Diabetes, Metabolic Syndrome and Obesity Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Low T3 Syndrome is Associated with Imbalance of Bone Turnover Biomarker in Patients with Type 2 Diabetes

Chenglin Xu[1,*], Song Wen[1,2,*], Zhimin Xu[1,*], Meiyuan Dong[1,3], Yue Yuan[1], Yanyan Li[1], Ligang Zhou[1–4]

[1]Department of Endocrinology, Shanghai Pudong Hospital, Fudan University, Pudong Medical Center, Shanghai 201399, People's Republic of China; [2]Fudan Zhangjiang Institute, Fudan University, Shanghai 201203, People's Republic of China; [3]Hebei Medical University, Shijiazhuang 050013, People's Republic of China; [4]Shanghai Key Laboratory of Vascular Lesions Regulation and Remodeling, Shanghai Pudong Hospital, Fudan University Pudong Medical Center, Shanghai, People's Republic of China

*These authors contributed equally to this paper

Correspondence: Ligang Zhou, Department of Endocrinology, Shanghai Pudong Hospital, Fudan University, Pudong Medical Center, Shanghai, 201399, People's Republic of China, Tel +8613611927616, Email zhouligang1n1@163.com

Diabetes, Metabolic Syndrome and Obesity downloaded from https://www.dovepress.com/
For personal use only.

Objectives: To investigate the variation in bone turnover biomarkers among patients with type 2 diabetes (T2D) and low triiodothyronine levels (Low T3 syndrome).

Materials and Methods: This retrospective analytic study included 418 inpatient records from Shanghai Pudong Hospital covering the years 2021 to 2023. Laboratory data related to metabolic and bone turnover biomarkers in patients were analyzed with T2D and the low T3 syndrome.

Results: The results indicated that patients with reduced serum T3 levels exhibited statistically significant variations in thyroid function, age, fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), and the proportion of medication history associated with diabetes in comparison to euthyroid patients. In addition to parathyroid hormones, bone turnover biomarkers including N-terminal middle molecular fragment of osteocalcin (NMID), plasma calcium (Ca^{2+}), β C-terminal cross-linking telopeptide of type 1 collagen (β-CTX), and 25-hydroxyvitamin D3 (25 OH VitD3) exhibited significant changes in patients with decreased T3 levels. Evident irregularities were observed in patients with a decreased T3 level, including elevated serum creatinine (SCr), decreased concentrations of albumin and total protein, and a decreased estimated glomerular filtration rate (eGFR), as assessed through hepatic and renal testing, respectively. Significant associations between bone turnover biomarkers and the subsequent variables (gender, adiposity, hepatic, renal, and thyroid function) were revealed through the correlational analysis. Further investigation utilized multivariate linear regression to determine that, in addition to thyroid function, several other factors such as age, gender, bodyweight, pancreatic, hepatic, and renal function, affected the variability in bone turnover biomarkers among patients demonstrating a low serum T3 level.

Conclusions: This comparative study demonstrated that despite age, gender, bodyweight, hepatic, renal function, thyroid hormone and pancreatic function were significant factors associated with bone metabolism in patients with T2D and Low T3 syndrome, which may increase the risk of osteoporosis.

Keywords: type 2 diabetes, low T3, bone turnover biomarker, NMID, β-CTX

Introduction

Type 2 diabetes (T2D) is a chronic medical condition characterized by uncontrolled high blood sugar levels, which ultimately result in dysfunction of the thyroid and an imbalance in bone metabolism. Research has emerged in recent decades suggesting that T2D may be associated with a higher incidence of complications such as thyroid dysfunction[1–3] and diabetic osteoporosis.[4] Osteoporosis and diabetic osteopenia may result from abnormal glucose metabolism, which is partially attributable to the microvascular pathological lesion that nourishes osteoblasts and osteoclasts,[5] as well as

Received: 10 June 2024
Accepted: 1 October 2024
Published: 9 October 2024

© 2024 Xu et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

inflammation,[6] hepatic or renal insufficiency,[7–9] oxidative stress.[10] Recent epidemiological studies have identified osteoporosis as a significant risk factor for frailty among elderly individuals with diabetes.[11] Additionally, our prior research indicated a correlation between HbA1c levels and bone mass density (BMD).[12] According to our previous research,[13] in severe cases of diabetes, such as diabetic ketoacidosis (DKA), the activity of osteoblasts decreases as indicated by the serum level of the N-terminal middle molecular fragment of osteocalcin (NMID). In contrast, the activity of osteoclasts increases as indicated by β C-terminal cross-linking telopeptide of type 1 collagen (β-CTX). We also found that recurrent DKA is associated with an increased risk of osteoporosis and bone fracture in some patients with inadequate glycemic control. Consequently, it is critical to monitor bone mass and quality, particularly in patients with type 2 diabetes who are elderly or have inadequate blood glucose management.

However, the thyroid hormone, a sensitive hormone closely associated with blood glucose regulation, plays a substantial role in numerous physiological processes, including energy and hormone homeostasis, stress management, cardiovascular equilibrium, neuronal production and excitability, and bone metabolism.[14,15] It has been discovered that abnormal thyroid function, including hyperthyroidism and hypothyroidism, is associated with abnormal bone turnover biomarker activity and increases the risk of developing osteoporosis and bone fracture.[16,17] Recent research indicates that abnormalities in thyroid function among patients with T2D may be correlated with serum iron levels; gender, age, kidney function, and intestinal flora may be the most influential factors.[3] Additionally, our prior research indicated that low TSH levels are correlated with reduced bone mineral density (BMD) at the femoral neck and hip joint in postmenopausal female T2D patients who are euthyroid.[2] However, it was observed that substantial changes referred to as non-thyroidal illness syndrome (NTIS) were common among severe patients who also had systemic diseases, such as sepsis, respiratory failure, uremia, heart failure, acute diabetic complications (DKA), or hyperosmolar hyperglycemic state (HHS). While many patients with these conditions did not have thyroidal disease, the alteration in thyroid function could potentially serve as an indicator of mortality and severity.[18]

Thyroid dysfunction may be caused by T2D through a variety of mechanisms. It has been found that a hyperglycemic state may affect the production of triiodothyronine from thyroxine by attenuating the activity of deiodinase 1 (D1), which promotes reverse T3 (r-T3) conversion by D3.[1,19] About 77% of circulation thyroxine in normal individuals could be converted into T3 (35%) and rT3 (42%), while only 6.8%-12% to T3 in DM. A comparative clinical study reveals that metabolic control but not aging was one intimate factor of low T3 condition in T2DM.[20] The index of T3/T4 is negatively correlated with the level of blood glucose and could be remission with the improvement of diet control and insulin therapy. In addition, it is also demonstrated that the receptor of T3 could also be downregulated in DM,[21] which could be passively attributed to the accumulated by-product in DM, such as ketone. Lower T3 may be associated with the change in insulin resistance.[22,23] In our previous investigation, we demonstrated that impaired T3 was positively linked with the severity of DKA, but elevated bodyweight represented by BMI could be a protected factor for both bone turnover biomarkers and thyroid function.[24] In DKA, the response to the thyrotropin hormone (TRH) by TSH may be suppressed and even retarded after recovery. Other pathological changes of low T3 in DM may be related to: 1) the disorder of specific transporters responsible for T4 into the certain cells that generate T3;[25] 2) decreased ATP production by the liver due to hyperbilirubinemia or increased non-esterified fatty acids;[26] 3) decreased TRH mRNA expression within the hypothalamus.[27] It has been determined that the TRH expression within hypothalamus could be regulated by the ratio of T3/T4 via T3β2 receptor and phosphorylated cAMP response element bound protein (CREB), wherein low T3 level decreases T3β2 binding to the targeted gene loci of TRH, and TRH may be downregulated by the competition binding of CREB and other regulatory factors, including arcuate nucleus (ARC) released peptide: α-melanin stimulating hormone (α-MSH), cocaine- and amphetamine-regulated transcript (CART), agouti-related protein (AgRP), and neuropeptide Y (NPY), etc;[28,29] 4) inflammatory cytokine expression which suppress the T3 conversion such as IL-6, IL-1, TNF-α, IFN-γ.[30] Furthermore, lower T3 is even a progression index in diabetic complications, such as diabetic nephropathy (DN),[31] diabetic neuropathy (DPN),[32] and frailty,[33] as demonstrated by multiple clinical studies.

