
B-CTX (ng/mL)	0.34 (0.22, 0.44)	0.34 (0.23, 0.45)	0.687
PINP (ng/mL)	31.06 (24.61, 39.70)	37.31 (29.16, 47.79)	<0.001*

Note: *Denotes significance at a P value of <0.05.
Abbreviations: BMI, Body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; TT3, total triiodothyronine; TT4, total thyroid hormone; TSH, thyroid-stimulating hormone; HbA1c, glycated hemoglobin; OC, osteocalcin; β-CTX, type I collagen carboxyterminal peptide beta special sequence; PINP, N-terminal propeptide of type I collagen.

FBG, HbA1c) (β=8.255, P<0.001), model 5 (adjusted for age, BMI, duration of diabetes, TC, TG, HDL, LDL, FBG, HbA1c, TT4, TSH) (β=6.632, P=0.005) (Table 4).

Also, TT3 levels were positively correlated with PINP levels in patients with low TT3 levels, regardless of whether an unadjusted or adjusted model was used (model 1: β=17.683, P=0.001; model 2: β=20.848, P=0.001; model 3: β=24.104, P<0.001; model 4: β=21.211, P=0.002; model 5: β=19.784, P=0.008) (Table 5).

However, TT3 levels were not associated with β-CTX levels in patients with low TT3 levels, regardless of whether an unadjusted or adjusted model was used (model 1: β=−0.181, P=0.065; model 2: β=−0.128, P=0.259; model 3: β=−0.109, P=0.3651; model 4: β=−0.170, P=0.183; model 5: β=−0.207, P=0.123) (Table 6).

Comparisons of BTMs in the Low TT3 Group After Dividing Patients into Four Groups Based on Their Serum TT3 Levels

Patients with T2DM and low TT3 levels were divided into four groups according to their TT3 levels: group 1, TT3 < 1.00 nmol/L; group 2, 1.00 nmol/L ≤ TT3 < 1.10 nmol/L; group 3, 1.10 nmol/L ≤ TT3 < 1.20 nmol/L; and group 4, 1.20 nmol/L ≤ TT3 < 1.30 nmol/L.

The difference in BTMs among the four groups is shown in Figure 3. On categorizing patients into four groups according to TT3 levels, differences were noted in OC and PINP levels between at least two of the four groups (P = 0.008 and P = 0.022, respectively). After a pairwise comparison, the OC and PINP levels were significantly lower in patients with TT3 < 1.00 mmol/L than in those with TT3 ≥1.00 mmol/L. No difference was found in β-CTX (P = 0.276) among the four groups (Table 7).

Discussion

To our knowledge this is first study examining the relationship between low TT3 levels and BTMs in T2DM patients without thyroid disease. Seppel et al found no significant difference in OC levels between patients with low T3 levels and healthy people; no correlation was found between OC and T3,[7] but all of this subjects without T2DM. This study was novel in reporting that T2DM patients with low TT3 levels had lower OC and PINP

