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Correlational Analysis of Hemoglobin, Red Cell Distribution Width and Homocysteine Levels with Bone Mineral Density in Patients with Type 2 Diabetes Mellitus

Zhuowei Zhang[1], Qiaohui Zhang[2*], Zhi-Qing Zhao[3*]

[1]Department of Human Resources, Shanxi Medical University, Taiyuan, China
[2]Department of Endocrinology, Yuncheng Central Hospital Affiliated to Shanxi Medical University, Yuncheng, China
[3]Division of Biomedical Sciences, Mercer University School of Medicine, Savannah, Georgia, USA
Email: *zhangqiaohui489@163.com, *zhao_z@mercer.edu

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Abstract

Background: Early detection of Bone Mineral Density (BMD) loss is critical for identifying individuals at increased risk of osteoporosis and related fractures, particularly in vulnerable populations. **Aim:** This study aimed to evaluate the correlation between Hemoglobin (Hb), Red cell Distribution Width (RDW), and Homocysteine (Hcy) levels and BMD in elderly male patients diagnosed with Type 2 Diabetes Mellitus (T2DM). **Methods:** A total of 208 male patients with T2DM, who were hospitalized in the Endocrinology Department of Yuncheng Central Hospital, between January 2020 and December 2023, were included in the study. Based on their BMD measurements, the patients were categorized into three groups: normal bone mass (control, n = 64), osteopenia (n = 92), and osteoporosis (n = 52). After adjusting for some potential confounding factors, inter-group comparisons and correlation analyses were conducted to assess the relationships between Hb, RDW, and Hcy levels and BMD. **Results:** The prevalence of osteoporosis in T2DM patients with anemia was nearly twice as high as that in the control group. Compared to the normal bone mass group, the osteoporosis group showed a significant reduction in plasma Hb levels by 8.8% ± 1.1%, along with significant increases in RDW and Hcy levels by 15.7% ± 1.2% and 18.2% ± 2.2%, respectively (all $P < 0.001$). Univariate logistic regression analysis revealed that Hb was negatively correlated with BMD loss ($P < 0.001$), whereas RDW and Hcy were positively correlated with BMD loss (all $P < 0.001$) in the total hip and femoral neck. **Conclusions:** These univariate logistic analyses suggest that changes in these hematologic indices may serve not only as markers of bone health but also as potential predictors of the progression of diabetes-related complications, including BMD loss and

fracture risk.

Keywords

Anemia, Hemoglobin, Homocysteine, Osteoporosis, Red Cell Distribution Width, Type 2 Diabetes Mellitus

1. Introduction

Bone Mineral Density (BMD) is a measure of the amount of calcium and other minerals in bone tissue. Reduction in Bone Mineral Density (BMD) is associated with the development of osteopenia and an increased risk of osteoporosis, ultimately rendering bones more fragile and prone to fractures, particularly in the total hip, femoral neck, and lumbar spine. Low BMD and osteoporosis together affect approximately 53.6 million (54%) older adults in the United States, resulting in two million osteoporosis-related fractures annually [1] [2]. Common causes of low BMD include aging, family history, inadequate intake of calcium and vitamin D, hormonal changes, smoking, excessive alcohol consumption, a sedentary lifestyle, and certain medications [2]. From a clinical practice point of view, it is important to identify a simple, sensitive, and specific prognostic index for the early detection of osteopenia and osteoporosis, as well as to facilitate effective management and intervention. Recent studies have reported that alterations in Hemoglobin (Hb), Red cell Distribution Width (RDW), and Homocysteine (Hcy) levels are associated with declining BMD, highlighting their potential role in the early identification of osteopenia and osteoporosis.

Low Hb levels, indicative of anemia, have been associated with reduced BMD of the total hip and femoral neck in elderly patients [3] [4]. It has been suggested that assessing Hb levels and anemia status may help identify individuals at higher risk of osteoporosis and related fractures [3] [4]. RDW is a measure of the variation in the volume and size of red blood cells and is routinely assessed as part of a complete blood count. As a readily obtainable marker of systemic inflammation, recent clinical studies have shown that changes in RDW levels may be associated with the incidence and prognosis of BMD-related osteoporosis and bone fractures. In a cross-sectional study investigating the relationship between RDW and BMD at the femoral neck and lumbar spine, Qi *et al.* reported a positive association between RDW and spinal BMD in men, suggesting the potential of RDW as a marker for identifying individuals at higher risk of osteoporosis [5]. In another study, Kim *et al.* found that increased RDW was significantly associated with hip fractures in elderly men who did not have anemia. This finding may reflect the neuromuscular effects of aging rather than a reduction in BMD [6]. Elevated plasma Hcy levels have been associated with an increased risk of osteoporotic fractures. Joyce *et al.* previously reported that the association between Hcy levels and fracture risk appears to be independent of BMD and other potential fracture risk factors in older men and women [7]. Subsequent studies have further confirmed this

correlation, indicating that elevated Hcy levels may represent an independent risk factor for osteoporotic fractures in the elderly, even in the absence of reduced BMD [8] [9].

With an aging population, the incidence of diabetes in the elderly is steadily increasing. Osteoporosis is a common chronic complication of Type 2 Diabetes Mellitus (T2DM) and is a significant contributor to morbidity and mortality in affected individuals. In the early stages of diabetes, BMD often declines without obvious clinical symptoms. However, osteoporosis tends to worsen as the disease advances. It is now well established that patients with T2DM typically exhibit lower BMD and an increased risk of fractures [10] [11].