To date, however, despite the possibility that thyroid function can be reversed with supplementing with thyroid hormone, such as Euthyrox (Levothyroxine), it remains debatable whether this supplementing could improve the outcome.[34] Therefore, identifying the factors and pathological mechanisms associated with this condition is crucial. We investigated the impact of low triiodothyronine (low T3) syndrome, a common form of non-thyroidal illness syndrome (NTIS), on bone turnover biomarker activity in patients with T2D. Our aim was to identify the bone outcome

in these extremely sick patients and identify potential associated factors or determinants that could guide more effective therapeutic strategies. Our investigation will further analyze the severe T2D patients in low T3 condition without HHS or DKA and hypothyroidism or hyperthyroidism to explore its relationship with the bone metabolic markers, revealing its potential risks for deteriorated bone metabolism in the background of low T3.

Materials and Methods

Source of inpatient data

From the inpatient database, we collected information on 418 adult diabetic patients admitted to the Department of Endocrinology at Shanghai Pudong Hospital between 2018 and 2022. One hundred and three patients were diagnosed with low triiodothyronine (T3) syndrome, which is characterized by a decreased concentration of T3 without an elevated thyroid-stimulating hormone (TSH) level. Patients with primary or secondary hypothyroidism or hyperthyroidism were excluded from the study. In the control group of 314 diabetic patients with euthyroid function evident. All patients diagnosed with diabetes satisfied the T2D diagnostic criteria as established in the 1999 guidelines of the World Health Organization (WHO). The inclusion and exclusion process can be found in Figure 1. Although the patients with euthyroid function had a prior diagnosis of T2DM, none of them presented with diabetic ketoacidosis, hyperosmolar hyperglycemia, or other severe or acute comorbidities or complications. The patient's demographic information, glucose metabolic status, and thyroid function are compared and summarized in Table 1.

Blood sampling and methods of laboratory assessment

All patients admitted to the ward were conscious with a Glasgow Coma Scale (GCS) score of 15. Patients with type 2 diabetes (T2D) received oral anti-diabetic medication, such as metformin, Sulfonylurea, glinides, pioglitazone, SGLT-2 inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase inhibitors (DPP-IV inhibitors), or injectables including GLP-1 receptor agonists, insulin therapy (basal insulin or combined with prandial insulin or premixed insulin). Calcium or vitamin D supplements were not administered to patients unless being diagnosed with osteoporosis or severe osteopenia after blood sampling. Biomarkers of bone turnover, including 25-hydroxyvitamin D3 (25 OH VitD3), N-MID, and β-CTX, were collected from all DM patients. The measurement of bone formation biomarker NMID was processed using a Fluorescence immunochromatography assay on the Dry Fluorescence Immunoassay Analyzer (AFS2000A), while the bone resorption biomarker β-CTX was processed using an Enzyme-linked immunosorbent assay on the Enzyme label analyzer (RT-6100). Parathyroid hormone (PTH) was measured using the Chemiluminescence method on the ADVIA Centaur XP device from Siemens, and blood calcium was analyzed using colorimetry on the ADVIA Chemistry XPT device, also from Siemens. The following parameters were examined: fasting blood glucose, lipid parameters, hepatic function, and kidney function indicators: estimated glomerular filtration rate (eGFR), creatinine, and uric acid (UA) were analyzed via full-automatic biochemical analyzer (ADVIA chemistry XPT, SIEMENS, USA). Hemoglobin A1C (HbA1C) was analyzed by an HbA1C analyzer (TOSOH G8), which reflects the level of glycemic control in the past 3 months. C-peptide and thyroid function indicators: thyroid stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), and anti-thyroid peroxidase antibody (TPOAb), anti-thyroid globin antibody (TgAb), two biomarkers of chronic lymphatic thyroiditis, were processed via chemiluminescence methods, in a full-automatic chemiluminescence immunoassay analyzer (ADIVA Centaur XPT, SIEMENS, USA).

Statistical analyses

The statistical analysis was performed using SPSS (IBM, version 26.0) and Prism (GraphPad, version 9.0) software. Laboratory data, including bone turnover biomarkers, were analyzed using non-parametric tests or independent sample *t*-tests to compare the low T3 and DM groups. The comparison of bone turnover biomarkers between the low T3 group and DM group was analyzed using independent sample *t*-tests or non-parametric tests. The relationship between the metabolic parameters and bone turnover biomarkers was analyzed using parametric Pearson or nonparametric Spearman correlation analyses according to the characteristics of parameter data. Multivariate linear regression analyses were conducted to identify the best predictors of bone turnover biomarker change in the low T3 group. A significance level of $p<0.05$ was used for all statistical analyses.

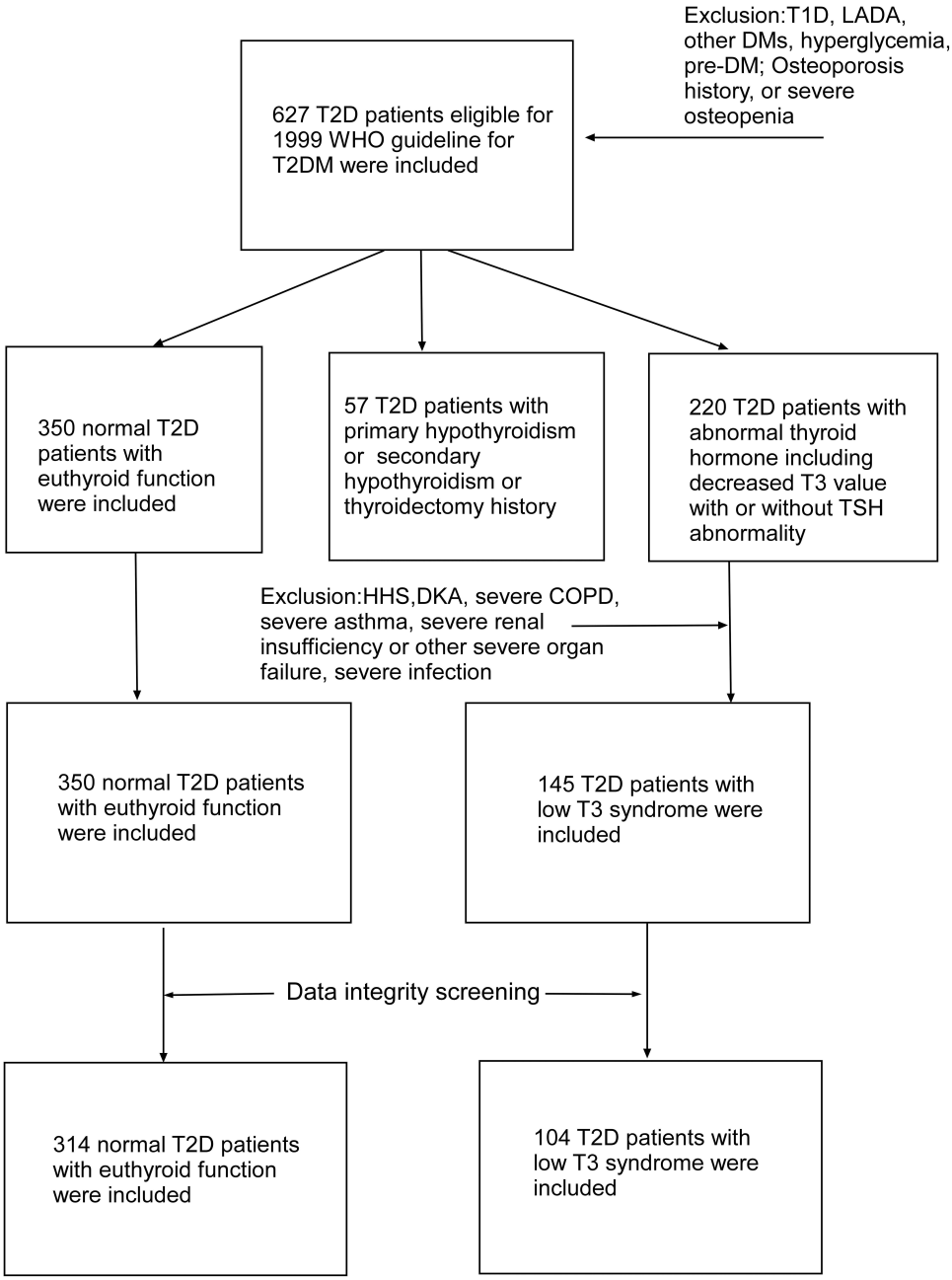

Figure 1 The inclusion and exclusion process of the current retrospective study.
Abbreviations: T2D, type 2 diabetes mellitus; T1D, type1 diabetes; LADA, latent autoimmune diabetes in adults; DM, diabetes mellitus; T3, triiodothyronine; TSH, thyroid stimulating hormone; HHS, hyperglycemia hyperosmolar state; DKA, diabetic ketoacidosis; COPD, chronic obstructive pulmonary disease.