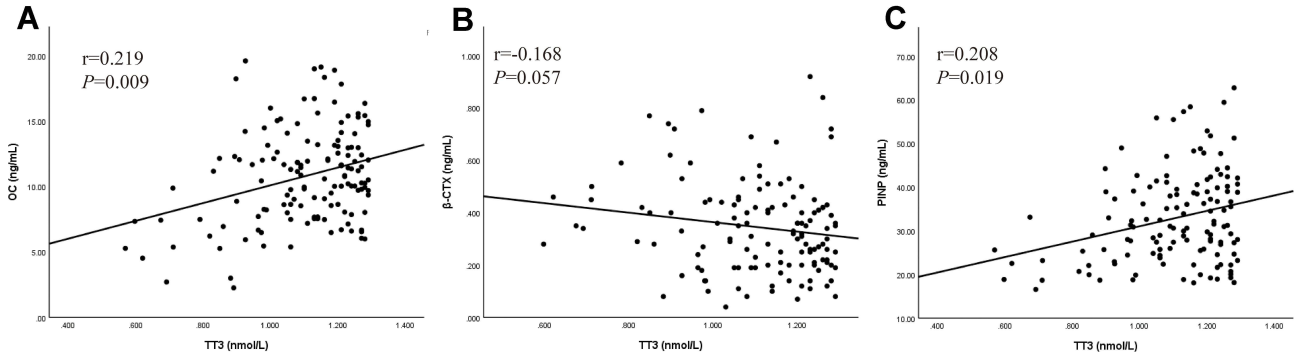

Figure 2 The correlation between bone turnover markers levels and TT3 levels in the low TT3 group. (**A**) The correlation between OC levels and TT3 levels in the low TT3 group. (**B**) The correlation between β-CTX levels and TT3 levels in the low TT3 group. (**C**) The correlation between PINP levels and TT3 levels in the low TT3 group.

Table 3 Correlation Between BTMs and Other Parameters in T2DM Patients with Low TT3 Levels

		OC	β-CTX	PINP
BMI (kg/m^2)	*r* value	–0.085	–0.169	0.070
	P-value	0.334	0.063	0.446
TC (mmol/L)	*r* value	0.129	0.041	0.168
	P-value	0.139	0.653	0.063
TG (mmol/L)	*r* value	–0.012	0.111	0.049
	P-value	0.888	0.219	0.588
LDL-C (mmol/L)	*r* value	0.064	–0.011	0.132
	P-value	0.457	0.902	0.140
HDL-C (mmol/L)	*r* value	0.235	0.016	0.101
	P-value	0.006*	0.194	0.263
FBG (mmol/L)	*r* value	–0.238	–0.066	–0.143
	P-value	0.005*	0.455	0.106
HbA1c (%)	*r* value	–0.202	0.035	–0.150
	P-value	0.020	0.694	0.095
TT3 (nmol/L)	*r* value	0.219	−0.168	0.206
	P-value	0.009*	0.057	0.019*
TT4 (nmol/L)	*r* value	0.188	0.159	0.114
	P-value	0.027*	0.071	0.198
TSH (μIU/mL)	*r* value	0.135	−0.222	0.140
	P-value	0.113	0.011*	0.114

Note: *Denotes significance at a *P* value of <0.05.

Abbreviations: BMI, Body mass index; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; TT3, total triiodothyronine; TT4, total thyroid hormone; TSH, thyroid-stimulating hormone; HbA1c, glycated hemoglobin; OC, osteocalcin; β-CTX, type I collagen carboxyterminal peptide beta special sequence; PINP, N-terminal propeptide of type I collagen.

Table 4 Correlation Between TT3 and OC in Patients with Low TT3 Levels

	B (95% CI)	Std.Error	Beta	t	*P*
Model 1	6.803 (3.252, 10.353)	1.795	0.308	3.789	<0.001
Model 2	7.948 (4.131, 11.764)	1.929	0.346	4.121	<0.001
Model 3	9.135 (5.223, 13.047)	1.975	0.401	4.625	<0.001
Model 4	8.225 (4.051, 12.459)	2.122	0.360	3.891	<0.001
Model 5	6.632 (2.065, 11.199)	2.304	0.289	2.878	0.005

Table 5 Correlation Between TT3 and PINP in Patients with Low TT3 Levels

	B (95% CI)	Std.Error	Beta	t	*P*
Model 1	17.683 (6.948, 28.418)	5.425	0.278	3.260	0.001
Model 2	20.848 (8.842, 32.855)	6.063	0.309	3.439	0.001
Model 3	24.104 (11.679, 36.530)	6.268	0.361	3.846	<0.001
Model 4	21.211 (7.856, 34.566)	6.733	0.314	3.150	0.002
Model 5	19.784 (5.249, 34.318)	7.326	0.293	2.700	0.008