This retrospective study aimed to investigate the correlation among Hb, RDW, Hyc levels and BMD in elderly individuals with T2DM, with the goal of providing clinical insights into the diagnosis, treatment, and prognosis of osteoporosis.

2. Materials and Methods

2.1. Subjects

A retrospective analysis was conducted on elderly male patients (aged > 60 years) with T2DM who were hospitalized in the Endocrinology Department of Yuncheng Central Hospital between January 2020 and December 2023. T2DM was diagnosed according to the American Diabetes Association criteria [12]. Exclusion criteria were as follows: 1) patients with type 1 diabetes; 2) patients with acute complications of diabetes; 3) patients with acute and chronic infectious arrhythmia; 4) patients in the acute stage of cardiovascular and cerebrovascular diseases; 5) patients suffering from other endocrine and metabolic diseases that affect bone metabolism, such as adrenal diseases, growth hormone deficiency, hypogonadism, thyroid and parathyroid dysfunction; 6) patients with hemolytic anemia, autoimmune anemia, aplastic anemia, thalassemia and other blood diseases; 7) patients with hematological malignancies; osteoarthritis; rheumatoid arthritis; chronic gastrointestinal, liver, or kidney diseases; connective tissue diseases; bone metastases or primary bone tumors, and hereditary or constitutional bone disorders; 8) patients who used medications affecting bone metabolism (e.g., glucocorticoids, androgens, anticonvulsants, bisphosphonates, or fluorides) within the previous six months. The diagnostic criteria for osteopenia and osteoporosis were based on World Health Organization (WHO) standards [13]. Normal BMD: T-score of −1.0 or higher. Osteopenia (Low Bone Mass): T-score between −1.0 and −2.5 (between 1 and 2.5 SD below the mean). Osteoporosis: T-score of −2.5 or lower (2.5 SD or more below the mean). Severe Osteoporosis: T-score of −2.5 or lower with one or more fragility fractures. All patients were classified into three groups: 1) normal BMD group; 2) osteopenia group (BMD decreased but did not meet the diagnostic criteria for osteoporosis); 3) osteoporosis group (BMD met the diagnostic criteria for osteoporosis). Anemia in adult males was diagnosed according to the WHO criteria, [14] defined as a Hb concentration of less than 13.0 g/L. A total of 208 male patients who met the eligibility criteria were included in the study

(Figure 1).

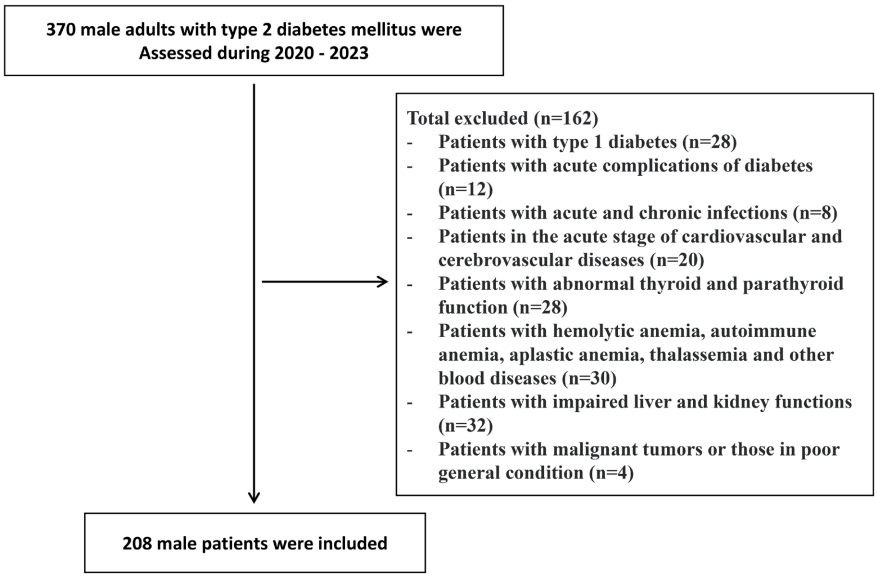

Figure 1. Flow chart of patient participant enrollment.

2.2. General Information and Biochemical Tests

Age, T2DM duration, and Body Mass Index (BMI) were recorded for all patients. Following a 10-hour overnight fast, 5 mL of venous blood was collected on the next morning from each patient. Glycated hemoglobin (HbA1c), Hb, RDW, Hcy, Fasting Plasma Glucose (FPG), and Serum creatinine (Scr) levels were measured. Additional parameters assessed included Serum Uric Acid (SUA), total type I procollagen amino-terminal peptide propeptide (PINP), and β-Collagen-Specific Sequence (β-CTX). Inflammatory markers such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and Osteocalcin (OC) were also measured. All assays were performed using a fully automated electrochemiluminescence analyzer (F. Hoffmann-La Roche Ltd., Basel, Switzerland) with the corresponding reagents and kits provided by biomedical laboratory in the hospital.

2.3. Measurement of Bone Mineral Density

Bone mineral density was measured using a Dual-Energy X-ray Absorptiometry (DEXA) with a GE Lunar Prodigy Advance scanner (GE Healthcare, USA). The measurement sites included the total hip, femoral neck and lumbar spine (L1 - L4). The diagnosis of osteoporosis was based on WHO criteria, as previously described [13].