Results

The comparisons of bone turnover biomarkers between patients with low T3 syndrome and euthyroid function

The results showed that compared with the group, the concentration of serum Ca^{2+}(LowT3 vs euthyroid: 2.12±0.14 vs 2.21±0.11 mmol/L, p<0.0001; reference level: 2.08~2.65mmol/L), 25 OH VitD3 (LowT3 vs euthyroid: 15.32±6.61 vs 20.32±8.73ng/mL, p<0.0001; reference level: >30.0ng/ml, and NMID (LowT3 vs euthyroid: 1.51±3.59 vs 12.72±6.41ng/mL, p<0.0001; reference level: female: pre-menopause: 11–43 ng/ml, post-menopause: 15–46 ng/ml; male 18–30 years old: 24–70 ng/ml, 31–47 years old : 14–46 ng/ml) were significantly lower in the low T3 group (p<0.05), which was in

Table 1 The Demographic and Metabolic Status of Patients in Euthyroid Vs Low T3 Syndrome

	Total	Low T3	Euthyroid	Reference Range	P value
Numbers	418	104	314	/	/
Age (years)	67.39±11.86	72.24±11.55	65.77±11.54	/	<0.0001
Gender (M/F)	194/224	45/59	149/165	/	0.497
Diabetic durations (years)	11.75±8.0	12.72±9.11	11.43±7.58	/	0.194
Naïve/Insulin/OADs/Combine	50/104/164/100	16/35/34/19/	34/69/130/81	/	0.031
Bodyweight (Kg)	67.48±12.43	64.32±11.69	68.44±12.51	/	0.004
FPG (mmol/L)	8.87±3.99	10.37±4.80	8.38±3.56	4.1–5.9	<0.0001
FPCP (nmol/L)	0.42±0.34	0.46±0.50	0.41±0.27	0.27–1.28	0.263
PPCP (nmol/L)	0.84±0.73	0.63±0.67	0.91±0.73	1.35–2.50	0.002
HbA1c (%)	9.44±2.24	9.96±2.13	9.27±2.13	4.0–6.0	0.013
TPOAb (U/mL)	90.62±236.73	39.83±14.04	93.37±242.75	<30	0.365
TgAb (IU/mL)	33.47±70.22	31.39±46.63	33.58±71.32	<75	0.901
FT3 (pmol/L)	4.11±0.87	2.95±0.67	4.49±0.52	3.5–6.5	<0.0001
TT3 (nmol/L)	1.26±0.38	0.73±0.15	1.43±0.25	0.92–2.79	<0.0001
FT4 (pmol/L)	15.20±2.33	14.59±2.93	15.40±2.06	11.5–22.7	0.01
TT4 (nmol/L)	92.51±19.09	75.15±17.54	98.25±15.85	58.1–140.6	<0.0001
TSH (mIU/L)	2.08±1.05	1.45±0.98	2.29±0.99	0.55–4.78	<0.0001

Abbreviations: FPG, fasting plasma glucose; FPCP, fasting plasma C-peptide; PPCP, 2h postprandial plasma C-peptide; HbA1c, glycated hemoglobin A1c; FT3, free triiodothyronine; FT4, free thyroxine; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid stimulating hormone.

contrast with the level of β-CTX (LowT3 vs euthyroid: 8.64±15.32 vs 0.37±0.21ng/mL, p<0.0001; reference level: pre-menopause: ≤0.57 ng/ml, post-menopause: ≤1.01 ng/ml; male: >50 years old : ≤ 0.85 ng/ml); however, no obvious disparity was observed in PTH (LowT3 vs euthyroid: 6.85±5.81 vs 8.49±33.98 pmol/L, p=0.66; reference level: 1.96–9.33 pmol/L) between the low T3 and euthyroid group. (Figure 2)

The comparisons of hepatic and renal function between low T3 and euthyroid

Step further, we observed the disparity in hepatic and renal function and only found a significantly lower level of serum albumin (Alb: LowT3 vs euthyroid: 35.65±3.79 vs 38.72±4.63 g/L, p<0.0001; reference level: 40–55 g/L; TP: LowT3 vs euthyroid: 62.05±6.34 vs 63.97±8.43 g/L, p=0.0125; reference level: 65–85 g/L) in the hepatic function test, whereas there were increased Scr (LowT3 vs euthyroid: 91.98±65.11 vs 66.19±26.15 μmol/L, p=0.0002; reference level: 45–84 μmol/L) and decreased eGFR (LowT3 vs euthyroid: 79.29±26.61 vs 90.94±21.28 mL/min*1.73m^2, p=0.0001) detected in renal function (p<0.05). (Figure 3)

Correlational Relationships Between Bone Turnover Biomarker and Other Parameters

We in advance tested the relationship between bone turnover biomarkers and other assessed parameters in low T3 group and euthyroid group, and found a significant correlational relationship between bone turnover biomarkers and metabolic parameters. The results are shown in Table 2.