Table 6 Correlation Between TT3 and β-CTX in Patients with Low TT3 Levels

	B (95% CI)	Std. Error	Beta	t	*P*
Model 1	−0.181 (−0.374, 0.011)	0.097	−0.164	−1.863	0.065
Model 2	−0.128 (−0.352, 0.095)	0.113	−0.108	−1.136	0.259
Model 3	−0.109 (−0.346, 0.128)	0.120	−0.093	−0.909	0.365
Model 4	−0.170 (−0.421, 0.081)	0.126	−0.144	−1.341	0.183
Model 5	−0.207 (−0.470, 0.057)	0.133	−0.176	−1.557	0.123

levels compared with those with normal thyroid hormone levels. Furthermore, in the low TT3 group, TT3 positively correlated with OC and PINP, regardless of whether confounding factors were adjusted for.

Thyroid hormones are necessary for bone growth, maturation, basic metabolism, and bone turnover. Bone turnover is a periodic dynamic process involving bone formation and bone resorption.[8] The imbalance between bone formation and bone resorption can lead to osteoporosis. OC and PINP are bone formation markers. OC is the most sensitive marker reflecting osteogenic cell activity and bone formation, and PINP is the specific sensitive indicator reflecting new bone formation. The results of this study suggested that low TT3 levels are associated with impaired bone formation, may can lead to a low bone turnover state and may cause osteoporosis. So, we hypothesize that low TT3 levels may are a risk factor of osteoporosis for patients with T2DM, although they have normal TT4 and TSH levels. Further, finding that bone formation was significantly impaired in this study when the TT3 level was <1.00 mmol/L was of great clinical significance. This suggested that an intervention is required to prevent osteoporosis when TT3 was <1.00 mmol/L in patients with T2DM.

Accordingly, underlying mechanisms of impaired bone formation due to low TT3 remain unexplored. The underlying mechanism may be that T3 can act directly or indirectly influence osteoblasts. The T3 receptor also exists in bone tissue; T3 can effect osteoblasts by binding to the T3 receptor in the nucleus.[9,10] T3 mainly acts on osteoblasts, regulates intramembranous and endochondral ossification, and controls the efficiency of bone formation, bone maturation, and mineralization.[11] Thyroid hormones could not only directly bind to thyroid receptors in bone tissue but also induce the production of growth factors and metalloproteinases, stimulating osteoblast differentiation and increase osteoblast activity, thus affecting the balance of bone turnover.[12]

