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Vitamin D Status Is Negatively Related to Insulin Resistance and Bone Turnover in Chinese Non-Osteoporosis Patients With Type 2 Diabetes: A Retrospective Cross-Section Research

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Background and Objectives: Vitamin D status is closely related to blood glucose and bone metabolism in patients with type 2 diabetes (T2DM). Vitamin D affects bone density and bone metabolism, leading to osteopenia and osteoporosis. Insulin resistance increases the risk of osteoporosis in patients with T2DM. Our previous studies have shown a negative correlation between insulin resistance and 25-hydroxy vitamin D [25(OH)D] levels. The aim of the present study was to determine the association between vitamin D status and insulin resistance and bone metabolism in patients with T2DM.

Subjects and Methods: A retrospective cross-section research was carried out among 109 non-osteoporosis patients with T2DM. Their fasting blood glucose (FBG), 25(OH)D, fasting blood insulin (FINS), glycosylated hemoglobin (HbA1c), serum creatinine (SCr), calcium (Ca), phosphorus (P), insulin-like growth factor-1 (IGF-1), bone alkaline phosphatase (BALP), body mass index (BMI), glomerular filtration rate (eGFR), homeostatic model estimates of insulin resistance (HOMA-IR), and calcium-phosphorus product were measured routinely.

Results: Both in men and women, 25(OH)D was negatively correlated with BALP ($\beta = -0.369$, $p \leq 0.001$)and HOMA-IR ($\beta = -0.349$, $p \leq 0.001$), and positively associated with IGF-1($\beta = 0.672$, $p \leq 0.05$). There was a negative correlation between HOMA-IR and IGF-1 ($\beta = -0.464$, $p \leq 0.001$), and a positive correlation between HOMA-IR and BALP ($\beta = 0.344$, $p \leq 0.05$), adjusted by confounding factors.

Conclusion: Our study demonstrates that 25(OH)D concentrations are negatively correlated with insulin resistance and bone turnover. Insulin resistance increases with the decrease of 25(OH)D concentration, which can enhance bone turnover, and increases the risk of osteoporosis in non-osteoporosis patients with T2DM. This is the first study to clarify the relationship between serum vitamin D status, insulin resistance, and bone metabolism in non-osteoporosis patients with T2DM in China.

Keywords: vitamin D, insulin resistance, bone turnover, type 2 diabetes, Chinese non-osteoporosis patients

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INTRODUCTION

Both osteoporosis and diabetes are metabolism diseases, which increase rapidly in the world, especially in Asia. In Asian countries, the predicted prevalence of diabetes by the year 2030 is more than double-rates that in 2000 (1). Hip fractures occurring in Asia will be responsible for 50% of that in the world by the year 2050 in forecast reports (2, 3). Diabetic osteopathy is a complication that leads to the decrease of bone formation and bone density and increases the risk of fracture healing difficulty. Patients with diabetic osteopathy show increased osteoclastogenesis and decreased osteoblastogenesis. Accumulated research studies have shown that vitamin D deficiency was commonly found in patients with type 2 diabetes (T2DM) (4–6). It is generally agreed that vitamin D is responsible for maintaining normal levels of serum Ca and P. Therefore, subjects with vitamin D deficiency are at high risk for osteoporosis. Diabetic osteopathy has a high incidence and delay healing, which is a result of disabilities and morbidity (7).

The prediction and early intervention of osteoporosis are essential to patients with diabetes-related disorders. Insulin resistance is the basic pathologic change in patients with T2DM, which raises the risk of osteoporosis. Based on the negative correlation between 25-hydroxy vitamin D [25(OH)D] concentration with insulin resistance found in our research before (8), we boldly hypothesized that vitamin D status may be negatively related to both insulin resistance and bone metabolism in patients with T2DM. There is limited information about the relationship between vitamin D levels, insulin resistance, and bone metabolism in patients with T2DM. This study determined the relationship between serum vitamin D levels, bone metabolism, and insulin resistance in Chinese non-osteoporosis patients with T2DM. Informed consents were unnecessary, due to the retrospective and the anonymously data-analyzing.

SUBJECTS AND METHODS

Subjects

Based on Levey et al.'s research (9), we identified 109 patients with T2DM without osteoporosis (10), who were treated in the outpatient Department of Endocrinology and Metabolism of Xiamen Second Hospital from January 1, 2014 to March 31, 2014, considering the effect of different seasons to vitamin D status. We followed the methods of Zhang et al. (8). Inclusion criteria were as follows: (i) age ranging from 20 to 70 years, (ii) history $<$ 10 years, (iii) serum parathyroid hormone concentration ranging from 15.0 to 65.0 pg/ml, (iv) a serum calcium (Ca) concentration $<$ 2.45 mmol/L, (v) normal routine blood tests of liver function, serum creatinine, serum urea nitrogen (BUN), and normal electrolytes, and not being treated with insulin or with a thiazolidinedione (TZD), estrogen, glucocorticoids, vitamin D, or drugs modulating vitamin D efficacy. The definition of osteoporosis was based on assessments of bone mineral density (BMD).

Major reasons for excluding individuals included (i) absence of T2DM or presence of diabetic ketoacidosis, ketonuria, or diabetic hyperosmolar syndrome, osteoporosis, (ii) serum phosphorus (P) $>$ 1.60 mmol/L, (iii) acute infection, (iv) tumors, and (v) pregnant or nursing women, (vi) diagnosis of osteoporosis [According to the WHO criteria (11), osteoporosis was defined as "a BMD that lies 2.5 SD or more below the mean value (a T-score of $<$-2.5 SD)". The BMD was checked by using a Lunar iDXA (GE Healthcare, Chicago, IL, USA) at both the whole spine and hip lumbar spine (L1–L4)].

Anthropometric and Biochemical Analysis

Basic characteristics (sex, age, and family history of T2DM) of the participants were collected. Anthropometric values, such as body weight, height, body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), were measured. Blood samples were drawn between 08:00 a.m. and 09:00 a.m. for laboratory analysis of biochemical variables 25(OH)D, fasting blood glucose (FBG), glycosylated hemoglobin A1c (HbA1c), fasting insulin (FINS), bone alkaline phosphatase (BALP), fasting serum C peptide, insulin-like growth factor-1 (IGF-1), total cholesterol (TC), high-density lipoprotein (HDL-C), triglyceride (TG), low-density lipoprotein (LDL-C), intact parathyroid hormone (iPTH), serum creatinine (SCr), BUN, Ca, P, cystatin C (Cys), homocysteine (Hcy), apolipoprotein-A1 (Apo-A1), and apolipoprotein-B (Apo-B). The anthropometric and biochemical results were analyzed as previously described (8).

Statistical Analysis

SPSS 19.0 software was used for statistical analysis. Non-normal distribution variables are expressed as median and interquartile ranges. Continuous variables were shown as the mean $\pm$ SD. Independent-sample *t*-test was used to compare 25(OH)D, homeostatic model estimates of insulin resistance (HOMA-IR), and glucose metabolism indices (FBG, FINS, and HbA1c), Ca, P, BALP, iPTH, IGF-1 in male and female subjects. Multiple linear regression analysis was used to examine the association between two indices below: (1)serum 25(OH)D concentration and insulin resistance index (HOMA-IR), HOMA-IR analyzed as a dependent variable with the other significantly associated variables [25(OH)D, eGFR, BMI, and age] as independent variables, (2) serum 25(OH)D concentration and bone metabolism indices (Ca, P, calcium-phosphorus production, BALP, and IGF-1), 25 (OH)D, analyzed as the independent variable with the other significantly associated variables (Ca, P, calcium-phosphorus production, BALP, IGF-1, eGFR, BMI, and age) as the dependent variables, (3) HOMA-IR, and bone metabolism indices (Ca, P, calcium-phosphorus production, BALP, and IGF-1), HOMA-IR, analyzed as the independent variable with the other significantly associated variables (Ca, P, calcium-phosphorus production, BALP, IGF-1, eGFR, BMI, and age) as dependent variables. Significance was set at $p < 0.05$.

TABLE 1 | Characteristics of the study population.

Characteristics		N
Age (year)[a]	49.79 ± 13.53	109
History (year)[b]	3.00 (0.00–8.00)	109
Male *n* (%)[c]	55.05	60
BMI (kg/m^2)[a]	24.99 ± 3.30	109
SBp (mmHg)[a]	125.76 ± 14.97	109
DBp (mmol/L)[a]	80.76 ± 9.45	109
FINS (pmol/L)[b]	114.55 (70.78–156.52)	109
FBG (mmol/L)[a]	8.15 ± 3.28	109
HOMA-IR[a]	5.68 ± 2.05	109
Fasting peptide C (μIU/mL)[a]	2.05 ± 1.01	109
25(OH)D (ng/mL)[a]	21.10 ± 10.39	109
Vitamin D deficiency [*n* (%)][c]	54.13	59
Vitamin D insufficiency [*n* (%)][c]	24.77	27
Vitamin D sufficiency [*n* (%)][c]	21.10	23
HbA1c (%)[a]	9.49 ± 2.79	109
TG (mmol/L)[b]	1.65 (1.06–2.63)	109
TC (mmol/L)[a]	5.15 ± 1.13	109
HDL-C (mmol/L)[b]	1.23 (1.10–1.45)	109
LDL-C (mmol/L)[a]	3.08 ± 1.02	109
Apo-A1 (g/L)[b]	1.37 (1.18–1.74)	109
Apo-B (g/L)[a]	1.03 ± 0.32	109
Bun (mmol/L)[b]	4.80 (4.15–5.64)	109
Cr (μmol/L)[b]	56.50 (48.23–69.68)	109
eGFR (mL/min)[b]	111.70 (93.85–130.25)	109
Ca (mmol/L)[a]	2.33 ± 0.13	109
P (mmol/L)[a]	1.36 ± 0.15	109
Calcium [(mg/dL)^2][a]	39.24 ± 5.11	109
iPTH (pg/mL)[a]	43.05 ± 14.27	109
BALP (u/L)[a]	184.72 ± 14.77	109
IGF-1 (pg/mL)[a]	276.65 ± 146.52	109
Cys (mg/L)[b]	0.98 (0.91–1.14)	109
Hcy (μmol/L)[a]	9.10 ± 4.11	109

[a]*Mean ± SD.*
[b]*Median (interquartile range).*
[c]*Percentage.*
HOMA-IR, homeostatic model estimates of insulin resistance; 25(OH)D, 25-hydroxy vitamin D; TC, total cholesterol; LDL, low-density lipoprotein; Ca, serum calcium; P, serum phosphorus; eGFR, glomerular filtration rate; FINS, fasting blood insulin; TG, triglyceride; HDL, high-density lipoprotein; BUN, blood urea nitrogen; SCr, serum creatinine; HbA1c, glycated hemoglobin A1c; iPTH, intact parathyroid hormone.

RESULTS

Baseline Characteristics and Bone Metabolism

A total of 109 patients were enrolled in this study. The characteristics of the study subjects and bone metabolism are shown in **Table 1**. The population had an even sex distribution (55.05% men) and a normal BMI (mean BMI = 24.99 ± 3.30 kg/m^2) and middle age (mean age = 49.79 ± 13.53 years). The mean 25(OH)D value was 21.10 ± 10.39 ng/ml (52.75 ± 25.98 nmol/L), below the sufficiency cutoff value of 30 ng/ml.

TABLE 2 | Comparison of insulin resistance, glucose (FBG, FINS, and HbA1c) and bone metabolism (Ca, P, calcium, and phosphorus production, iPTH, BALP, and IGF-1) indexes between male and female.

	Male	Female	*p*-value
25(OH)D (ng/mL)[a]	20.27 ± 11.43	22.10 ± 8.97	0.364
HOMA-IR[a]	5.79 ± 2.17	5.54 ± 1.90	0.562
HbA1c (%)	10.03 ± 3.02	8.82 ± 2.34	<0.05
FINS (pmol/L)[a]	135.26 ± 76.02	115.90 ± 57.21	0.144
FBG (mmol/L)[a]	7.98 ± 3.76	8.36 ± 2.69	0.545
iPTH (pg/mL)[a]	40.31 ± 14.47	46.40 ± 13.42	<0.05
Ca (mmol/L)[a]	2.29 ± 0.14	2.36 ± 0.12	<0.05
P (mmol/L)[a]	1.35 ± 0.15	1.37 ± 0.13	0.536
Calcium phosphorus production [(mg/dL)^2][a]	38.47 ± 5.17	40.18 ± 4.93	0.083
BALP (u/L)[a]	184.84 ± 13.96	184.57 ± 15.85	0.927
IGF-1 (pg/mL)[a]	252.45 ± 138.43	306.28 ± 152.06	0.056

[a]*Mean ± SD. HOMA-IR, homeostatic model estimates of insulin resistance; 25(OH)D, 25-hydroxy vitamin D; Ca, serum calcium; P, serum phosphorus; FINS, fasting blood insulin; HbA1c, glycated hemoglobin A1c; iPTH, intact parathyroid hormone; BALP, bone alkaline phosphatase; IGF-1, insulin-like growth factor-1.*

The measurement results of bone metabolism indexes were as follows: Ca 2.33 ± 0.13 mmol/L, P 1.6 ± 0.15 mmol/L, calcium phosphorus production 34.02 ± 9.42 mg/dl, BALP 184.72 ± 14.77 U/L, and IGF-1 276.65 ± 146.52 pg/ml (shown in **Table 1**).

Comparison of Men and Women of Insulin Resistance and Glucose (FBG, FINS, and HbA1c) and Bone Metabolic Indices (Ca, P, Calcium-Phosphorus Production, iPTH, BALP, and IGF-1)

The values of serum 25(OH)D, insulin resistance, glucose indices (FBG, FINS levels, and HbA1c), and bone metabolism indices (Ca, P, calcium-phosphorus production, iPTH, BALP, and IGF-1) are shown in **Table 2**. FINS, FBG, HbA1c, HOMA-IR, 25(OH)D, P, calcium-phosphorus production, BALP, and IGF-1 showed no statistical differences between female and male subjects, but the HbA1c level of female subjects was significantly lower than that of male subjects, while the calcium and iPTH levels of female subjects were significantly higher than those of male subjects.

Relationship Between Serum 25(OH)D Concentrations and Bone Metabolism Indices (Ca, P, Calcium-Phosphorus Production, iPTH, BALP, and IGF-1)

The *Pearson* correlation coefficient showed a positive correlation between 25(OH)D and IGF-1 ($r = 0.664$, $p \leq 0.001$; showed in **Figure 1**), and a negative correlation between 25(OH)D and BALP ($r = -0.355$, $p \leq 0.001$; showed in **Figure 2**). In the multiple linear regression analysis (shown in **Table 3**), vitamin D status was a predictor of IGF-1 ($\beta = 0.672$, $p \leq 0.001$), BALP ($\beta = -0.369$, $p \leq 0.001$), as the dependent variable, but not Ca, P, calcium-phosphorus production, eGFR, BMI, and age, as independent variables.

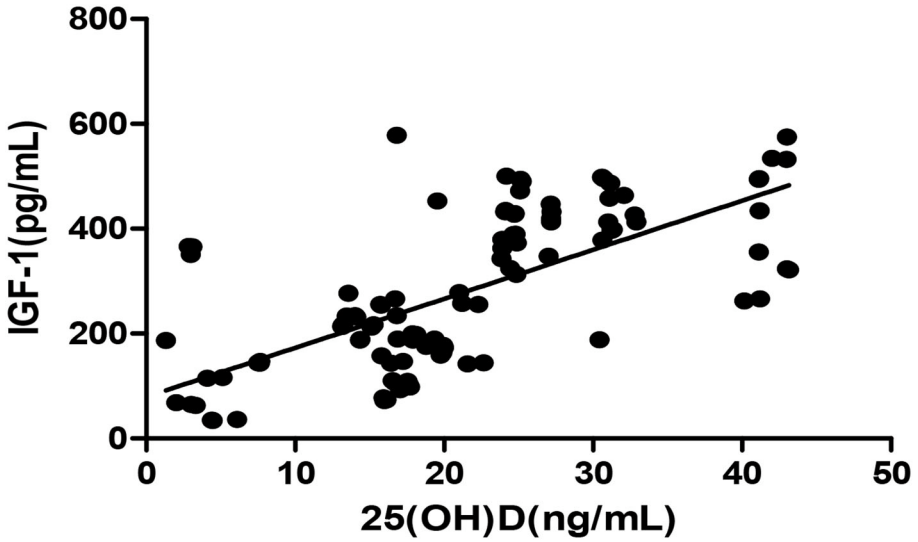

FIGURE 1 | *Pearson* correlation between 25(OH)D and IGF-1 ($r = 0.664$, $p < 0.05$). 25(OH)D, 25-hydroxy vitamin D; TGF-1, insulin-like growth factor-1.

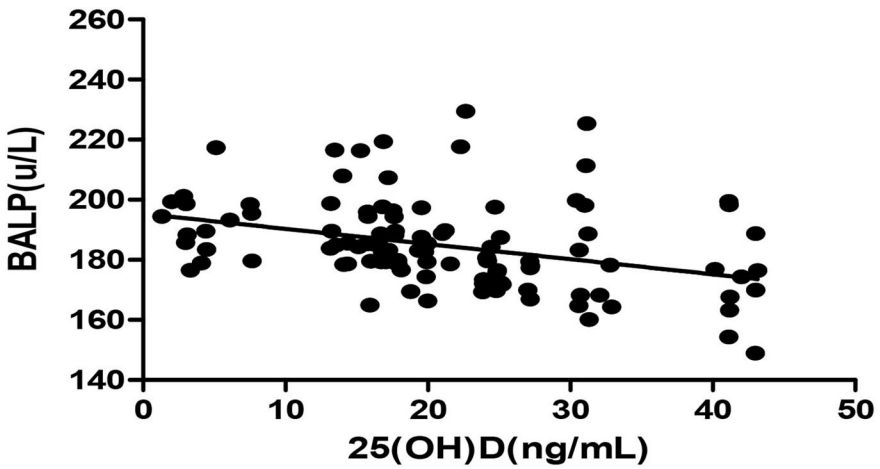

FIGURE 2 | *Pearson* correlation between 25(OH)D and BALP ($r = -0.355$, $p < 0.05$). 25(OH)D, 25-hydroxy vitamin D; BALP, bone alkaline phosphatase.

The Multiple Linear Regression Analysis of 25(OH)D and HOMA-IR

The *Pearson* correlation coefficient showed a negative correlation between 25(OH)D concentration and HOMA-IR ($r = -0.364$, $p \leq 0.001$; shown in **Figure 3**). In the multiple linear regression analysis (shown in **Table 4**), vitamin D status was a predictor of HOMA-IR ($\beta = -0.349$, $p \leq 0.001$), as the dependent variable, but not eGFR, BMI, age, and gender, as independent variables.

The Multiple Linear Regression Analysis of HOMA-IR and Bone Metabolic Indices (Ca, P, Calcium-Phosphorus Production, IGF-1, BALP, and iPTH)

The *Pearson* correlation coefficient showed that a negative correlation between HOMA-IR and IGF-1 ($r = -0.460$, $p \leq 0.001$; shown in **Figure 4**) and a positive correlation with BALP ($r = 0.342$, $p \leq 0.001$; shown in **Figure 5**). In the multiple linear regression analysis, HOMA-IR was a predictor of IGF-1 ($\beta = -0.464, p \leq 0.001$), BALP ($\beta = 0.344, p \leq 0.001$) as the dependent variable, but not Ca, P, calcium-phosphorus production, eGFR, BMI, and age as independent variables (shown in **Table 5**).

DISCUSSION

In this retrospective cross-section trial, the mean 25(OH)D concentration of all subjects was below the vitamin D sufficient status. We found a significant negative interaction between vitamin D status and HOMA-IR, independent of eGFR, BMI, and age. 25(OH)D concentration showed a negative correlation with BALP and a positive correlation with IGF-1, indicating the decline of osteoblast, risk of osteoporosis. HOMA-IR

was significantly negatively associated with IGF-1, positively associated with BALP, adjusted by BMI, eGFR, and age.

The vitamin D receptor being found expressed in many organs in the 1980s, much interest in the extraskeletal effects of vitamin D has attracted considerable scientists (12, 13). Not only regulation of calcium and bone metabolism, but also pleiotropic metabolic roles of vitamin D were found (14). Low vitamin D status was associated with glucose intolerance in man epidemiological studies (15). Abundance research studies suggested that a regulation disruption in vitamin D within the body may result in the development of T2DM (16). In one randomized control trial (RCT), 92 obese adults consumed vitamin D amount to 2,000 IU once a day or 400 mg of calcium twice a day for 16 weeks (17), beta-cell function and insulin secretion were significantly improved in participants supplemented vitamin D, but not in those supplemented calcium alone. However, contrary findings were reported in another RCT (18). Third National Health and Nutrition Examination Survey showed a negative correlation between vitamin D status and morbidity of diabetes, possibly relating with insulin resistance in non-Hispanic whites and Mexican Americans but not non-Hispanic blacks, of which different race might be the reason (19).

It is confirmed that vitamin D and calcium play a vital role in supporting the health of the skeletal system (20). Absorption of calcium in the intestines was reduced because of low levels of vitamin D, leading to an increase of parathyroid hormone levels and bone turnover, subsequently, osteopenia and osteoporosis (21). One research demonstrated that the BMD was less in type 2 diabetic patients who have higher insulin resistance than diabetic patients with less insulin resistance (22).

The growth hormone (GH)/IGF axis is a major determinant of bone mass acquisition. Circulating IGF-1, produced by the liver, is similar to insulin in structure (23) and is responsible for mediating the skeletal growth-promoting actions of GH. IGF-1, acting in a paracrine manner hypothetically, is also produced by bone muscle tissue locally. Along with systemic

TABLE 3 | The multiple linear regression analysis of 25(OH)D and bone metabolism indices (Ca, P, calcium-phosphorus production, IGF-1, BALP, and iPTH).

	β	*p*-value
Ca	0.214	0.035
P	0.173	0.079
Calcium phosphorus production	0.233	0.019
IGF-1	0.672	<0.001
BALP	−0.369	<0.001
iPTH	0.108	0.281
Gender	−0.054	0.518

Variables, such as BMI, age, eGFR, and gender, are adjusted in the linear regression models.
BMI, body mass index; eGFR, glomerular filtration rate; Ca, serum calcium; P, serum phosphorus; iPTH, intact parathyroid hormone; BALP, bone alkaline phosphatase; IGF-1, insulin-like growth factor-1.

TABLE 4 | The multiple linear regression analysis of 25(OH)D and HOMA-IR.

	β	*p*-value
HOMA-IR	−0.349	<0.001
Age	0.139	0.210
BMI	−0.040	0.688
eGFR	−0.009	0.928
Gender	0.008	0.941

BMI, body mass index; eGFR, glomerular filtration rate; HOMA-IR, homeostatic model estimates of insulin resistance.

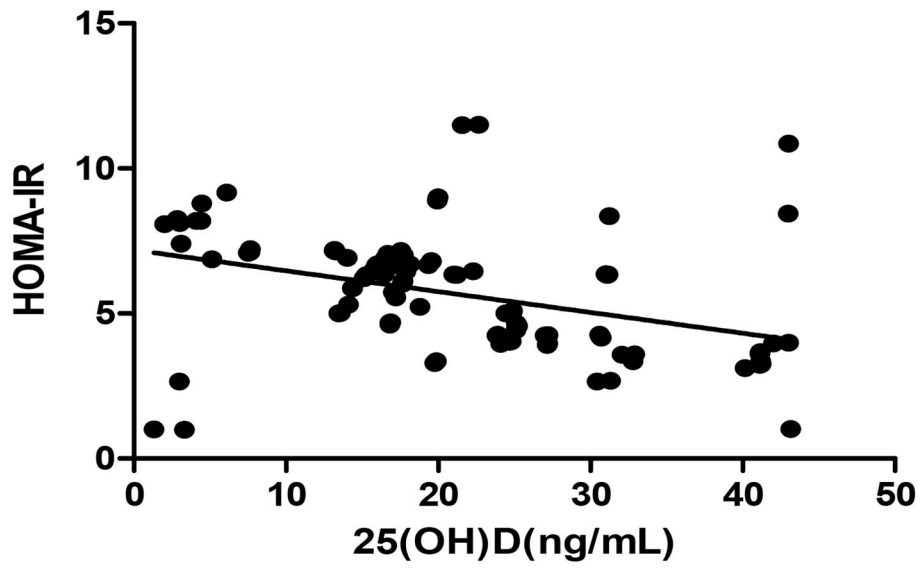

FIGURE 3 | *Pearson* correlation between 25(OH)D and HOMA-IR ($r = -0.364$, $p < 0.05$). HOMA-IR, homeostatic model estimates of insulin resistance; 25(OH)D, 25-hydroxy vitamin D.