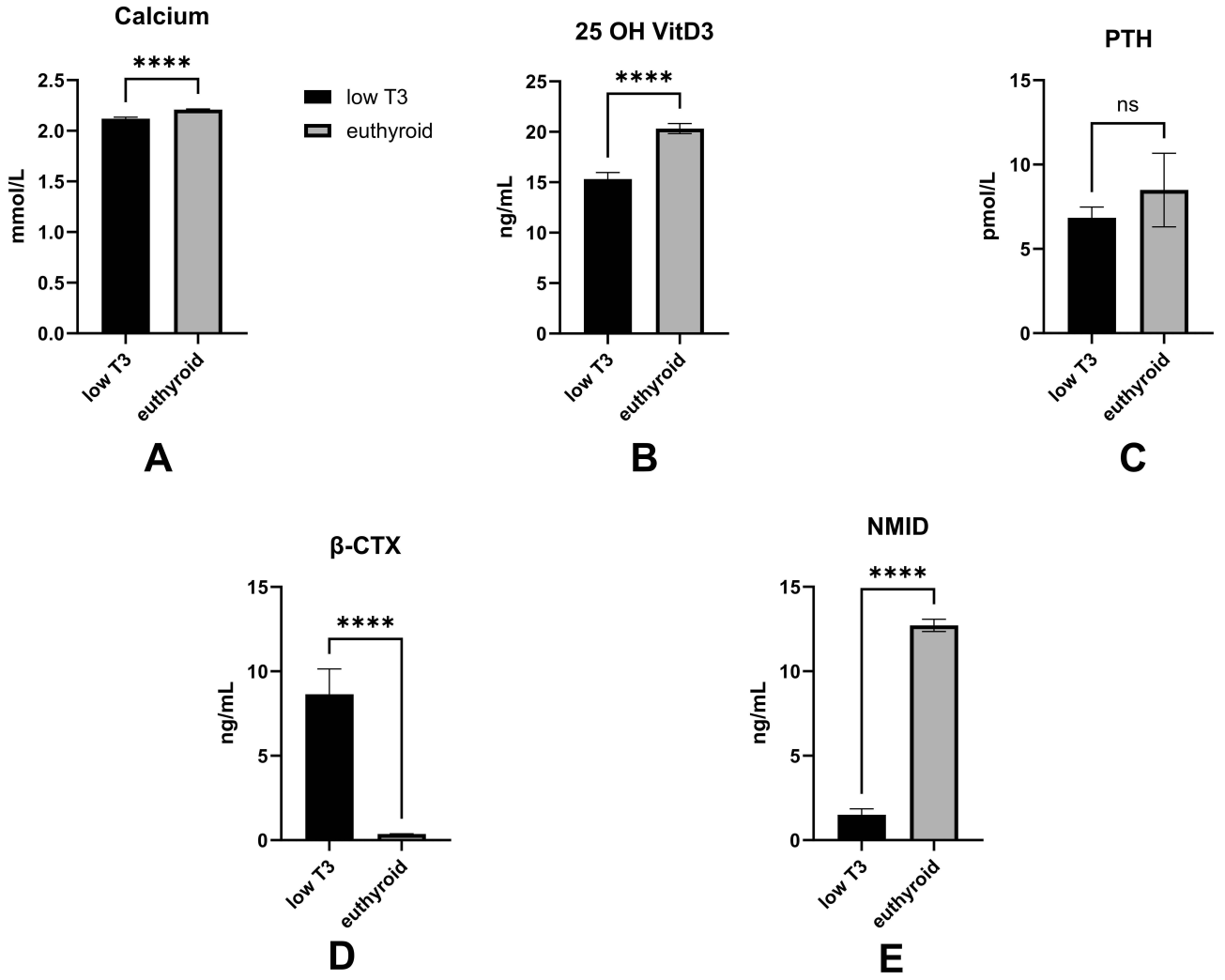

Figure 2 The comparisons between low T3 and euthyroid showed the disparity in the concentration of serum Ca^{2+} ($p<0.0001$) (**A**), 25 OH Vit D3 ($p<0.0001$) (**B**), PTH ($p>0.05$) (**C**), β-CTX ($p<0.0001$) (**D**), and NMID ($p<0.0001$) (**E**).
Note: ****$p<0.0001$.
Abbreviations: ns, no significance; Ca^{2+}, calcium; 25 OH Vit D3, 25-hydroxyvitamin D3; β-CTX, βC-terminal cross-linking telopeptide of type I collagen; NMID, N-terminal middle molecular fragment of osteocalcin.

Multilinear regression analyses of bone turnover biomarkers in the state of low FT3 state and euthyroid group

Thereafter, we assessed the multivariate linear regression relationship between the bone turnover biomarkers change and the multiple metabolic parameters. The results are shown in Tables 3–13.

Discussion

Our findings show that in T2D patients with low T3 syndrome, there is a significant alteration in bone metabolism-related markers change. This tendency reveals the activity of bone formation (NMID) decreases, whereas the marker for bone reabsorption (β-CTX) increase, and this alteration is not directly caused by the disarrangement of calcium-related regulatory hormones such as PTH and 25-OH Vit D3, suggested by the regression analyses. Our study reveals that in T2D patients with low T3 syndrome, due to multiple severe diabetic complications, there may be significant changes in bone metabolism, if untreated they would experience higher risk of osteoporosis or bone fractures compared with normal T2D. Our analyses also show a range of another metabolic parameters could be served as risk factors associated with aberrant bone metabolic markers in low T3 including renal function, bodyweight, pancreatic function (Figure 4).

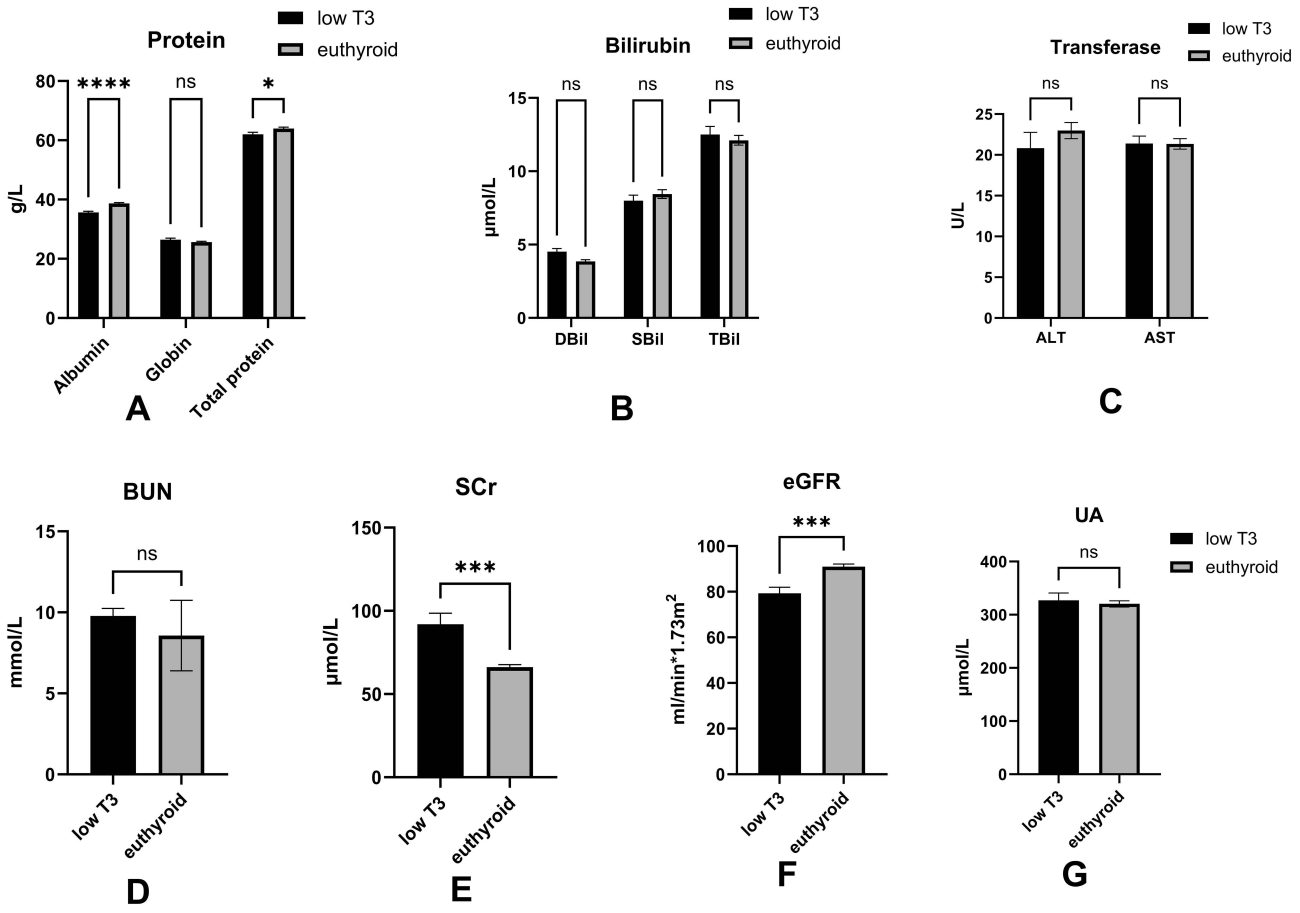

Figure 3 The analyses showed that serum albumin (p<0.0001) (**A**), bilirubin (p>0.005) (**B**), Transferase (p>0.05) (**C**), BUN(p>0.05)(D), Scr (p<0.001)(E), and eGFR (p<0.001) (**F**), UA(p>0.05) (**G**) were different between the low T3, and euthyroid groups.
Note: *p<0.05; ***p<0.001; ****p<0.0001.
Abbreviations: ns, no significant; DBil, direct bilirubin; SBil, indirect bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SCr, serum creatinine; eGFR, estimated glomerular infiltration; UA, uric acid.

Individuals diagnosed with T2D are susceptible to developing a range of complications if their glycemia levels failing to achieve the intended goal. These complications may include but are not limited to cerebral impairment, emotional disorders, osteoporosis, cancer, and frailty. Relatively severe acute diabetic dysregulation, such as diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemia (HHS), was associated with decreased bone turnover biomarker activity in T2D, according to our recent research.[24] Impaired thyroid function was also observed in those patients, as indicated by a low T3 level.[24] In those patients with DKA and HHS, the adaptive modification in thyroid activity did not indicate the thyroid lesion per se, but rather potentially as a disruption in the functioning of the hypothalamic-pituitary-thyroid axis (HPA axis). In our current study, as indicated by the concentration adjustments of serum NMID and β-CTX, regression analyses indicated that the adaptive modification in thyroid activity was also associated with bone turnover biomarker activity in the patients without DKA and HHS, which provides further support for our hypothesis that thyroid function is closely associated with bone metabolism in T2D patients with severe conditions. There is a lack of research that examines the correlation between low T3 syndrome and alterations in bone metabolism in T2D patients with severe conditions. The current research provided prognostic values that can be utilized to evaluate and predict the bone prognosis of individuals diagnosed with severe type 2 diabetes (Figure 4).