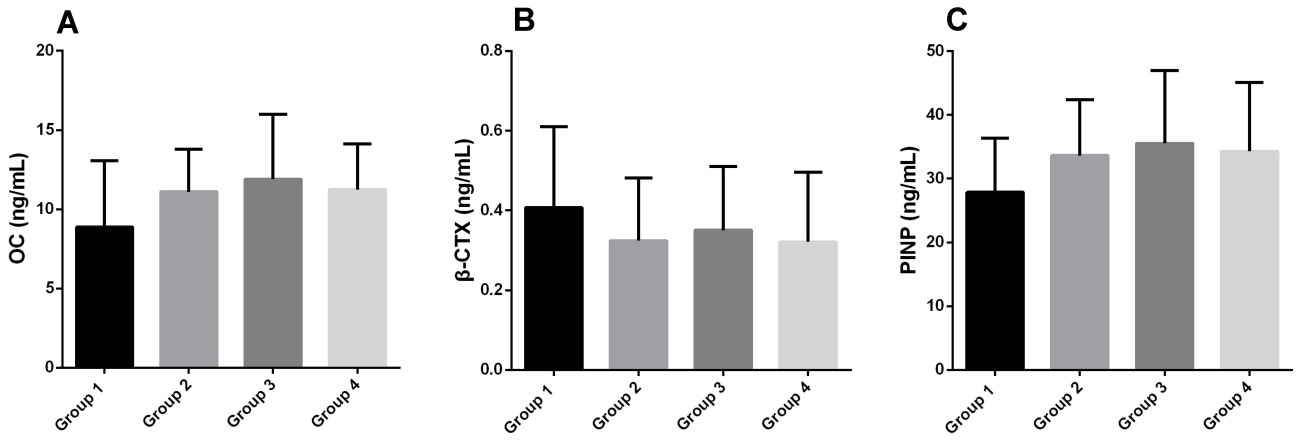

Figure 3 BTMs of patients with T2DM and low TT3 levels, stratified according to serum TT3 levels. (**A**) Comparisons of OC levels in four groups. (**B**) Comparisons of β-CTX levels in four groups. (**C**) Comparisons of PINP levels in four groups.Group 1: TT3 < 1.00 nmol/L; Group 2:1.00 nmol/L ≤ TT3 < 1.10 nmol/L; Group 3:1.10 nmol/L ≤ TT3 < 1.20 nmol/L; and Group 4: 1.20 nmol/L ≤ TT3 < 1.30 nmol/L.

The relationship betweenT2DM and thyroid hormones is a complex one. Such patients are more susceptible to have low TT3 levels, especially when the HbA1c level is higher than 10.5–11%.[13,14] This study also found that the low TT3 group had significantly higher HbA1c levels compared with control group. The prevalence of low TT3 levels was significantly higher in patients with HbA1c ≥10.5% than in patients with HbA1c <10.5% (P < 0.001). These findings indicated that patients with T2DM and low TT3 levels had more inadequate blood glucose control. Long-term hyperglycemia can directly damage osteoblasts[15] and also produce excessive reactive oxygen species to induce the apoptosis of osteoblasts,[16] ultimately reducing bone formation and leading to a low bone turnover state. Patients with T2DM and low TT3 levels had a higher HbA1c level, and hyperglycemia could impair bone formation, which might also be a cause of the low bone turnover state in the low TT3 group.

There were limitations to this study. First, our study is that this is based on data from a single center, so the conclusion found in our study could not be extrapolated to all T2DM patients, thus necessitating the need for further large-scale studies on different centers and hospitals. Second, the free T3 and free T4 levels should be considered in future studies of thyroid function.

In conclusion, this study may have important clinical implications. The results of our study would suggest that TT3 values lower than 1 mmol/L, even TT4 and TSH in the reference range, may be not safe for bone metabolism in T2DM patients. Finally, our data would encourage to measure thyroid hormones in all T2DM patients even in the absence of thyroid disease.

Conclusions

In conclusion, this study found that OC and PNIP levels significantly decreased in patients with T2DM and low TT3 levels, and TT3 positively correlated with OC and PINP. It hypothesize that low TT3 levels may are a risk factor of osteoporosis for patients with T2DM. And we suggested that even if patients with T2DM did not suffer from hypothyroidism, early intervention should be taken to prevent the occurrence and development of osteoporosis when the TT3 < 1.00 mmol/L.

Table 7 Comparison of BTMs in the Low TT3 Group, Stratified According to the Serum TT3 Level

	TT3 < 1.00 nmol/L N = 35	1.00 nmol/L ≤ TT3 < 1.10 nmol/L N = 24	1.10 nmol/L ≤ TT3 < 1.20 nmol/L N = 29	1.20 nmol/L ≤ TT3 < 1.30 nmol/L N = 53	P
OC (ng/mL)	8.87 ± 4.19	11.10 ± 2.70	11.38 (8.74–12.51)	11.24 ± 2.89	0.008*
B-CTX (ng/mL)	0.41 ± 0.20	0.32 ± 0.16	0.35 ± 0.16	0.29 (0.21–0.39)	0.276
PINP (ng/mL)	15.62 (20.70–32.99)	33.60 ± 8.80	35.42 ± 11.66	34.27 ± 10.84	0.022*