2.4. Statistical Analyses

Statistical analyses were conducted using SPSS version 26.0. Continuous variables with a normal distribution are expressed as mean ± Standard Deviation (SD). Comparisons between two groups were performed using the independent samples

t-test, where Analysis Of Variance (ANOVA) was applied for comparisons among three or more groups. Categorical variables are expressed as frequencies and percentages (%), and group differences were assessed using the chi-square (χ^2) test. Spearman's correlation analysis was used to evaluate the relationship between BMD and other variables. Logistic regression analysis was performed to identify the factors independently associated with BMD. Statistical significance set at $P < 0.05$ was considered significant.

3. Results

3.1. Baseline Characteristics of the Study Participants

Among the 208 patients with T2DM, 44 were diagnosed with anemia. Of these anemic patients, 28 (63.6%) had low bone mass, and 16 (36.4%) had osteoporosis. In contrast, among the 164 non-anemic patients (control group), 64 (39%) had low bone mass, and 36 cases (21.9%) had osteoporosis. The prevalence of osteoporosis in T2DM patients with anemia was nearly twice as high as in the control group (Table 1).

Table 1. Baseline characteristics and associations with bone mineral density in the studied groups.

Index	Normal BMD (n = 64)	Osteopenia (n = 92)	Osteoporosis (52)	P values	F/H/X²
Age	68 ± 6.6	68 ± 6.3	68 ± 5.2	0.971	0.030
T2DM (year)	13 ± 2.5	13 ± 3.2	13 ± 3.2	0.658	0.421
FPG (mmol/L)	8.2 ± 2.3	8.5 ± 1.8	8.4 ± 2.2	0.151	0.860
Scr (μmol/L)	55.6 ± 15.4	58.3 ± 15.6	57.5 ± 15.8	>0.05	0.372
CRP (ng/L)	10.1 ± 5.2	9.02 ± 5.6	9.8 ± 5.2	>0.05	1.429
IL-6 (pg/mL)	11.0 ± 6.9	10.3 ± 5.9	10.6 ± 5.6	0.747	-
TNF-α (pg/ml)	12.4 ± 11.2	12.7 ± 14.0	13.4 ± 12.7	0.607	-
SUA (μmol/L)	273.1 ± 78.0	274.8 ± 74.0	269.5 ± 5.2	>0.05	0.253
PINP (ng/mL)	41.6 ± 16.2	43.4 ± 14.8	51.3 ± 22.6	0.244	0.115
HbA1c (%)	8.33 ± 1.76	8.90 ± 2.53	9.41 ± 3.14	0.914	0.663
Anemia (%)	8 (13)	15 (16)	21 (40)	0.001	-
Hb (g/dL)	13.7 ± 15	12.9 ± 1.3	12.5 ± 1.4	0.001	2.769
RDW (%)	12.4 ± 1.2	15.5 ± 0.63	15.7 ± 1.2	0.001	6.937
Hcy (μmol/L)	7.0 ± 1.4	11.5 ± 1.7	18.2 ± 2.2	0.001	258.9
B-CTX (ng/mL)	0.40 ± 0.1	0.57 ± 0.1	0.78 ± 0.2	0.001	94.2
BMI (kg/m²)	23.5 ± 2.7	22.1 ± 2.6	22.1 ± 2.1	0.001	6.944
OC (ng/mL)	29.4 ± 2.2	19.1 ± 2.1	10.3 ± 1.4	0.001	576.3
TH (g/cm²)	1.03 ± 1.10.1	0.85 ± 0.1	0.70 ± 0.2	0.001	37.6
FN (g/cm²)	0.96 ± 0.11	0.81 ± 0.2	0.68 ± 0.1	0.001	31.1

Continued

LS (g/cm^2)	1.2 ± 1.1	0.95 ± 0.2	0.79 ± 0.1	0.001	44.2
Mean (g/cm^2)	1.05 ± 0.1	0.87 ± 0.2	0.72 ± 0.1	0.001	36.2

Data are presented as mean ± SD. P values indicate whether there are statistically significant differences in the measured variables between the osteopenia or osteoporosis groups as compared to the normal Bone Mineral Density (BMD) group. P = 0.001 denotes a statistically significant difference. Total Hip (TH), Femoral Neck (FN), and Lumbar Spine (LS).

3.2. Comparison of General Information, Biochemical Indicators and BMD among Groups

There were no statistically significant differences among the three groups in age, duration of DM, FPG, Scr, CRP, IL-6, TNFα, SUA, PINP, and HbA1c (Table 1, all P > 0.05). The proportion of patients with anemia in the osteopenia and osteoporosis groups was significantly higher than that in the normal bone mass group (P < 0.001). Hb levels were significantly lower in the osteoporosis group than in the normal bone mass group (P < 0.001). The levels of RDW, Hcy and β-CTX in the osteopenia and osteoporosis groups were higher than those in the normal bone mass group, while BMI and OC were lower than those in the normal bone mass group (P < 0.001). There were statistically significant differences in the BMD at the total hip, femoral neck, and lumbar spine among the groups (P < 0.001, Table 1).

3.3. Spearman Correlation Analysis between BMD and Related Indices

Spearman's correlation analysis was performed to examine whether both variables were continuous or ordinal as summarized in Table 2. The results demonstrated that BMI, Hb, OC, RDW, Hcy, and β-CTX were all significantly correlated with BMD at both the total hip and femoral neck (all P < 0.001). Notably, RDW was correlated with BMD in the total hip, with a correlation coefficient (r) of −0.247,

Table 2. A stratified analysis of the relationship between measured variables and bone mineral density across different locations.