Initially, we conducted a comparative analysis of demographic characteristics and metabolic status between the groups with low T3 and euthyroidism (Table 1). The age difference implies that elderly patients may have a slower rate of metabolism than younger patients, which may contribute to the higher prevalence of low T3 in this population. The medication history also suggests the advanced progression of T2D in low T3, though, the diabetic duration in two groups

Table 2 The Correlational Relationship Between the Bone Turnover Biomarkers and Parameters Related to Metabolism

β-CTX												
Low T3	**TP**	**SCr**	**eGFR**	**TSH**	**PTH**	**FPCP**						
r	0.245	0.251	-0.207	0.429	0.290	0.193						
P	0.012	0.013	0.041	<0.0001	0.007	0.05						
Euthyroid	**Age**	**Sex**	**Bw**	**ALB**	**PTH**	**25OHVitD**	**NMID**					
r	0.144	0.184	-0.194	-0.123	0.255	-0.134	0.610					
P	0.011	0.001	0.001	0.030	`<0.0001	0.018	<0.0001					
NMID												
Low T3	**Sex**	**Bw**										
r	0.199	-0.212										
P	0.042	0.038										
Euthyroid	**Age**	**Sex**	**Bw**	**SBil**	**eGFR**	**FT4**	**PTH**	**25OHVitD**	**β-CTX**			
r	0.140	0.263	-0.187	-0.117	-0.176	-0.143	0.230	-0.138	0.610			
P	0.013	<0.0001	0.001	0.039	0.002	0.011	<0.0001	0.015	<0.0001			
25(OH)D3												
Low T3	**Sex**	**Bw**	**ALB**	**ALT**	**Ca^{2+}**							
r	-0.284	0.206	0.311	0.236	0.288							
P	0.004	0.045	0.001	0.016	0.003							
Euthyroid	**Sex**	**TP**	**ALB**	**ALT**	**SCr**	**Ca^{2+}**	**TT3**	**FT3**	**PTH**	**β-CTX**	**NMID**	
r	-0.216	0.154	0.133	0.139	0.144	0.134	0.165	0.175	-0.263	-0.134	-0.318	
P	<0.0001	0.006	0.019	0.013	0.011	0.018	0.003	0.002	<0.0001	0.018	0.015	

PTH														
Low T3	**Age**	**PPCP**	**SCr**	**eGFR**	**UA**	**Ca^{2+}**	**TT3**	**β-CTX**						
r	0.222	0.231	0.283	-0.282	0.300	-0.226	-0.242	0.290						
P	0.041	0.048	0.011	0.011	0.007	0.038	0.026	0.007						
Euthyroid	**eGFR**	**UA**	**Ca^{2+}**	**TT3**	**25OHVitD**	**β-CTX**	**NMID**							
r	-0.133	0.143	-0.220	-0.164	-0.263	0.255	0.230							
P	0.038	0.026	0.001	0.011	<0.0001	<0.0001	<0.0001							
Ca^{2+}														
Low T3	**TP**	**ALB**	**FT3**	**PTH**	**25OHVitD3**									
r	0.462	0.450	0.205	-0.226	0.288									
P	<0.0001	<0.0001	0.038	0.038	0.003									
Euthyroid	**PPCP**	**TP**	**ALB**	**GLO**	**TBil**	**SBil**	**ALT**	**AST**	**UA**	**TT3**	**FT3**	**PTH**	**FPCP**	**25OHVitD**
r	0.136	0.517	0.550	0.278	0.148	0.206	0.199	0.240	0.206	0.136	0.135	-0.220	0.212	0.134
P	0.020	<0.0001	<0.0001	<0.0001	0.009	<0.0001	<0.0001	<0.0001	<0.0001	0.016	0.017	0.001	<0.0001	0.018
FT3														
Low T3	**Age**	**ALB**	**GLO**	**Ca^{2+}**										
r	-0.194	0.324	-0.243	0.205										
P	0.049	0.001	0.013	0.038										
Euthyroid	**Age**	**Sex**	**Duration**	**Bw**	**TP**	**ALB**	**ALT**	**BUN**	**eGFR**	**Ca^{2+}**	**TT3**	**FT4**	**25OHVitD**	
r	-0.391	-0.341	-0.143	0.232	0.114	0.247	0.196	-0.155	0.282	0.135	0.565	0.185	0.175	
P	<0.0001	<0.001	0.011	<0.0001	0.043	<0.0001	<0.0001	0.006	<0.0001	0.017	<0.0001	0.001	0.002	

Abbreviations: TP, total protein; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone; PTH, parathyroid hormone; FPCP, fasting plasma C- peptide; PPCP, 2h postprandial plasma C-peptide; Bw, bodyweight; TBil, total bilirubin; ALB, albumin; GLO, globin; ALT, alanine aminotransferase; Ca^{2+}, calcium; UA, uric acid; FT3, free triiodothyronine; TT3, total triiodothyronine; β-CTX, βC-terminal cross-linking telopeptide of type I collagen; NMID, N-terminal middle molecular fragment of osteocalcin; PTH, parathyroid hormone; 25 OH VitD3, 25 hydroxyvitamin D3.

https://doi.org/10.2147/DMSO.S472946 DovePress

Table 3 The Multilinear Regression Model of Variables to the NMID Change in Low T3

Multilinear Regress	R	0.244	R^2	0.059	Adjusted R^2	0.050	Tolerance	VIF
Low T3	Variables	B	SE	β	t	Sig		
	Constant	6.517	2.002		3.255	0.002		
	Bw	−0.078	0.031	−0.244	−2.540	0.013	1.000	1.000

Table 4 The Multilinear Regression Model of Variables to the NMID Change in Euthyroid Function

Multilinear Regress	R	0.633	R^2	0.401	Adjusted R^2	0.391	Tolerance	VIF
Euthyroid	Variables	B	SE	β	T	Sig		
	Constant	15.446	2.773		5.570	<0.0001		
	β-CTX	16.813	1.445	0.539	11.639	<0.0001	0.908	1.101
	FT4	−0.450	0.139	−0.145	−3.247	0.001	0.977	1.023
	Sex	1.318	0.595	0.103	2.217	0.027	0.905	1.105
	25OHVitD3	−0.072	0.033	0.098	−2.161	0.031	0.938	1.067
	eGFR	−0.028	0.014	−0.092	−2.030	0.043	0.945	1.058

Abbreviations: Bw, bodyweight; β-CTX, β-C-terminal cross-linking telopeptide of type I collagen; FT4, free thyroxine; 25OHVitD3, 25-hydroxyvitamin D3; eGFR, estimated glomerular filtration rate.

Table 5 The Multilinear Regression Model of Variables to the β-CTX Change in Low T3

Multilinear Regress	R	0.849	R^2	0.721	Adjusted R^2	0.712	Tolerance	VIF
Low T3	Variables	B	SE	β	T	Sig		
	Constant	−36.532	4.805		−7.602	<0.001		
	SCr	0.236	0.019	0.973	12.229	<0.0001	0.441	2.267
	eGFR	0.261	0.044	0.439	5.990	<0.0001	0.519	1.926
	FPCP	6.062	1.880	0.198	3.225	0.002	0.738	1.354

Table 6 The Multilinear Regression Model of Variables to the β-CTX Change in Euthyroid Function

Multilinear Regress	R	0.592	R^2	0.350	Adjusted R^2	0.346	Tolerance	VIF
Euthyroid	Variables	B	SE	β	T	Sig		
	Constant	0.294	0.082		3.594	<0.0001		
	NMID	0.019	0.001	0.581	12.709	<0.0001	0.999	1.001
	ALB	−0.04	0.002	−0.095	2.076	0.039	0.999	1.001

Abbreviations: SCr, serum creatinine; eGFR, estimated glomerular filtration rate; FPCP, fasting plasma C-peptide; UA, uric acid; TSH, thyroid stimulating hormone; NMID, N-terminal middle molecular fragment of osteocalcin; HbA1c, Glycated hemoglobin A1c; FT3:free iodothyronine; TBil, total bilirubin.