Note: *Denotes significance at a *P* value of <0.05.
Abbreviations: TT3, Total triiodothyronine; OC, osteocalcin; β-CTX, type I collagen carboxyterminal peptide beta special sequence; PINP, N-terminal propeptide of type I collagen.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Ozair M, Noor S, Raghav A, Siddiqi SS, Chugtai AM, Ahmad J. Prevalence of thyroid disorders in North Indian Type 2 diabetic subjects: a cross sectional study. *Diabetes Metab Syndr*. 2018;12(3):301–304. doi:10.1016/j.dsx.2017.12.016
2. Zhu Y, Xu F, Shen J, et al. Prevalence of thyroid dysfunction in older Chinese patients with type 2 diabetes-A multicenter cross-sectional observational study across China. *PloS one*. 2019;14(5):e0216151.
3. Zeng Q, Li N. The prevalence of osteoporosis in China, a Nationwide, Multicenter DXA Survey. *J Bone Miner Res*. 2019;34(10):1789–1797. doi:10.1002/jbmr.3757
4. Völzke H, Krohn U, Wallaschofski H, Lüdemann J, John U, Kerner W. The spectrum of thyroid disorders in adult type 1 diabetes mellitus. *Diabetes Metab Res Rev*. 2007;23(3):227–233. doi:10.1002/dmrr.676
5. Lademann F, Tsourdi E, Hofbauer LC, Rauner M. Thyroid hormone actions and bone remodeling - The role of the Wnt signaling pathway. *Exp Clin Endocrinol Diabetes*. 2020;128(6–07):450–454. doi:10.1055/a-1088-1215
6. Wojcicka A, Bassett JH, Williams GR. Mechanisms of action of thyroid hormones in the skeleton. *Biochim Biophys Acta*. 2013;1830(7):3979–3986. doi:10.1016/j.bbagen.2012.05.005
7. Seppel T, Becker A, Lippert F, Schlaghecke R. Serum sex hormone-binding globulin and osteocalcin in systemic nonthyroidal illness associated with low thyroid hormone concentrations. *J Clin Endocrinol Metab*. 1996;81(4):1663–1665. doi:10.1210/jcem.81.4.86\36386
8. Kremer R, Gilsanz V. Fat and bone: an odd couple. *Front Endocrinol (Lausanne)*. 2015;6:190. doi:10.3389/fendo.2015.00190
9. Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Biochemistry, cellular and molecular biology, and physiological roles of the iodothyronine selenodeiodinases. *Endocr Rev*. 2002;23(1):38–89.
10. Williams AJ, Robson H, Kester MHA, et al. Iodothyronine deiodinase enzyme activities in bone. *Bone*. 2008;43(1):126–134. doi:10.1016/j.bone.2008.03.019
11. Duncan bassett JH, Williams GR. Analysis of physiological responses to thyroid hormones and their receptors in bone. *Methods Mol Biol*. 2018;1801:123–154.
12. Barnard JC, Williams AJ, Rabier B, et al. Thyroid hormones regulate fibroblast growth factor receptor signaling during chondrogenesis. *Endocrinology*. 2005;146(12):5568–5580. doi:10.1210/en.2005-0762
13. Moura Neto A, Parisi MC, Tambascia MA, Alegre SM, Pavin EJ, Zantut-Wittmann DE. The influence of body mass index and low-grade systemic inflammation on thyroid hormone abnormalities in patients with type 2 diabetes. *Endocr J*. 2013;60(7):877–884. doi:10.1507/endocrj.EJ13-0030
14. Yuan Z, Xu X, Ye H, Jin L, Zhang X, Zhu Y. High levels of plasma selenium are associated with metabolic syndrome and elevated fasting plasma glucose in a Chinese population: a case-control study. *J Trace Elem Med Biol*. 2015;32:189–194. doi:10.1016/j.jtemb.2015.07.009
15. Dobnig H, Piswanger-Solkner JC, Roth M, et al. Type 2 diabetes mellitus in nursing home patients: effects on bone turnover, bone mass, and fracture risk. *J Clin Endocrinol Metab*. 2006;91(9):3355–3363. doi:10.1210/jc.2006-0460
16. Hussein RM. Biochemical relationships between bone turnover markers and blood glucose in patients with type 2 diabetes mellitus. *Diabetes Metab Syndr*. 2017;11(Suppl 1):S369–s72. doi:10.1016/j.dsx.2017.03.018