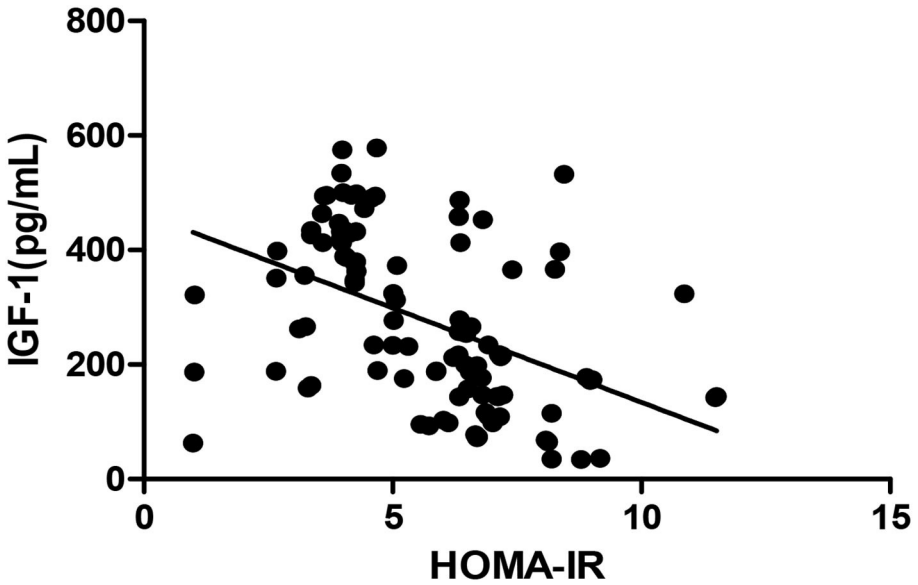

FIGURE 4 | *Pearson* correlation between HOMA-IR and IGF-1 ($r = -0.460$, $p < 0.05$). HOMA-IR, homeostatic model estimates of insulin resistance; TGF-1, insulin-like growth factor-1.

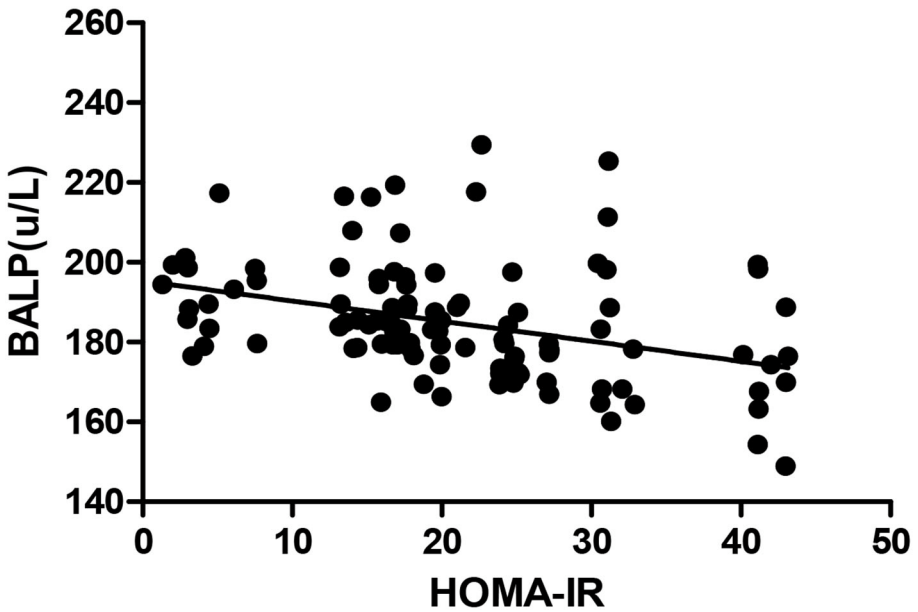

FIGURE 5 | *Pearson* correlation between HOMA-IR and BALP ($r = 0.342$, $p < 0.05$). BALP, bone alkaline phosphatase; HOMA-IR, homeostatic model estimates of insulin resistance.

GH and estradiol, IGF-1 concentration in local bone is regulated by 1,25-dihydroxyvitamin D3, PTH, and other growth factors and cytokines (24). IGF-1, increasing bone matrix deposition and osteoblastic cell recruitment, and decreasing collagen degradation, is considered a key anabolic regulator of bone cell activity (23–25). BALP reflecting bone strength is also assumed as an index for bone quality, quite apart from bone mass (26). The increase of BALP is positively related to osteoporosis. The relationship between the two bone turnover markers, IGF-1 and BALP, with 25(OH)D concentrations indicates that a higher 25(OH)D concentration is good for osteoblast. Contrarily, HOMA-IR may be the risk factor of osteoblast with a significantly negative association with IGF-1, positive one with BALP. In one Korean research, HOMA-IR showed the negative benefits in adolescents' bone mineral content (BMC) (27), which may reasonably assumed the risk of osteoporosis. With the 25(OH)D

TABLE 5 | The multiple linear regression analysis of HOMA-IR and bone metabolic indices (Ca, P, calcium-phosphorus production, IGF-1, BALP, and iPTH).

	β	*p*-value
Ca	−0.004	0.970
P	−0.120	0.225
Calcium phosphorus production	−0.103	0.302
IGF-1	−0.464	<0.001
BALP	0.344	<0.001
iPTH	0.008	0.934
Gender	0.019	0.868

Variables, such as BMI, age, eGFR, and gender, are adjusted in the linear regression models.
BMI, body mass index; eGFR, glomerular filtration rate; Ca, serum calcium; P, serum phosphorus; iPTH, intact parathyroid hormone; BALP, bone alkaline phosphatase; IGF-1, insulin-like growth factor-1.

concentrations decreasing, HOMA-IR indices increased, which showed the deteriorating insulin sensitivity. The same result was shown in SIR—Studies in animals that vitamin D deficiency is correlated to impaired insulin sensitivity, and that vitamin D supplementation increased insulin secretion (28). Although all the subjects were non-osteoporosis patients with T2DM in our research, more than half of the subjects (54.13%) were with vitamin D deficiency. It is commonly agreed that vitamin D is responsible to maintain normal levels of Ca and P, vitamin D deficient subjects indicated a high risk of osteoporosis.

As a result, 25(OH)D concentrations are negatively related to both insulin resistance and bone turnover, which increases the risk of osteoporosis. As reported that supplementation of vitamin D ameliorated insulin resistance in patients with T2DM, it is thought that vitamin D deficiency results in a decrease of insulin sensitivity (29). Some vitro trials also proved that vitamin D regulated the insulin release directly or via vitamin D receptor (30–33). As in our research, regardless of age, BMI, eGFR, HOMA-IR negative related to IGF-1 and positively related to BALP, we assumed that it is possible insulin resistance decreases the bone turnover, raises the risk of osteoporosis. The casual relationship should be conferred by further research. We speculate that insulin resistance could be one of the mechanisms of osteoporosis in T2DM.

Calcium-phosphorus production, phosphorus, BALP, IGF-1, HOMA-IR, FINS, and FBG show no difference between men and women, except levels of calcium and iPTH in men lower than that in women, probably effect in climacteric female subjects.

As to our knowledge, this is the first research to discuss the association between vitamin D status, insulin resistance, and bone metabolism in Chinese non-osteoporosis patients with T2DM.

LIMITATION

As the limit capacity of the fund, only two indices of bone turnover were used to evaluate the bone metabolism status. However, Bandeira et al. suggested since in most cases bone formation mirrors bone resorption, and vice versa, a single bone turnover marker could be used in clinical practice, considering the cost, sometimes (34). Considering the seasonal effects on vitamin D status, the recruitment of the subjects was restricted to 3 months. The number of recruited subjects was not large enough to analyze in subgroup to adjust the effect of female climacteric. As the nature of the observation trial, the casual relationship could not be proved.

CONCLUSION

As the 25(OH)D concentrations were decreased, HOMA-IR and BALP were increased, and IGF-1 was decreased. 25(OH)D concentrations are negatively related to both insulin resistance and bone turnover, which increase the risk of osteoporosis. Whether vitamin D supplement is needed in pre-osteoporosis stage patients with T2DM is required more research to clarify.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xiamen Second Hospital Affiliated Xiamen Medical College. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

JZ established the original concept and wrote the first draft. YL, DLa, and DLu collected clinical blood samples. ZL, JK, YX, and SC conducted experiments. All authors discussed the results and edited the manuscript.

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