Table 7 The Multilinear Regression Model of Variables to the 25 OH VitD3 Change in Low T3

Multilinear Regress	R	0.416	R^2	0.173	Adjusted R^2	0.157	Tolerance	VIF
Low T3	Variables	B	SE	β	t	Sig		
	Constant	−3.688	9.017		−0.409	0.683		
	Sex	−4.209	1.196	−0.318	−3.519	0.001	1.000	1.000
	Ca^{2+}	12.067	4.136	0.264	2.917	0.004	1.000	1.000

Table 8 The Multilinear Regression Model of Variables to the 25 OH VitD3 Change in Euthyroid Function

Multilinear Regress	R	0.306	R^2	0.094	Adjusted R^2	0.085	Tolerance	VIF
Euthyroid	Variables	B	SE	β	T	Sig		
	Constant	20.469	3.362		6.088	<0.0001		
	Sex	−3.150	0.988	−0.180	−3.190	0.002	0.914	1.094
	TT3	5.001	1.926	0.142	2.597	0.010	0.976	1.025
	NMID	−0.197	0.076	−0.145	−2.591	0.010	0.934	1.071

Abbreviations: Ca^{2+}, Serum calcium; TSH, thyroid stimulating hormone; NMID, N-terminal middle molecular fragment of osteocalcin; FT3, Free iodothyronine.

Table 9 The Multilinear Regression Model of Variables to the PTH Change in Low T3 but Showed No Significant Variables Was Associated with PTH of Euthyroid Function Group

Multilinear Regress	R	0.463	R^2	0.215	Adjusted R^2	0.191	Tolerance	VIF
Low T3	Variables	B	SE	β	t	Sig		
	Constant	7.446	7.327		1.016	0.312		
	UA	0.012	0.003	0.318	3.551	0.001	0.982	1.018
	Age	0.137	0.040	0.302	3.400	0.001	0.986	1.005
	Ca^{2+}	−6.848	3.261	−0.188	−2.100	0.038	0.981	1.019

Abbreviations: UA, uric acid; TT4, total thyroxine; Ca^{2+}, serum calcium.

Table 10 The Multilinear Regression Model of Variables to the Ca^{2+} Change in Low T3

Multilinear Regress	R	0.468	R^2	0.219	Adjusted R^2	0.211	Tolerance	VIF
Low T3	Variables	B	SE	β	t	Sig		
	Constant	1.488	0.119		12.479	<0.0001		
	ALB	0.018	0.003	0.468	5.346	<0.0001	1.000	1.000

Table 11 The Multilinear Regression Model of Variables to the Ca^{2+} Change in Euthyroid Function

Multilinear Regress	R	0.638	R^2	0.407	Adjusted R^2	0.395	Tolerance	VIF
Euthyroid	Variables	B	SE	β	T	Sig		
	Constant	1.443	0.055		26.402	<0.0001		
	ALB	0.017	0.002	0.705	7.949	<0.0001	0.245	4.076
	UA	0.000238	0.000047	0.224	5.005	<0.0001	0.969	1.032
	DBil	0.009	0.001	0.433	6.505	<0.0001	0.435	2.297
	GLO	0.008	0.001	0.340	6.132	<0.0001	0.630	1.587
	TBil	−0.004	0.001	−0.210	−3.123	0.002	0.429	2.332
	TP	−0.003	0.001	−0.240	−2.626	0.009	0.231	4.330

Abbreviations: ALB, serum album; UA, uric acid; TBil, total bilirubin.

were comparable, in that there were more proportion of patients with drug naïve, administered oral anti-diabetic drugs rather than insulin utilization. Due to the possibility of malnutrition in aged low T3 patients, their bodyweight was slightly lower than euthyroid. We could also observe elevated mean fasting glucose (FPG) in low T3, as well the glycemic control level seems more higher than euthyroid. In terms of thyroid function, the thyroid hormones were also significantly lower in these cohorts.

Table 12 The Multilinear Regression Model of Variables to the FT3 Change in Low T3

Multilinear Regress	R	0.398	R^2	0.158	Adjusted R^2	0.142	Tolerance	VIF
Low T3	Variables	B	SE	Β	T	Sig		
	Constant	1.881	0.664		2.831	0.006		
	ALB	0.055	0.016	0.312	3.415	0.001	1.000	1.000
	GLO	−0.034	0.012	−0.251	−2.752	0.007	1.000	1.000

Table 13 The Multilinear Regression Model of Variables to the FT3 Change in Euthyroid Function

Multilinear Regress	R	0.677	R^2	0.458	Adjusted R^2	0.451	Tolerance	VIF
Euthyroid	Variables	B	SE	Β	T	Sig		
	Constant	3.325	0.293		11.349	<0.0001		
	TT3	1.044	0.092	0.499	11.373	<0.0001	0.912	1.096
	Sex	−0.221	0.044	−0.213	−4.968	<0.0001	0.956	1.046
	Age	−0.009	0.002	−0.196	−4.434	<0.0001	0.900	1.111
	FT4	0.038	0.011	0.151	3.558	<0.0001	0.974	1.026

Abbreviations: FT4, free thyroxine; TT4, total thyroxine; TT3, total triiodothyronine; ALB, serum albumin; Bw, bodyweight; TSH, thyroid stimulating hormone; GLO, serum globin; eGFR, estimated glomerular filtration rate; NMID, N-terminal middle molecular fragment osteocalcin; AST, aspartate aminotransferase; Ca^{2+}, Serum calcium.

Subsequently, we examined the bone turnover biomarkers in both groups and identified decreased serum calcium levels, 25(OH)D3, and NMID, which indicate calcium depletion and a disruption in the regulation of calcium-regulating hormones (Figure 2). This may be attributed to factors, such as malnutrition, aging, absorption disorders, and VitD3 metabolic disorder. A significant increase in the activity of β-CTX and a decrease in the activity of NMID were also observed, suggesting that the equilibrium between bone anabolism and catabolism was disrupted. Our data may indicate

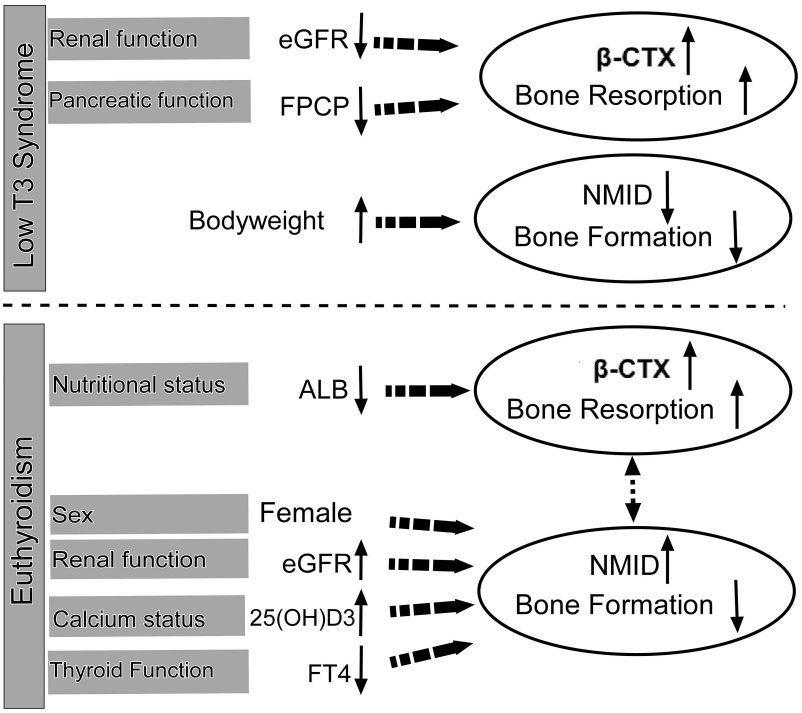

Figure 4 An illustration of the impact that variation has on the homeostasis of biomarkers for bone turnover (β–CTX and NMID). In T2D patients with low T3 syndrome, β-CTX levels demonstrated an increase as determined by eGFR and free plasma c-peptide (FPCP), whereas NMID levels declined exclusively in association with increased body weight. Conversely, in euthyroid T2D patients, the change of NMID was concurrently in line with that of β-CTX, although a tendency of increase in bone reabsorption activity was observed, and a few factors such as sex, albumin, FT4, eGFR, and 25 OH VitD3 influenced their activities.

that low T3 participants may be more susceptible to developing osteoporosis and bone fractures compared to euthyroid individuals. Simultaneously, an analysis of the hepatic and renal functions in both groups was conducted. The results indicated malnutrition and impaired protein synthesis in the low T3 group, as well as increased catabolism and decreased renal filtration function as indicated by elevated SCr and lower eGFR (Figure 2).