Index	Total hip		Femoral neck		Lumber vertebrae (L1 - 4)	
	r/rs	P value	r/rs	P value	r/rs	P value
BMI	0.367	<0.001	0.420	<0.001	0.144	0.039
Hb	0.493	<0.001	0.319	<0.001	0.027	0.698
OC	0.243	<0.001	0.331	<0.001	0.127	0.069
RDW	−0.247	<0.001	−0.179	<0.001	−0.024	0.736
Hcy	−0.353	<0.001	−0.267	<0.001	−0.049	0.486
B-CTX	−0.224	<0.001	−0.129	0.063	−0.035	0.616

r/rs stands for Spearman's rank correlation coefficient. P-values indicate whether there are statistically significant differences in the analyzed variables in different locations of the bone. P < 0.001 denotes a statistically significant difference.

indicating a relationship between these two continuous variables. These correlation analyses revealed statistically significant differences in clinical variables between patients in the osteopenia and osteoporosis groups and those in the normal BMD group. However, additional correlation analysis focusing on BMD in the lumbar spine (L1 - L4) showed no statistically significant associations with the aforementioned variables**,** suggesting site-specific variation in bone density regulation (Table 2).

3.4. Univariate Logistic Regression Analysis

Univariate logistic regression is a statistical technique used to assess the association between a single independent variable (predictor) and a binary outcome (e.g., presence or absence of a disease). This method estimates the log-odds of the outcome as a function of the predictor and provides key statistical metrics. Univariate logistic regression analysis was conducted. To assess the relationship between individual clinical indicators and the presence of osteoporosis, univariate logistic regression analysis was conducted. The β coefficient, Wald χ^2 statistic, odds ratio (OR), 95% Confidence Interval (CI), and P value were calculated for each variable.

As summarized in Table 3, Hb showed a significant negative association with osteoporosis (Hb: $\beta = -0.062$, OR = 0.94, 95% CI: 0.92 - 0.96, P < 0.001), suggesting that lower levels of Hb are associated with an increased risk of osteoporosis. RDW and Hcy both showed significant positive associations with osteoporosis (RDW: $\beta = 1.065$, OR = 2.9, 95% CI = 1.70 - 4.94; Hcy: $\beta = 1.758$, OR = 1.17, 95% CI = 1.07 - 1.46; both P < 0.001), indicating that higher levels of RDW and Hcy increase the risk of osteoporosis. BMI was negatively associated ($\beta = 0.061$, OR =1.06, 95% CI = 1.03 - 1.09, P < 0.001), suggesting that a higher BMI may reduce the risk of osteoporosis.

Table 3. Univariate logistic regression analysis of factors associated with a reduction of bone mineral density.

Index	β	SE	Wald χ^2	OR	95% CI	P value
Hb	−0.062	0.011	30.14	0.94	0.92 - 0.96	<0.001
RDW	1.065	0.271	15.42	2.9	1.70 - 4.94	<0.001
Hcy	1.758	0.511	11.82	1.17	1.07 - 1.46	<0.001
BMI	0.061	0.014	17.54	1.06	1.03 - 1.09	<0.001

Results from a multivariate logistic regression model containing all explanatory variables. The abbreviations above represent the univariate logistic regression coefficient (β), Wald χ^2 statistic, Odds Ratio (OR), and 95% Confidence Interval (CI). P values show statistically significant differences in the analyzed variables.

4. Discussion

In this retrospective analysis of 208 male patients with T2DM, aged > 60 years and with an average diabetes duration of 13 years, we found a significant decline in BMD, particularly in the total hip and femoral neck regions. The risk of develop-

ing osteopenia and osteoporosis was notably higher in the T2DM group. A substantial reduction in BMD was negatively correlated with Hb, BMI, and OC levels, and positively correlated with RDW, Hcy, and β-CTX levels. These findings suggest that changes in these biochemical and anthropometric indices may serve not only as markers of bone health but also as potential predictors for the progression of diabetes-related complications, including reduced BMD and increased fracture risk.

Anemia is defined as a reduction in the proportion of healthy red blood cells or hemoglobin, resulting in a diminished capacity of the blood to carry oxygen. In the present study, anemia was indicated by abnormally high RDW and low Hb concentrations in both the osteopenia and osteoporosis groups. Recent studies have reported that lower Hb levels (typically < 13.5 g/dL in men) and the presence of anemia are associated with an increased risk of fractures [15] [16], particularly in older male adults [17] [18]. The observed linear relationship between Hb and BMD in the present study supports the use of actual Hb levels, rather than relying solely on the diagnosis of anemia as a contributing risk factor for estimating BMD loss. Therefore, incorporating Hb levels into the assessment of BMD reduction appears to be a feasible and informative diagnostic approach.

There are inconsistent reports regarding the role of Hb in predicting the reduction of BMD. Several previous studies have shown a significant correlation between Hb levels and BMD in aging populations, with lower Hb levels associated with a higher risk of osteoporosis [19] [20]. However, other studies suggest that changes in Hb levels and the presence of anemia may be epiphenomena of osteoporosis rather than causal factors [21]. Therefore, the role of Hb level in predicting osteoporosis risk remains uncertain and requires further investigation through longitudinal studies [20]. In the present study, we primarily included male patients with a diabetes history of >13 years. Our findings demonstrated a negative correlation between lower Hb levels and the development of osteoporosis, suggesting that the discrepancies among previous reports may be partly attributed to differences in sex, age, and duration of diabetes. Our results are consistent with those of the previous studies [10] [11].

Multiple mechanisms underlying the relationship between anemia and BMD loss have been proposed. Chronic anemia significantly impairs oxygen delivery to tissues and disrupts bone metabolism. It is well established that anemia can alter hormone levels, contributing to reduced BMD and increased bone fragility. In patients with T2DM, reductions in erythropoietin and parathyroid hormone levels are associated with dysregulation of osteoblast and osteoclast activity, impairing bone development and remodeling. [19] [20] Additionally, a reduction in Hb levels may lead to fatigue and reduced physical activity, both of which are essential for maintaining BMD [21]. Moreover, anemia is frequently accompanied by nutritional deficiencies, such as vitamin B12, folate, and iron deficiencies, which are crucial for proper bone metabolism [22].

An increased RDW is commonly associated with anemia, reflecting variability

in red blood cell size due to impaired erythropoiesis. Understanding the association between RDW and BMD is crucial for elucidating the potential contribution of RDW to osteoporosis pathogenesis [5] [6] [23]. In the present study, a positive linear association between RDW and BMD was identified in the total hip and femoral neck in patients with T2DM, whereas no such association was observed in the lumbar spine. The reasons for this site-specific association are complex and likely involve shared underlying pathophysiological mechanisms. The differing associations between the hip (total hip and femoral neck) and the lumbar spine may be attributed to variations in bone composition. The hip contains a higher proportion of cortical (compact) bone, whereas the lumbar spine is predominantly trabecular (spongy). T2DM may affect these bone types differently, for instance, by increasing cortical bone density while simultaneously impairing overall bone quality and strength, changes that are not fully reflected in BMD measurements alone. As a result, individuals with T2DM may have an increased fracture risk despite apparently higher BMD values. Furthermore, chronic hyperglycemia and associated factors in T2DM, including advanced glycation end-products and altered bone turnover, impair bone quality and microarchitecture, especially in the metabolically active trabecular bone of the spine [10] [11]. These results align with those of a recent cross-sectional study that reported a positive association between RDW and femoral neck BMD in both men and postmenopausal women [5]. Collectively, these findings suggest that RDW may serve as a potential marker for identifying individuals at increased risk of osteoporosis. Similar to the reduction in Hb levels in the prediction of BMD loss, RDW, an indicator of erythrocyte size heterogeneity, has been associated with underlying factors contributing to anemia, including deficiencies in folate, vitamin B12, and iron. These findings support the proposition that RDW, similar to anemia, may serve as a potential marker for identifying individuals at risk of BMD decline [5] [6]. Moreover, elevated RDW has been associated with several factors, such as oxidative stress, systemic inflammation, physical inactivity, and malnutrition, all of which are recognized as established triggers for osteoporosis [10] [11].

Hcy is a sulfur-containing amino acid formed during the demethylation of the essential amino acid methionine during its conversion to cysteine, and its levels can be influenced by the status of folate, vitamin B6, and vitamin B12. Elevated levels of Hcy in the blood (>15 μmol/L) are recognized as an independent risk factor for various diseases, including neurodegenerative disorders, myocardial infarction, stroke, thrombosis, dementia, and kidney disease. Recent studies have reported that elevated Hcy levels contribute to osteoclastogenesis and increase fracture risk by promoting osteoclast activity and suppressing osteoblast function [24] [25]. High Hcy levels are associated with increased inflammation and oxidative stress, disruption of calcium and mineral homeostasis, and impaired collagen synthesis in the bone. Accordingly, some findings suggest that reducing Hcy levels may improve BMD and lower the risk of osteoporosis [26] [27]. In the present study, we found that Hcy levels were significantly increased in the osteopenia and

osteoporosis groups in patients with T2DM and an average diabetes duration of 13 years (**Table 1**). We identified a significant positive correlation between Hcy levels and BMD using logistic regression, with BMD as the dependent variable and Hcy as the independent variable. Compared to the Hcy level in the non-osteoporosis group, Hcy increased by 2.6-fold along with a decrease in BMD in the osteoporosis group.

BMI is closely associated with BMD loss and the development of osteoporosis. Low BMI leads to a reduction in bone mass, whereas high BMI appears to have a protective effect on bone mass. Recent studies have demonstrated that postmenopausal women with a low BMI are more likely to experience osteopenia and progress to osteoporosis [28] [29], as low BMI is often associated with reduced mechanical loading on bones, lower levels of adipose-derived estrogen, dysregulated adipokine secretion, and decreased muscle mass [30] [31]. Accordingly, BMI, an established indicator of obesity, is frequently used in the prediction and monitoring of T2DM. The present cross-sectional study in patients with T2DM found that the BMI values were significantly lower in the osteoporosis group than in those with normal bone mass (**Table 1**). Logistic regression analysis revealed a significant negative association between the BMI and BMD in the osteoporosis group (**Table 3**). These findings are consistent with those of previous studies [28] [29].

5. Study Limitation

This study has several limitations. First, this cross-sectional study was conducted in a single hospital and was constrained by the relatively small sample size, which may reduce the robustness of the conclusions. We selected only older male individuals, primarily based on previous reports showing a high risk of fractures in older male patients [17] [18]. We cannot exclude the possibility that the older female patients with a prolonged duration of T2DM also experience similar outcomes as shown in the present study. Second, this was an observational study and the causal relationship between the observed variable levels and osteoporosis development could not be determined. The temporal relationship between changes in these variables and the onset of detectable bone loss on DEXA remains unclear. Therefore, identifying a reliable early-warning biomarker could help detect underlying imbalances in bone metabolism, and potentially predict bone density loss and fracture risk before they become clinically apparent [32] [33]. Third, deficiencies in folate, vitamin B6, or B12 cause anemia and Hb decline, which are mainly affected by the diet [34]. However, it is not known how these changes are associated with BMD loss, particularly in male T2DM. From a nutritional perspective, dietary assessment and modification may help to slow the progression of osteoporosis in patients with T2DM. Given the potential metabolic influence of dietary patterns, additional studies with larger populations are necessary to explore their effect on Hb, RDW, Hcy and T-score levels in T2DM patients. Fourth, it is well established that elevated levels of inflammatory cytokines play a crucial role in the progression of T2DM by promoting insulin resistance. Moreover, hyperglycemia

can further exacerbate inflammation, creating a vicious cycle that worsens both metabolic control and diabetes-related complications [35] [36]. In the present study, IL-6 and TNF-α levels were measured in both the normal and low BMD groups to explore their potential role in predicting the development of T2DM. However, no statistically significant differences were observed between the groups. Given that the data were obtained from patients with an average disease duration of 13 years, we cannot rule out the possibility that the changes in these inflammatory markers may have occurred during the early stages of T2DM. Therefore, further research with larger sample sizes and longitudinal assessments at different disease stages is needed to validate these findings and to enhance their generalizability.

6. Conclusion

This cross-sectional study demonstrates that reduced BMD is associated with the development of osteoporosis in individuals with T2DM, particularly among those aged > 60 years. The observed significant linear relationships between Hb, RDW, Hcy, and BMI levels and BMD at the total hip and femoral neck suggest that these biomarkers may have potential utility in identifying individuals with T2DM who are at increased risk of developing osteoporosis. Given the higher prevalence of osteoporosis and fractures in patients with T2DM, monitoring changes in these biomarkers in routine clinical practice may offer an opportunity to facilitate early intervention. More comprehensive, large-scale clinical studies, particularly prospective investigations, are warranted to further clarify the underlying mechanisms driving this association.

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Author Contributions

Z. W. Z.: Project administration, methodology, data analysis, and original draft preparation. **Q. H. Z.**: Conceptualization, validation, supervision, and funding acquisition. **Z. Q. Z.**: Wrote, reviewed and edited the manuscript. All the authors have read and approved the final version of the manuscript.

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Institutional Review Board Statements

This study was conducted in strict accordance with the ethical principles of the Declaration of Helsinki. The protocol was approved by the Clinical Ethics Committee of Yuncheng Central Hospital, specifically by the Human Research Ethics

Committee (approval no. YXLL2024141).

Informed Content Statement

All study participants provided written informed consent and measures were taken to ensure their confidentiality and anonymity prior to enrollment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wright, N.C., Looker, A.C., Saag, K.G., Curtis, J.R., Delzell, E.S., Randall, S., *et al.* (2014) The Recent Prevalence of Osteoporosis and Low Bone Mass in the United States Based on Bone Mineral Density at the Femoral Neck or Lumbar Spine. *Journal of Bone and Mineral Research*, **29**, 2520-2526. https://doi.org/10.1002/jbmr.2269

[2] Williams, S.A., Daigle, S.G., Weiss, R., Wang, Y., Arora, T. and Curtis, J.R. (2021) Economic Burden of Osteoporosis-Related Fractures in the US Medicare Population. *Annals of Pharmacotherapy*, **55**, 821-829. https://doi.org/10.1177/1060028020970518

[3] Oh, Y.H., Moon, J.H. and Cho, B. (2017) Association between Hemoglobin Level and Bone Mineral Density in Korean Adults. *Journal of Bone Metabolism*, **24**, 161-173. https://doi.org/10.11005/jbm.2017.24.3.161

[4] Liu, Y., Zeng, Y., Lu, J., Zhang, X., Zhang, Z., Li, H., *et al.* (2023) Correlation of Hemoglobin with Osteoporosis in Elderly Chinese Population: A Cross-Sectional Study. *Frontiers in Public Health*, **11**, Article 1073968. https://doi.org/10.3389/fpubh.2023.1073968

[5] Qi, Z., Zhang, L., Li, Z., Yu, H., Li, Q., Ma, L., *et al.* (2025) Red Cell Distribution Width: A Potential Marker of Reduced Femoral Neck Bone Mineral Density in Men and Postmenopausal Women. *Endocrine*, **87**, 1204-1215. https://doi.org/10.1007/s12020-024-04093-8

[6] Kim, K.M., Lui, L., Cauley, J.A., Ensrud, K.E., Orwoll, E.S., Schousboe, J.T., *et al.* (2020) Red Cell Distribution Width Is a Risk Factor for Hip Fracture in Elderly Men without Anemia. *Journal of Bone and Mineral Research*, **35**, 869-874. https://doi.org/10.1002/jbmr.3963

[7] van Meurs, J.B.J., Dhonukshe-Rutten, R.A.M., Pluijm, S.M.F., van der Klift, M., de Jonge, R., Lindemans, J., *et al.* (2004) Homocysteine Levels and the Risk of Osteoporotic Fracture. *New England Journal of Medicine*, **350**, 2033-2041. https://doi.org/10.1056/nejmoa032546

[8] Behera, J., Bala, J., Nuru, M., Tyagi, S.C. and Tyagi, N. (2017) Homocysteine as a Pathological Biomarker for Bone Disease. *Journal of Cellular Physiology*, **232**, 2704-2709. https://doi.org/10.1002/jcp.25693

[9] Zhu, Y., Shen, J., Cheng, Q., Fan, Y. and Lin, W. (2016) Plasma Homocysteine Level Is a Risk Factor for Osteoporotic Fractures in Elderly Patients. *Clinical Interventions in Aging*, **11**, 1117-1121. https://doi.org/10.2147/cia.s107868

[10] Nardone, I., Antonelli, R., Zaccaria, S., Wolde Sellasie, S., Falcone, S., Pecchioli, C., *et al.* (2024) Prevalence of Diabetes Mellitus and Clinical Differences in Patients with Severe Osteoporosis and Fragility Fractures. *Journal of Clinical Medicine*, **13**, Article 2670. https://doi.org/10.3390/jcm13092670

[11] Luo, W., Li, X., Zhou, Y., Xu, D. and Qiao, Y. (2024) Correlation between Bone Min-

eral Density and Type 2 Diabetes Mellitus in Elderly Men and Postmenopausal Women. *Scientific Reports*, **14**, Article No. 15078. https://doi.org/10.1038/s41598-024-65571-7

[12] Chamberlain, J.J., Rhinehart, A.S., Shaefer, C.F. and Neuman, A. (2016) Diagnosis and Management of Diabetes: Synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. *Annals of Internal Medicine*, **164**, 542-552. https://doi.org/10.7326/m15-3016

[13] Kanis, J.A. and Kanis, J.A. (1994) Assessment of Fracture Risk and Its Application to Screening for Postmenopausal Osteoporosis: Synopsis of a WHO Report. *Osteoporosis International*, **4**, 368-381. https://doi.org/10.1007/bf01622200

[14] Pasricha, S.R., Colman, K., Centeno-Tablante, E., Garcia-Casal, M.N., *et al.* (2018) Revisiting WHO Haemoglobin Thresholds to Define Anemia in Clinical Medicine and Public Health. *The Lancet Haematology*, **5**, e60-e62. https://doi.org/10.1016/s2352-3026(18)30004-8

[15] Jaiswal, R., Johansson, H., Axelsson, K.F., Magnusson, P., Harvey, N.C., Vandenput, L., *et al.* (2023) Hemoglobin Levels Improve Fracture Risk Prediction in Addition to FRAX Clinical Risk Factors and Bone Mineral Density. *The Journal of Clinical Endocrinology & Metabolism*, **108**, e1479-e1488. https://doi.org/10.1210/clinem/dgad399

[16] Bruce, K., Mangram, A., Sucher, J.F., Blake, N., Balcome, C.D., Prokuski, L., *et al.* (2024) Consequences of Anemia in Geriatric Hip Fractures: How Low Is Too Low? *Trauma Surgery & Acute Care Open*, **9**, e001175. https://doi.org/10.1136/tsaco-2023-001175

[17] Teng, Y., Teng, Z., Xu, S., Zhang, X., Liu, J., Yue, Q., *et al.* (2020) The Analysis for Anemia Increasing Fracture Risk. *Medical Science Monitor*, **26**, e925707. https://doi.org/10.12659/msm.925707

[18] Tari, E., Vörhendi, N., Kiss, S., Teutsch, B., Váradi, A., Sisák, K., *et al.* (2023) Anaemia Is Associated with an Increased Risk of Fractures, a Systematic Review, and Meta-Analysis. *Gerontology*, **69**, 1-13. https://doi.org/10.1159/000522591

[19] Lappin, K.M., Mills, K.I. and Lappin, T.R. (2021) Erythropoietin in Bone Homeostasis—Implications for Efficacious Anemia Therapy. *Stem Cells Translational Medicine*, **10**, 836-843. https://doi.org/10.1002/sctm.20-0387

[20] Marino, S. and Bellido, T. (2024) PTH Receptor Signalling, Osteocytes and Bone Disease Induced by Diabetes Mellitus. *Nature Reviews Endocrinology*, **20**, 661-672. https://doi.org/10.1038/s41574-024-01014-7

[21] Onal, E.D. and Usluogulları, A. (2012) Anemia and Osteoporosis: Causal Association or Epiphenomenon? *European Journal of Internal Medicine*, **23**, e117. https://doi.org/10.1016/j.ejim.2012.03.010

[22] Bowden Davies, K.A., Pickles, S., Sprung, V.S., Kemp, G.J., Alam, U., Moore, D.R., *et al.* (2019) Reduced Physical Activity in Young and Older Adults: Metabolic and Musculoskeletal Implications. *Therapeutic Advances in Endocrinology and Metabolism*, **10**, Article 2042018819888824. https://doi.org/10.1177/2042018819888824

[23] Cohen, C.T. and Powers, J.M. (2024) Nutritional Strategies for Managing Iron Deficiency in Adolescents: Approaches to a Challenging but Common Problem. *Advances in Nutrition*, **15**, Article 100215. https://doi.org/10.1016/j.advnut.2024.100215

[24] Saglam Oz, M., Toprak, B., Bora, R. and Demir, I. (2025) The Role of Hematological Parameters in Critically Ill Patients: Mortality Prediction in Elderly Intensive Care Unit Patients. *Cureus*, **17**, e82183. https://doi.org/10.7759/cureus.82183

[25] Wang, P., Liu, L. and Lei, S.F. (2021) Causal Effects of Homocysteine Levels on the Changes of Bone Mineral Density and Risk for Bone Fracture: A Two-Sample Mendelian Randomization Study. *Clinical Nutrition*, **40**, 1588-1595.

https://doi.org/10.1016/j.clnu.2021.02.045

[26] Watanabe, N., Ogawa, T., Takada. R., Amano. Y., Jinno, T., Koga, H., *et al.* (2023) Association of Osteoporosis and High Serum Homocysteine Levels with Intraoperative Periprosthetic Fracture during Total Hip Arthroplasty: A Propensity-Score Matching Analysis. *Archives of Orthopaedic and Trauma Surgery*, **143**, 7219-7227. https://doi.org/10.1007/s00402-023-04989-6

[27] McLean, R.R., Jacques, P.F., Selhub, J., Tucker, K.L., Samelson, E.J., Broe, K.E., *et al.* (2004) Homocysteine as a Predictive Factor for Hip Fracture in Older Persons. *New England Journal of Medicine*, **350**, 2042-2049. https://doi.org/10.1056/nejmoa032739

[28] Chucherd, O., Vallibhakara, O., Vallibhakara, S.A., Sophonsritsuk, A., Chattrakulchai, K. and Anantaburarana, M. (2025) Association of Sarcopenic Obesity and Osteoporosis in Postmenopausal Women: Risk Factors and Protective Effects of Hormonal Therapy and Nutritional Status. *Archives of Osteoporosis*, **20**, Article No. 83. https://doi.org/10.1007/s11657-025-01573-w

[29] Cui, P., Wang, W., Wang, Z., Hu, X., Liu, X., Kong, C., *et al.* (2024) The Association between Body Mass Index and Bone Mineral Density in Older Adults: A Cross-Sectional Study of Community Population in Beijing. *BMC Musculoskeletal Disorders*, **25**, Article No. 655. https://doi.org/10.1186/s12891-024-07782-7

[30] Stefanakis, K., Kokkorakis, M. and Mantzoros, C.S. (2024) The Impact of Weight Loss on Fat-Free Mass, Muscle, Bone and Hematopoiesis Health: Implications for Emerging Pharmacotherapies Aiming at Fat Reduction and Lean Mass Preservation. *Metabolism*, **161**, Article 156057. https://doi.org/10.1016/j.metabol.2024.156057

[31] Han, H., Li, R., Fu, D., Zhou, H., Zhan, Z., Wu, Y., *et al.* (2024) Correlation between Bone Density, Bone Metabolism Markers with Lipid Metabolism Markers and Body Mass Index. *BMC Musculoskeletal Disorders*, **25**, Article No. 162. https://doi.org/10.1186/s12891-024-07284-6

[32] Yang, J., Hu, X., Zhang, Q., Cao, H., Wang, J. and Liu, B. (2012) Homocysteine Level and Risk of Fracture: A Meta-Analysis and Systematic Review. *Bone*, **51**, 376-382. https://doi.org/10.1016/j.bone.2012.05.024

[33] Wawer, A.A., Jennings, A. and Fairweather-Tait, S.J. (2018) Iron Status in the Elderly: A Review of Recent Evidence. *Mechanisms of Ageing and Development*, **175**, 55-73. https://doi.org/10.1016/j.mad.2018.07.003

[34] De Martinis, M., Sirufo, M.M., Nocelli, C., Fontanella, L. and Ginaldi, L. (2020) Hyperhomocysteinemia Is Associated with Inflammation, Bone Resorption, Vitamin B12 and Folate Deficiency and MTHFR C677T Polymorphism in Postmenopausal Women with Decreased Bone Mineral Density. *International Journal of Environmental Research and Public Health*, **17**, Article 4260. https://doi.org/10.3390/ijerph17124260

[35] Antar, S.A., Ashour, N.A., Sharaky, M., Khattab, M., Ashour, N.A., Zaid, R.T., et al. (2023) Diabetes Mellitus: Classification, Mediators, and Complications; a Gate to Identify Potential Targets for the Development of New Effective Treatments. *Biomedicine & Pharmacotherapy*, **168**, Article 115734. https://doi.org/10.1016/j.biopha.2023.115734

[36] Lisco, G., Giagulli, V.A., De Pergola, G., Guastamacchia, E., Jirillo, E. and Triggiani, V. (2022) Hyperglycemia-Induced Immune System Disorders in Diabetes Mellitus and the Concept of Hyperglycemic Memory of Innate Immune Cells: A Perspective. *Endocrine, Metabolic & Immune Disorders—Drug Targets*, **22**, 367-370. https://doi.org/10.2174/1871530321666210924124336

Abbreviations

The following abbreviations are used in this manuscript.

BMD: Bone Mineral Density
Hb: Hemoglobin
RDW: Red Cell Distribution Width
Hcy: Homocysteine
T2DM: Type 2 Diabetes Mellitus
SUA: Serum Uric Acid
PINP: Total Type I Procollagen Amino-terminal Peptide Propeptide
β-CTX: β-Collagen-specific Sequence
CRP: C-Reactive Protein
IL-6: Interleukin-6
TNF-α: Tumor Necrosis Factor-alpha
OC: Osteocalcin