Additionally, we investigated the association between bone turnover indicators and the metabolic parameters described previously (Table 3). β-CTX, a biomarker of catabolism, showed positive associations with total protein, SCr, TSH, PTH, and FPCP, but a negative correlation with eGFR. This indicates that β-CTX can be used as an indicator of catabolism, and any increase in SCr or decrease in eGFR can lead to higher levels of β-CTX. While there is no notable change in TSH levels in patients with low T3, an increase in TSH indicates a decrease in the feedback inhibition of thyroid hormones. This increase in TSH may result in an elevation of β-CTX, which is consistent with a previous study that observed TSH receptors expressed in bone osteoclasts.[35] It is possible that TSH regulates the activity of these osteoclasts. PTH is a hormone that stimulates the uptake of calcium in bones to balance the levels of circulating calcium. Therefore, we have additionally observed a positive correlation between them. Remarkably, our results indicate that FPCP serves not only as a criterion for pancreatic function but also has a correlation with the activity of bone catabolism. This suggests that pancreatic function could be considered an indicator of the quality of bone turnover status, which aligns with our clinical observation.[36] Regarding the NMID, we discovered a negative correlation between it and bodyweight and total bilirubin. This suggests that low T3 levels, being male, having higher bodyweight, and experiencing liver injury may impede the bone's anabolism process. However, our findings indicate that the male gender, greater bodyweight, improved nutrition, and higher calcium concentration are significant factors in relation to 25 OH VitD3. Regarding PTH, the factors that significantly contribute to raised PTH levels include aging, increased SCr, reduced renal filtration and excretion of UA, decreased calcium levels, decreased TT3 levels, and increased β-CTX levels. These findings indicate that PTH may serve as a catabolic indicator. Furthermore, the serum calcium level had a positive correlation with total protein concentration, albumin level, raised FT3 level, and 25(OH) Vitamin D3(VitD3). Conversely, it exhibited a negative correlation with PTH, which serves as an indicator of nutritional status and disease severity. After conducting an analysis, we discovered that there is a negative association between aging and globin level with FT3. On the other hand, albumin and calcium concentration showed a positive relationship with FT3. This result indicates that the change in FT3 is closely related to the individual's nutrition status, suggesting that FT3 can be considered an indicator of anabolism status.

We have identified the factors that cause changes in bone turnover biomarker activities (Tables 3–13). Based on our research, we have determined that bodyweight has a negative impact on NMID. On the other hand, the change in β-CTX can be predicted by renal function, and pancreatic islet function. Through the examination of the factors influencing the levels of 25(OH) Vitamin D3(VitD3), we have discovered that being male, having higher blood calcium levels can lead to an increase its concentration. In addition, we found that uric acid (UA), aging, and reduced serum calcium were factors that influenced the PTH, the catabolic indicator. However, it was found that the storage of serum albumin is the only factor that affects the fluctuation of serum calcium, as the physiological function of calcium is intimately associated with level of albumin (ALB) and hepatic synthetic function.[37] Moreover, the regression analysis revealed that the changes in FT3, in addition to other thyroid function biomarkers, could be predicted with a confidence level of 62.7% based on the levels of ALB, and serum globin (GLO).

Non-thyroid illness syndrome (NTIS) is a bodily protective adaption to the stress condition, and Low T3 could be restoration as long as the stress be remission. Although, there were evidences that supplementation of thyroid hormone such as Euthyrox (Levothyroxine) in certain conditions may bestow benefits to the certain patients during caloric restriction, cardiovascular disorders, acute renal insufficiency, and burning patients; however, the outcome according to the previous comparative clinical trials proved no advantage with LT-4 supplementation. It is also reported that supplementation of TSH in chronic patients could normalize the rhythms of TRH release, while the power of the pertinent evidences seemed plausible. Some studies set out to examine the supplementation of T3 on the Low T3 patients also proved no better outcomes such as mortality despite the patients' condition or certain parameters improved, in that T3 may physiologically possess more effective bioactive function than T4. There were also investigations proving that suppress TSH level may prevent osteoporosis in thyroid disorders, however the outcomes by different research group varied. Therefore, whether supplementation of Euthyrox could relive the aberrant bone turnover biomarkers in the diabetic patients with low T3 syndrome still remain debatable.

Limitation

Due to lack of multicenter cooperation and limitations on sample size, we could not further explore the characteristics of these low T3 population, such as other demographic information, and follow-up on their thyroid function and bone metabolism, as well as assessment of the ultimate bone outcome. Nevertheless, our findings also indicate that thyroid function indicators and pancreatic function may serve as metabolic prognostic factors for the bone metabolism and reveal the risk of osteoporosis in low T3 syndrome.

Conclusion

In the present study, we compared the demographic and metabolic characteristics of patients with T2D who had low levels of T3 hormone and those with normal thyroid function. This study demonstrated that T2D patients with condition of low T3 syndrome may experience an aberrant bone metabolism represented by the elevation of bone reabsorption marker and suppressed bone formation marker, which in long-term may be served as risk factors to predict major bone fractures. In addition, we identified other systemic and metabolic parameters as risk factors in low T3 including age, bodyweight, gender, hepatic and renal function, as well as pancreatic function. The impact of nutrient conditions, calcium supplementation and renal function as well as alleviate toxicity of hyperglycemia on pancreatic function may benefit on the regulation of bone turnover biomarkers in patients with low T3 syndrome who have T2D.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethical statement

Ethical approval was obtained from the Shanghai Pudong Hospital (WZ-010) for the entire investigation, including blood sampling, physical examination, and access to or utilization of source data. Before participating in the investigation, all individuals were provided informed consent. The entire procedure was carried out per the Helsinki Declaration, which outlined the guidelines. Prior to utilization, each record utilized in this research was anonymized.

Acknowledgments

We would thank staff of Shanghai Pudong Hospital for whom provide numerous invaluable contributions to this study.

Author Contributions

All authors have made significant contributions to this work, including the conception of the study, study design, execution, data acquisition, analysis, and interpretation of the data. They have actively participated in drafting, revising, and critically reviewing the article. The final version to be published has received approval from all authors. They have collectively agreed on the journal to which the article has been submitted and are willing to take full responsibility for all aspects of the work.

Funding

This work was supported by the Integrated Traditional Chinese and Western Medicine (YC-2023-0404), Fudan Zhangjiang Clinical Medicine Innovation Fund Project (KP0202118), Project of Key Medical Discipline of Pudong Hospital of Fudan University (Zdxk2020-11), Project of Key Medical Specialty and Treatment Center of Pudong Hospital of Fudan University (Zdzk2020-24), Integrative Medicine special fund of Shanghai Municipal Health Planning Committee (ZHYY- ZXYJHZX-2-201712), Special Department Fund of the Pudong New Area Health Planning Commission (PWZzk2017-03), Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai (PWR12014-06), Pudong New Area Clinical Plateau Discipline Project (PWYgy-2021-03), the Natural Science Foundation of China (21675034), National Natural Science Foundation of China (81370932), Shanghai Natural Science Foundation (19ZR1447500), Pudong New Area Clinical Characteristic Discipline Project (PWYts2021-01), Wenzhou Medical University Education Grant (JG2021197).

Disclosure

The authors declare that there is no potential conflict of interest in this work.

References

1. Gauthier BR, Sola-García A, Cáliz-Molina M, et al.. Thyroid hormones in diabetes, cancer, and aging. *Aging Cell*. 2020;19(11):e13260. doi:10.1111/acel.13260
2. Liu C, Pan J, Wen S, et al.. Low TSH Levels Within Euthyroid Range Could Play a Negative Role on Bone Mineral Density in Postmenopausal Women with Type 2 Diabetes. *Diab, Metab Syndr Obes*. 2021;14:2349–2355. doi:10.2147/DMSO.S307633
3. Wang C, Wen S, Yuan X, et al.. The Relationship between Serum Iron and Thyroid Function in the Patients with Type 2 Diabetes. *Endocr Metab Immune Disord Drug Targets*. 2023;23(4):558–567. doi:10.2174/1871530322666220928144548
4. Hamann C, Kirschner S, Günther KP, Hofbauer LC. Bone, sweet bone--osteoporotic fractures in diabetes mellitus. *Nat Rev Endocrinol*. 2012;8(5):297–305. doi:10.1038/nrendo.2011.233
5. Mauricio D, Gratacòs M, Franch-Nadal J. Diabetic microvascular disease in non-classical beds: the hidden impact beyond the retina, the kidney, and the peripheral nerves. *Cardiovasc diabetol*. 2023;22(1):314. doi:10.1186/s12933-023-02056-3
6. Bott KN, Feldman E, de Souza RJ, et al.. Lipopolysaccharide-Induced Bone Loss in Rodent Models: a Systematic Review and Meta-Analysis. *J Bone Min Res*. 2023;38(1):198–213. doi:10.1002/jbmr.4740
7. Ninkovic M, Love SA, Tom B, Alexander GJ, Compston JE. High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. *Calcified Tissue Intl*. 2001;69(6):321–326. doi:10.1007/s00223-001-2028-4
8. Chun LF, Yu EL, Sawh MC, et al. Hepatic Steatosis is Negatively Associated with Bone Mineral Density in Children. *J Pediatr*. 2021;233:105–111. doi:10.1016/j.jpeds.2021.01.064
9. Bellorin-Font E, Rojas E, Martin KJ. Bone Disease in Chronic Kidney Disease and Kidney Transplant. *Nutrients*. 2022;15(1):167. doi:10.3390/nu15010167
10. Zhang C, Li H, Li J, Hu J, Yang K, Tao L. Oxidative stress: a common pathological state in a high-risk population for osteoporosis. *Biomed Pharmacothe*. 2023;163:114834.
11. Rubin MR. Skeletal fragility in diabetes. *Ann N.Y. Acad Sci*. 2017;1402(1):18–30. doi:10.1111/nyas.13463
12. Liu C, Pan J, Wen S, Zhou L. Correlation between bone metabolism biomarker and glycated hemoglobin in middle-and-old age patients with type 2 diabetes. *Fudan Univ J Med Sci*. 2022;49(5):733–738.
13. Xu C, Gong M, Wen S, Zhou M, Li Y, Zhou L. The Comparative Study on the Status of Bone Metabolism and Thyroid Function in Diabetic Patients with or without Ketosis or Ketoacidosis. *Diab, Metab Syndr Obes*. 2022;15:779–797. doi:10.2147/DMSO.S349769
14. Mendoza A, Hollenberg AN. New insights into thyroid hormone action. *Pharmacol Ther*. 2017;173:135–145. doi:10.1016/j.pharmthera.2017.02.012
15. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol*. 2017;14(1):39–55. doi:10.1038/nrcardio.2016.174
16. Lee SY, Pearce EN. Hyperthyroidism: a Review. *Jama*. 2023;330(15):1472–1483. doi:10.1001/jama.2023.19052
17. Roberts CG, Ladenson PW. Hypothyroidism. *Lancet*. 2004;363(9411):793–803. doi:10.1016/S0140-6736(04)15696-1
18. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. *Lancet Diabetes Endocrinol*. 2015;3(10):816–825. doi:10.1016/S2213-8587(15)00225-9
19. Balsam A, Ingbar SH. Observations on the factors that control the generation of triiodothyronine from thyroxine in rat liver and the nature of the defect induced by fasting. *J Clin Invest*. 1979;63(6):1145–1156. doi:10.1172/JCI109408
20. Kabadi UM, Premachandra BN. Low triiodothyronine and raised reverse triiodothyronine levels in patients over fifty years of age who have type II diabetes mellitus: influence of metabolic control, not age. *J Am Geriatr Soc*. 1984;32(5):375–379. doi:10.1111/j.1532-5415.1984.tb02043.x
21. Jolin T. Diabetes decreases liver and kidney nuclear 3,5,3'-triiodothyronine receptors in rats. *Endocrinology*. 1987;120(5):2144–2151. doi:10.1210/endo-120-5-2144
22. Wang CY, Yu TY, Shih SR, Huang KC, Chang TC. Low total and free triiodothyronine levels are associated with insulin resistance in non-diabetic individuals. *Sci Rep*. 2018;8(1):10685. doi:10.1038/s41598-018-29087-1
23. Spira D, Buchmann N, Dörr M, et al.. Association of thyroid function with insulin resistance: data from two population-based studies. *European Thyroid J*. 2022;11(2). doi:10.1530/ETJ-21-0063.
24. Gong M, Xu C, Wen S, et al.. The Effects of Obesity on Bone Turnover Markers in Diabetic Patients with Diabetic Ketosis or Ketoacidosis. *Endocr Metab Immune Disord Drug Targets*. 2023;23(13):1660–1667. doi:10.2174/1871530323666230509101203
25. Bianco AC, Dumitrescu A, Gereben B, et al.. Paradigms of Dynamic Control of Thyroid Hormone Signaling. *Endocr Rev*. 2019;40(4):1000–1047. doi:10.1210/er.2018-00275
26. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T3: local thyroid hormone metabolism during inflammation and infection. *Endocr Rev*. 2011;32(5):670–693. doi:10.1210/er.2011-0007
27. Ortiga-Carvalho TM, Chiamolera MI, Pazos-Moura CC, Wondisford FE. Hypothalamus-Pituitary-Thyroid Axis. *Compr Physiol*. 2016;6(3):1387–1428.
28. Fontes KN, Cabanelas A, Bloise FF, et al. Differential Regulation of Thyroid Hormone Metabolism Target Genes during Non-thyroidal [corrected] Illness Syndrome Triggered by Fasting or Sepsis in Adult Mice. *Front Physiol*. 2017;8:828. doi:10.3389/fphys.2017.00828
29. Fekete C, Kelly J, Mihály E, et al.. Neuropeptide Y has a central inhibitory action on the hypothalamic-pituitary-thyroid axis. *Endocrinology*. 2001;142(6):2606–2613. doi:10.1210/endo.142.6.8207
30. Wajner SM, Maia AL. New Insights toward the Acute Non-Thyroidal Illness Syndrome. *Front Endocrinol*. 2012;3:8. doi:10.3389/fendo.2012.00008
31. Han Q, Zhang J, Wang Y, et al. Thyroid hormones and diabetic nephropathy: an essential relationship to recognize. *Nephrology*. 2019;24(2):160–169. doi:10.1111/nep.13388
32. He W, Pang C, Chen L, et al.. Low T3 syndrome is associated with peripheral neuropathy in patients with type 2 diabetes mellitus. *Muscle Nerve*. 2022;66(6):723–729. doi:10.1002/mus.27719

33. Xiu S, Mu Z, Zhao L, Sun L. Low free triiodothyronine levels are associated with risk of frailty in older adults with type 2 diabetes mellitus. *Exp Gerontol*. 2020;138:111013. doi:10.1016/j.exger.2020.111013
34. Stathatos N, Levetan C, Burman KD, Wartofsky L. The controversy of the treatment of critically ill patients with thyroid hormone. *Best Pract Res Clin Endocrinol Metab*. 2001;15(4):465–478. doi:10.1053/beem.2001.0164
35. Abe E, Marians RC, Yu W, et al. TSH is a negative regulator of skeletal remodeling. *Cell*. 2003;115(2):151–162. doi:10.1016/S0092-8674(03)00771-2
36. Yan W, Li X. Impact of diabetes and its treatments on skeletal diseases. *Front Med*. 2013;7(1):81–90. doi:10.1007/s11684-013-0243-9
37. Grzych G, Pekar JD, Durand G, Deckmyn B, Maboudou P, Lippi G. Albumin-Adjusted Calcium and Ionized Calcium for Assessing Calcium Status in Hospitalized Patients. *Clin Chem*. 2019;65(5):703–705. doi:10.1373/clinchem.2018.300392

Diabetes, Metabolic Syndrome and Obesity Dovepress

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal