Research Square

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Association of high-density lipoprotein cholesterol with site- specific bone mineral density T-scores in patients with type 2 diabetes aged 50 years or older: a retrospective cross-sectional study

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Research Article

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Abstract

Background

The association between lipid metabolism and bone mineral density remains controversial, particularly in patients with type 2 diabetes mellitus (T2DM). This study aimed to investigate the relationship between HDL-C and site-specific bone mineral density T-scores in patients with T2DM aged 50 years or older.

Methods

This retrospective cross-sectional study included 2,568 hospitalized patients with T2DM who underwent bone mineral density assessment between February 2022 and December 2025. Patients were classified into normal BMD, osteopenia, and osteoporosis groups according to T-score criteria. Correlation analyses were performed to evaluate associations between lipid parameters and site-specific T-scores. Multivariable linear regression models were used to assess the independent association between HDL-C and lumbar spine T-score. Restricted cubic spline analysis and subgroup analyses were further performed.

Results

Among the 2,568 patients, 1,138 had normal BMD, 970 had osteopenia, and 460 had osteoporosis. HDL-C and ApoA1 levels increased progressively across worsening BMD categories. Correlation analysis showed that HDL-C was negatively correlated with T-scores at all skeletal sites, with the strongest correlation observed for lumbar spine T-score. In multivariable linear regression analysis, higher HDL-C was independently associated with lower lumbar spine T-score. This association remained significant after full adjustment for demographic characteristics, lifestyle factors, metabolic and clinical variables, lipid-lowering therapy, and bone-related medication use ($\beta = -0.79$, 95% CI: -1.22 to -0.35, $P < 0.001$). Site-specific analyses also showed inverse associations between HDL-C and total hip, femoral neck, and Ward's triangle T-scores. Restricted cubic spline analysis suggested an approximately linear inverse association between HDL-C and lumbar spine T-score, without evidence of nonlinearity. Subgroup analyses showed that the inverse association was more pronounced among patients with BMI < 24 kg/m², with a significant interaction by BMI.

Conclusion

Higher HDL-C levels were independently associated with lower lumbar spine T-score in patients with T2DM aged 50 years or older. This association was approximately linear and appeared stronger among patients with lower BMI. HDL-C may serve as a lipid-related marker associated with reduced lumbar

spine bone density in older patients with T2DM, although causal inference cannot be established due to the cross-sectional study design.

Background

Osteoporosis and type 2 diabetes mellitus (T2DM) are common chronic diseases in middle-aged and older adults [1]. Patients with T2DM are susceptible to osteoporosis and abnormal bone metabolism because chronic hyperglycemia, insulin resistance, oxidative stress, chronic low-grade inflammation, accumulation of advanced glycation end products, and impaired bone turnover may adversely affect bone remodeling and bone strength [2–6]. Therefore, identifying metabolic factors associated with reduced bone mineral density (BMD) in patients with T2DM is important for the early assessment of skeletal health in this population.

Lipid metabolism has been increasingly recognized as a potential factor related to bone health. Previous studies have investigated the associations between lipid profiles and BMD or osteoporosis, but the results remain inconsistent. Among lipid parameters, high-density lipoprotein cholesterol (HDL-C) is of particular interest. Some studies reported that higher HDL-C was associated with lower BMD or increased risk of bone loss [7, 8], whereas others suggested a positive or nonlinear association between HDL-C and lumbar BMD [9, 10]. However, many previous studies were conducted in the general population or selected non-diabetic populations, and evidence focusing specifically on middle-aged and older patients with T2DM remains limited. Moreover, some studies assessed osteoporosis status or fracture risk without detailed site-specific DXA-derived T-score data. DXA-derived T-scores remain the standard method for evaluating BMD and diagnosing osteoporosis in postmenopausal women and men aged 50 years or older [11]. Therefore, studies based on complete DXA measurements in middle-aged and older patients with T2DM may provide more direct evidence regarding the relationship between lipid metabolism and skeletal status.

In the present study, we included a relatively large sample of 2,568 hospitalized patients with T2DM aged 50 years or older who had completed DXA-based BMD assessment. We aimed to investigate the associations between lipid parameters, particularly HDL-C, and site-specific T-scores, including lumbar spine, total hip, femoral neck, and Ward’s triangle T-scores. We further evaluated the independent association and dose-response relationship between HDL-C and lumbar spine T-score, and explored whether this association differed by sex, age, or BMI subgroup.

Materials and Methods

2.1 Study design and participants

This retrospective cross-sectional study consecutively enrolled patients with type 2 diabetes mellitus who were hospitalized in the Department of Endocrinology, Affiliated Dongyang Hospital of Wenzhou Medical University, between February 2022 and December 2025.

Patients were eligible if they met the following criteria: 1) diagnosis of type 2 diabetes mellitus; 2) age ≥ 50 years; and 3) availability of fasting lipid profiles, fasting plasma glucose, and bone mineral density measurements during hospitalization. Patients were excluded if they had severe hepatic or renal dysfunction, diseases known to cause secondary osteoporosis such as parathyroid disorders, or a history of malignancy.

A total of 2,568 patients were included in the final analysis. According to bone mineral density status, 1,138 patients had normal BMD, 970 had osteopenia, and 460 had osteoporosis.

2.2 Data collection

Clinical data were retrospectively extracted from the hospital electronic medical record system. The collected data included demographic characteristics, lifestyle factors, medical history, physical examination results, laboratory parameters, BMD measurements, comorbidities, diabetes-related complications, and medication use.

Demographic and clinical variables included age, sex, diabetes duration, family history of diabetes, smoking status, drinking status, height, weight, body mass index, and blood pressure. Laboratory variables included HbA1c, fasting plasma glucose, glycated hemoglobin, fasting insulin or C-peptide, triglycerides, total cholesterol, HDL-C, LDL-C, apolipoprotein A1, apolipoprotein B, ApoA1/ApoB ratio, serum calcium, serum phosphorus, uric acid, albumin, prealbumin, globulin, serum creatinine, estimated glomerular filtration rate, liver function indices, complete blood count, and high-sensitivity C-reactive protein. Information on comorbidities, including hypertension, coronary heart disease, cerebral infarction, and fatty liver, was also collected. Medication use included glucose-lowering drugs, lipid-lowering drugs, calcium carbonate, active vitamin D, and anti-osteoporotic medications.

Variables with a missing rate greater than 30%, including blood pressure values, N-terminal osteocalcin, β-C-terminal telopeptide, bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, and 25-hydroxyvitamin D, were not included in the final statistical models.

2.3 Bone mineral density assessment

Bone mineral density was measured during hospitalization using dual-energy X-ray absorptiometry. T-scores at the lumbar spine, total hip, femoral neck, and Ward's triangle were recorded. BMD status was classified according to T-score criteria: normal BMD was defined as T-score ≥ -1.0, osteopenia as -2.5 < T-score < -1.0, and osteoporosis as T-score ≤ -2.5. When multiple skeletal sites were available, the lowest T-score was used for BMD classification. Site-specific T-scores were further analyzed as continuous outcomes.

2.4 Statistical analysis

All statistical analyses were performed using Python 3.10.6. Continuous variables were presented as mean ± standard deviation or median with interquartile range/range, depending on their distribution. Categorical variables were presented as numbers and percentages. Differences among the normal BMD,

osteopenia, and osteoporosis groups were assessed using one-way analysis of variance or the Kruskal–Walli's test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A two-sided P value < 0.05 was considered statistically significant.

Correlation analyses were performed to evaluate the associations between lipid parameters and site-specific T-scores. Pearson or Spearman correlation analysis was used according to variable distribution.

Multivariable linear regression models were constructed to assess the association between HDL-C and lumbar spine T-score. Covariates included in the multivariable models were selected based on previous studies and the results of univariate linear regression analysis in the present study, as shown in Supplementary Table S1. Sequential models were constructed as follows: the crude model was unadjusted; Model 1 was adjusted for age and sex; Model 2 was further adjusted for BMI, current smoking, and current drinking; Model 3 was further adjusted for HbA1c, fasting plasma glucose, eGFR, uric acid, albumin, hemoglobin, fatty liver, hypertension, and statin or fibrate use; and Model 4 was further adjusted for calcium carbonate use and active vitamin D use.

To assess site-specific associations, the fully adjusted model was further applied to total hip, femoral neck, and Ward's triangle T-scores. Restricted cubic spline analysis was performed to explore the dose-response relationship between HDL-C and lumbar spine T-score, with adjustment for covariates included in Model 4. P values for overall association and nonlinearity were calculated.

Subgroup analyses were performed according to sex, age, and BMI. Interaction effects were assessed by adding multiplicative interaction terms between HDL-C and subgroup variables to the fully adjusted model.

Ethical statement

This study was approved by the Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University, with the approval number 2026-YX-181. All patients provided informed consent during hospitalization. Patient information was anonymized before analysis.

Results

3.1 Baseline characteristics of the study population

As shown in Table 1, a total of 2,568 patients with type 2 diabetes aged ≥50 years were included, of whom 1,138 had normal BMD, 970 had osteopenia, and 460 had osteoporosis. Significant differences were observed among the three groups in demographic characteristics, lifestyle factors, lipid parameters, nutritional and biochemical indices, site-specific T-scores, comorbidities, and bone-related medication use.

Compared with patients with normal BMD, those with osteopenia and osteoporosis were older, more likely to be female, and had lower BMI. The median age increased from 60 years in the normal BMD group to 64 years in the osteopenia group and 70 years in the osteoporosis group. The proportion of

women increased markedly across the three groups, from 18.28% to 52.06% and 84.78%, respectively. BMI decreased progressively from 25.19 kg/m² in the normal BMD group to 23.81 kg/m² in the osteopenia group and 22.31 kg/m² in the osteoporosis group.

Regarding lipid parameters, triglyceride levels decreased across worsening BMD categories, whereas HDL-C, ApoA1, and the ApoA1/ApoB ratio increased progressively. HDL-C levels were 0.97, 1.07, and 1.13 mmol/L in the normal BMD, osteopenia, and osteoporosis groups, respectively. ApoA1 levels were 0.99, 1.05, and 1.08 g/L, respectively, and the ApoA1/ApoB ratio was 1.34, 1.46, and 1.48, respectively. These findings suggest that higher HDL-C and ApoA1 levels were associated with poorer BMD status.

For nutritional, hepatic, renal, and hematological indices, uric acid, albumin, prealbumin, serum creatinine, eGFR, alanine aminotransferase, red blood cell count, and hemoglobin levels tended to decrease across worsening BMD categories, whereas globulin and platelet count were relatively higher in patients with lower BMD. Patients with osteoporosis had lower uric acid, albumin, prealbumin, red blood cell count, and hemoglobin levels than those with normal BMD.

As expected, lumbar spine, total hip, femoral neck, and Ward's triangle T-scores differed significantly among the three groups and decreased progressively from normal BMD to osteopenia and osteoporosis. The median lumbar spine T-scores were 1.0, -1.1, and -2.6, respectively; total hip T-scores were 0.6, -0.7, and -1.75; femoral neck T-scores were 0.4, -0.9, and -1.8; and Ward's triangle T-scores were 0.6, -1.2, and -2.35.

With respect to comorbidities and medications, patients with osteoporosis had higher proportions of coronary heart disease and cerebral infarction, but a lower prevalence of fatty liver. The prevalence of fatty liver decreased from 58.88% in the normal BMD group to 49.90% in the osteopenia group and 34.35% in the osteoporosis group. The use of calcium carbonate and active vitamin D was substantially more frequent in patients with osteopenia and osteoporosis, reflecting a higher likelihood of receiving bone-related treatment among patients with lower BMD.

Overall, patients with lower BMD were older, predominantly female, had lower BMI and poorer nutritional profiles, and showed higher HDL-C and ApoA1 levels but lower TG levels.

3.2 Correlations between lipid parameters and site-specific T-scores

Correlation analysis was performed to evaluate the associations between lipid parameters and site-specific T-scores in patients with type 2 diabetes aged 50 years or older. As shown in Table 2, HDL-C was negatively correlated with all site-specific T-scores, with the strongest correlation observed for lumbar spine T-score ($r = -0.30$, 95% CI: -0.33 to -0.26, $P < 0.001$). ApoA1 was also negatively correlated with Ward's triangle, femoral neck, total hip, and lumbar spine T-scores, particularly lumbar spine T-score ($r = -0.24$, 95% CI: -0.27 to -0.20, $P < 0.001$). The ApoA1/ApoB ratio showed weak negative correlations with all site-specific T-scores.

In contrast, TG was weakly positively correlated with all T-scores. LDL-C and ApoB were weakly positively correlated with Ward's triangle, femoral neck, and total hip T-scores, but were not significantly correlated with lumbar spine T-score. TC showed only weak and inconsistent correlations with site-specific T-scores. Overall, although several lipid parameters were statistically associated with T-scores, the correlation coefficients were generally small, indicating weak linear correlations.

Given that HDL-C showed the strongest and most consistent negative correlation with lumbar spine T-score, subsequent analyses focused on the independent association between HDL-C and lumbar spine T-score.

3.3 Multivariable association between HDL-C and site-specific T-scores

Based on previous studies and the results of univariate linear regression analysis in the present study (Supplementary Table S1), multivariable linear regression models were constructed to further evaluate the association between HDL-C and lumbar spine T-score. As shown in Table 3, HDL-C was inversely associated with lumbar spine T-score across all regression models. In the crude model, each 1 mmol/L increase in HDL-C was associated with a 1.92-unit decrease in lumbar spine T-score (β = -1.92, 95% CI: -2.15 to -1.68, P < 0.001). The association was attenuated but remained statistically significant after sequential adjustment for demographic factors, lifestyle factors, metabolic and clinical variables, and bone-related medications. In the fully adjusted model, HDL-C remained independently associated with lower lumbar spine T-score (β = -0.79, 95% CI: -1.22 to -0.35, P < 0.001).

In site-specific analyses based on the fully adjusted model, HDL-C was inversely associated with lumbar spine, total hip, femoral neck, and Ward's triangle T-scores (Table 4). The strongest association was observed for lumbar spine T-score.

3.4 Dose-response relationship between HDL-C and lumbar spine T-score

Restricted cubic spline analysis was performed to further explore the dose-response relationship between HDL-C and lumbar spine T-score. As shown in Figure 1, after adjustment for covariates included in Model 4, HDL-C was significantly associated with lumbar spine T-score (P for overall = 0.018). No significant evidence of nonlinearity was observed (P for nonlinearity = 0.947), suggesting an approximately linear inverse association between HDL-C and lumbar spine T-score.

3.5 Subgroup analyses of the association between HDL-C and lumbar spine T-score

Subgroup analyses were further performed according to sex, age, and BMI (Figure 2). The inverse association between HDL-C and lumbar spine T-score was generally consistent across all subgroups. In sex-stratified analyses, the association was statistically significant in women (β = -0.74, 95% CI: -1.28 to -0.19, P = 0.01), whereas a similar but non-significant inverse association was observed in men (β = -0.56, 95% CI: -1.19 to 0.07, P = 0.08). No significant interaction by sex was observed (P for interaction = 0.54).

In age-stratified analyses, HDL-C was significantly associated with lower lumbar spine T-score among patients aged 50–64 years (β = -1.22, 95% CI: -1.82 to -0.63, P < 0.01), but not among those aged ≥65 years (β = -0.50, 95% CI: -1.12 to 0.12, P = 0.11). The interaction by age was not statistically significant (P for interaction = 0.31).

In BMI-stratified analyses, the inverse association was more pronounced among patients with BMI <24 kg/m² (β = -0.96, 95% CI: -1.50 to -0.42, P < 0.01), whereas the association was attenuated and not statistically significant among those with BMI ≥24 kg/m² (β = -0.39, 95% CI: -1.12 to 0.32, P = 0.28). A significant interaction by BMI was observed (P for interaction = 0.03), suggesting that BMI may modify the association between HDL-C and lumbar spine T-score.

The association between HDL-C and reduced lumbar spine T-scores was consistent in direction across gender and age subgroups, with no significant interactions observed for gender or age; however, BMI significantly modified this association, with the negative correlation being more pronounced in patients with a BMI <24 kg/m².

Discussion

In this retrospective cross-sectional study of 2,568 patients with T2DM aged 50 years or older who underwent DXA-based BMD assessment, we found that higher HDL-C was independently associated with lower lumbar spine T-score. This association remained significant after adjustment for demographic characteristics, lifestyle factors, metabolic and clinical variables, lipid-lowering therapy, and bone-related medication use. Correlation analysis also showed that HDL-C was negatively correlated with T-scores at multiple skeletal sites, with the strongest correlation observed at the lumbar spine. In addition, restricted cubic spline analysis showed a significant overall association without evidence of nonlinearity, suggesting an approximately linear inverse association between HDL-C and lumbar spine T-score. These findings suggest that HDL-C may be a lipid-related marker associated with reduced lumbar spine bone density in middle-aged and older patients with T2DM.

Although HDL-C has traditionally been regarded as a cardioprotective lipid marker [12], its circulating concentration alone does not fully capture the compositional and functional heterogeneity of HDL particles [13, 14]. In patients with T2DM, small HDL particles may exhibit impaired ABCA1-mediated cholesterol efflux [15], while hyperglycemia-related glycation and oxidative modification of apo A-I and HDL [16-18], together with remodeling of their lipid and protein cargo, may compromise the anti-inflammatory and antioxidant functions of HDL. Moreover, experimental evidence indicates that HDL-related skeletal effects may depend on receptor-mediated pathways rather than HDL-C concentration alone: Scarb1-null mice exhibited increased HDL-associated cholesterol together with enhanced osteoblast activity, bone formation, and trabecular bone mass [19]. Dysregulated lipid metabolism may also disturb bone remodeling through oxidative stress, chronic inflammation, impaired osteogenic differentiation, and increased osteoclast genesis [20]. Therefore, higher HDL-C levels in patients with

T2DM should not necessarily be interpreted as evidence of preserved HDL function or more favorable skeletal health.

This may help explain why our results differ from those of Zolfaroli et al. [9], who reported that HDL-C, but not TC, LDL-C, or triglycerides, was positively associated with lumbar spine and femoral neck BMD in postmenopausal women. Their study population was a relatively homogeneous cohort of postmenopausal women, rather than patients with diabetes. Thus, diabetes status may be an important factor modifying the relationship between HDL-C and BMD. In non-diabetic postmenopausal women, higher HDL-C may reflect a more favorable metabolic profile, whereas in patients with T2DM, HDL-C may be more strongly influenced by glucose dysregulation, insulin resistance, inflammation, and HDL dysfunction.

In subgroup analyses, the inverse association between HDL-C and lumbar spine T-score was generally consistent across sex, age, and BMI subgroups. No significant interaction was observed by sex or age, whereas BMI significantly modified this association. Specifically, the negative association between HDL-C and lumbar spine T-score was more pronounced among patients with BMI <24 kg/m². Low BMI is a well-recognized risk factor for reduced BMD and osteoporosis [21]. Lower body weight provides less osteogenic mechanical loading and may coexist with lower lean mass, lower fat mass, and poorer nutritional reserve, all of which have been associated with lower BMD [22]. In postmenopausal women, lower adipose mass may additionally reduce peripheral estrogen production [23]. Conversely, greater body weight and lean mass—and, to a lesser extent, fat mass—may support BMD through increased mechanical loading and body-composition-related pathways [24]. These background effects may partially offset bone loss and thereby dilute the observed association between HDL-C and lumbar spine T-score in patients with higher BMI. Accordingly, the stronger inverse association observed in patients with BMI <24 kg/m² may indicate that the skeletal correlates of HDL-C-related metabolic alterations are more readily detectable when the potentially protective effects associated with greater body mass are less prominent. These findings highlight the importance of considering body composition and nutritional status when interpreting the relationship between HDL-C and bone health.

Clinically, our findings may provide useful information for bone health assessment in middle-aged and older patients with T2DM. HDL-C is a routinely measured lipid parameter in clinical practice, and our results suggest that higher HDL-C should not always be interpreted as a favorable metabolic indicator in relation to skeletal health, especially in patients with T2DM. The independent association between higher HDL-C and lower lumbar spine T-score indicates that clinicians may need to pay more attention to BMD evaluation in diabetic patients with elevated HDL-C, particularly those with lower BMI. These findings also highlight the importance of considering lipid metabolism and body composition together when assessing the risk of reduced bone density in patients with T2DM.

Our study has several strengths. First, we focused on middle-aged and older patients with T2DM, a population at high risk of abnormal bone metabolism. Second, all included patients completed DXA-based BMD assessment, and we analyzed site-specific T-scores, including lumbar spine, total hip,

femoral neck, and Ward's triangle. Third, the sample size was relatively large, and the association between HDL-C and lumbar spine T-score was evaluated using multivariable regression models, restricted cubic spline analysis, and subgroup analyses. However, several limitations should also be acknowledged. First, the cross-sectional design does not allow causal inference. Second, this was a single-center study of hospitalized patients, which may limit generalizability. Third, some important variables, including menopausal status, 25-hydroxyvitamin D, bone turnover markers, and detailed body composition, were unavailable or had high missing rates and therefore were not included in the final models. Fourth, HDL function was not directly measured; therefore, we could not determine whether dysfunctional HDL mediated the observed association. Finally, information on incident fractures was unavailable. Future prospective studies with repeated DXA measurements, fracture outcomes, menopausal status, HDL functional assays, and body composition assessment are needed to further clarify the role of HDL-C in diabetes-related bone loss.

Conclusion

Higher HDL-C levels were independently associated with lower lumbar spine T-score in patients with type 2 diabetes aged 50 years or older. This association was approximately linear and was more pronounced among patients with BMI <24 kg/m². These findings suggest that HDL-C may be a lipid-related marker associated with reduced lumbar spine bone density in older patients with type 2 diabetes.

Abbreviations

Abbreviation	Full name
T2DM	Type 2 diabetes mellitus
BMD	Bone mineral density
DXA	Dual-energy X-ray absorptiometry
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
TC	Total cholesterol
TG	Triglycerides
BMI	Body mass index
HbA1c	Glycated hemoglobin
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoA1/ApoB ratio	Apolipoprotein A1 to apolipoprotein B ratio
FPG	Fasting plasma glucose
eGFR	Estimated glomerular filtration rate
CI	Confidence interval
RCS	Restricted cubic spline

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Affiliated Dongyang Hospital of Wenzhou Medical University (Approval No. 2026-YX-181) and was conducted in accordance with the Declaration of Helsinki. Owing to the retrospective nature of the study and the use of anonymized clinical data, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available because they contain information that could compromise participant privacy but are available from the corresponding

author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

KJ: Conceptualization, Data curation, Writing – original draft; XL: Writing – review & editing, Methodology, Investigation; JM: Writing – review & editing, Data curation; XH: Writing – review & editing, Project administration.

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Authors' information (optional)

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References

1. Epstein S, Defeudis G, Manfrini S, Napoli N, Pozzilli P. Diabetes and disordered bone metabolism (diabetic osteodystrophy): time for recognition[J]. Osteoporos Int. 2016;27(6):1931–51.
2. Cai R, Liu Y, Kong Q, Sun J. Capsanthin Attenuates Osteoporosis by Targeting the Urotensin II Receptor Pathway to Inhibit Oxidative Stress and NLRP3 Inflammasome Activation[J]. Calcif Tissue Int, 2026, 117(1).
3. Koromani F, Oei L, Shevroja E, Trajanoska K, Schoufour J, Muka T, Franco OH, Ikram MA, Zillikens MC, Uitterlinden AG, Krestin GP, Anastassiades T, Josse R, Kaiser SM, Goltzman D, Lentle BC, Prior JC, Leslie WD, Mccloskey E, Lamy O, et al. Vertebral Fractures in Individuals With Type 2 Diabetes: More Than Skeletal Complications Alone[J]. Diabetes Care. 2019;43(1):137–44.
4. Qamar F, Sharma M. Beyond Hyperglycaemia in Diabetic Bone Disease: Refining Experimental Models of Diabetes-Induced Osteopathy[J]. Diabetes Metab Res Rev. 2026;42(5):e70186.
5. Wang H, Ma X, Sun Y, Guo Z, Wang J, Sun M. Hyperbaric oxygen therapy for osteoporosis: A systematic review of preclinical evidence and mechanisms[J]. Bone. 2026;205:117772.
6. Yamamoto M, Sugimoto T. Advanced Glycation End Products, Diabetes, and Bone Strength[J]. Curr Osteoporos Rep. 2016;14(6):320–6.
7. Wang Y, Du Y, Zuo J, He L, Shi Y, Yuan Y, Liu Y, Zheng H, Wang H. Clinical Manifestations and Risk Factors of Osteoporosis in Patients with Type 2 Diabetes Mellitus[J]. J Inflamm Res.

2026;19:575474.

8. Zhang Q, Zhang X, Zhang S, Lv G, Wang Y, Shi X, Li Y, Ding L, Li D. Adiposity-lipid-glycemic clusters as potential warning signals of bone mass reduction in Asia's largest urban communities - based bone health assessment via ultrasound[J]. Lipids Health Dis. 2025;24(1):371.
9. Zolfaroli I, Ortiz E, García-Pérez M-Á, Hidalgo-Mora JJ, Tarín JJ, Cano A. Positive association of high-density lipoprotein cholesterol with lumbar and femoral neck bone mineral density in postmenopausal women[J]. Maturitas. 2021;147:41–6.
10. He Y-H, Gu S-L, Chen Y-Y, Xue M-M, Liu S-J, Guo F-F, Liang C-H. Nonlinear relationship between lumbar bone mineral density and high-density lipoprotein cholesterol in patients with type 2 diabetes[J]. Front Endocrinol (Lausanne). 2025;16:1570841.
11. Mccloskey E, Leslie WD. Goal-directed therapy in osteoporosis[J]. J Bone Min Res. 2013;28(3):439–41.
12. Rosenson RS. The High-Density Lipoprotein Puzzle: Why Classic Epidemiology, Genetic Epidemiology, and Clinical Trials Conflict?[J]. Arterioscler Thromb Vasc Biol. 2016;36(5):777–82.
13. Shah AS, Tan L, Long JL, Davidson WS. Proteomic diversity of high density lipoproteins: our emerging understanding of its importance in lipid transport and beyond[J]. J Lipid Res. 2013;54(10):2575–85.
14. Cai Y, Li K, Ma H, Wu J, Zheng Y. Biology of HDL: From Structural Heterogeneity to Dysfunctional Remodeling in Cardiovascular Disease and Comorbidities[J]. Antioxid (Basel), 2026, 15(7).
15. He Y, Ronsein GE, Tang C, Jarvik GP, Davidson WS, Kothari V, Song HD, Segrest JP, Bornfeldt KE, Heinecke JW. Diabetes Impairs Cellular Cholesterol Efflux From ABCA1 to Small HDL Particles[J]. Circ Res. 2020;127(9):1198–210.
16. Liu D, Ji L, Zhao M, Wang Y, Guo Y, Li L, Zhang D, Xu L, Pan B, Su J, Xiang S, Pennathur S, Li J, Gao J, Liu P, Willard B, Zheng L. Lysine glycation of apolipoprotein A-I impairs its anti-inflammatory function in type 2 diabetes mellitus[J]. J Mol Cell Cardiol. 2018;122:47–57.
17. Hussein H, Saheb S, Couturier M, Atassi M, Orsoni A, Carrié A, Therond P, Chantepie S, Robillard P, Bruckert E, Chapman MJ, Kontush A. Small, dense high-density lipoprotein 3 particles exhibit defective antioxidative and anti-inflammatory function in familial hypercholesterolemia: Partial correction by low-density lipoprotein apheresis[J]. J Clin Lipidol. 2015;10(1):124–33.
18. Kontush A, Chapman MJ. Functionally defective high-density lipoprotein: a new therapeutic target at the crossroads of dyslipidemia, inflammation, and atherosclerosis[J]. Pharmacol Rev. 2006;58(3):342–74.
19. Martineau C, Martin-Falstrault L, Brissette L, Moreau R. The atherogenic Scarb1 null mouse model shows a high bone mass phenotype[J]. Am J Physiol Endocrinol Metab. 2013;306(1):E48–57.
20. Sul O-J, Kim J-E, Ke K, Suh J-H, Choi H-S. Atherogenic diet-induced bone loss is primarily due to increased osteoclastogenesis in mice[J]. J Nutr Biochem. 2020;79:108337.
21. Ho-Pham LT, Nguyen UDT, Nguyen TV. Association between lean mass, fat mass, and bone mineral density: a meta-analysis[J]. J Clin Endocrinol Metab. 2013;99(1):30–8.

22. Coin A, Sergi G, Benincà P, Lupoli L, Cinti G, Ferrara L, Benedetti G, Tomasi G, Pisent C, Enzi G. Bone mineral density and body composition in underweight and normal elderly subjects[J]. Osteoporos Int. 2000;11(12):1043–50.
23. Suzuki N, Yano T, Nakazawa N, Yoshikawa H, Taketani Y. A possible role of estrone produced in adipose tissues in modulating postmenopausal bone density[J]. Maturitas, 1995, 22(1).
24. Zhu K, Hunter M, James A, Lim EM, Walsh JP. Associations between body mass index, lean and fat body mass and bone mineral density in middle-aged Australians: The Busselton Healthy Ageing Study[J]. Bone. 2015;74:146–52.

Tables

Table 1

Baseline characteristics of patients with diabetes according to bone mineral density status

Variable	Total	Normal BMD	Osteopenia	Osteoporosis	P value
n	2568	1138	970	460	—
Age, years	64.64 ± 9.39	62.01 ± 8.86	65.4 ± 9.2	69.53 ± 8.79	< 0.001
Female, n (%)	1103 (42.95)	208 (18.28)	505 (52.06)	390 (84.78)	< 0.001
BMI, kg/m²	24.47 ± 3.61	25.42 ± 3.04	24 ± 3.39	22.8 ± 4.63	< 0.001
Current smoking, n (%)	920 (35.83)	594 (52.20)	270 (27.84)	56 (12.17)	< 0.001
Current drinking, n (%)	909 (35.40)	544 (47.80)	284 (29.28)	81 (17.61)	< 0.001
Fasting plasma glucose, mmol/L	8.64 ± 3.95	8.73 ± 3.87	8.61 ± 3.81	8.45 ± 4.4	0.535
Fasting insulin, μIU/mL	13.41 ± 50.04	13.73 ± 51.13	12.29 ± 45.21	15.04 ± 56.97	0.65
HbA1c, %	9.05 ± 2.23	9.09 ± 2.18	9.1 ± 2.28	8.85 ± 2.26	0.129
Triglycerides, mmol/L	1.91 ± 1.84	2.14 ± 2.16	1.81 ± 1.72	1.57 ± 1.06	< 0.001
Total cholesterol, mmol/L	4.13 ± 1.14	4.09 ± 1.14	4.15 ± 1.15	4.17 ± 1.12	0.351
HDL-C, mmol/L	1.06 ± 0.27	0.98 ± 0.2	1.1 ± 0.28	1.18 ± 0.32	< 0.001
LDL-C, mmol/L	2.41 ± 0.93	2.42 ± 0.9	2.4 ± 0.95	2.4 ± 0.96	0.943
ApoA1, g/L	1.06 ± 0.24	1.01 ± 0.2	1.09 ± 0.25	1.14 ± 0.28	< 0.001
ApoB, g/L	0.76 ± 0.25	0.77 ± 0.25	0.76 ± 0.26	0.75 ± 0.25	0.401
ApoA1/ApoB ratio	1.57 ± 0.91	1.48 ± 0.87	1.62 ± 1.01	1.68 ± 0.75	< 0.001
Serum calcium, mmol/L	2.18 ± 0.12	2.17 ± 0.11	2.18 ± 0.11	2.18 ± 0.13	0.071

Variable	Total	Normal BMD	Osteopenia	Osteoporosis	P value
Serum phosphorus, mmol/L	1.09 ± 0.19	1.09 ± 0.19	1.1 ± 0.18	1.09 ± 0.21	0.813
Uric acid, μmol/L	306.81 ± 91.55	323.89 ± 88.91	300.32 ± 91.87	278.09 ± 88.51	< 0.001
Total protein, g/L	67.3 ± 5.76	67.43 ± 5.71	67.34 ± 5.66	66.86 ± 6.08	0.185
Albumin, g/L	39.95 ± 3.69	40.4 ± 3.7	39.83 ± 3.54	39.1 ± 3.84	< 0.001
Prealbumin, mg/L	224.77 ± 53.06	232.49 ± 52.95	221.98 ± 52.86	211.77 ± 50.69	< 0.001
Globulin, g/L	27.35 ± 4.03	27.04 ± 3.9	27.51 ± 4.09	27.76 ± 4.18	0.002
Serum creatinine, μmol/L	72.53 ± 45.58	76.1 ± 42.47	69.93 ± 36.82	69.23 ± 64.89	0.002
eGFR, mL/min/1.73 m^2	90.33 ± 21.99	91.8 ± 21.64	90.21 ± 21.7	87.06 ± 23.05	0.001
Alanine aminotransferase, U/L	26.58 ± 33.54	29.42 ± 36.1	25.5 ± 31.54	21.92 ± 30.38	< 0.001
Aspartate aminotransferase, U/L	23.41 ± 23.68	24.38 ± 27.73	22.94 ± 21.77	22 ± 15.14	0.145
White blood cell count, $\times 10^9$/L	6.19 ± 2.25	6.16 ± 2.04	6.15 ± 2.36	6.33 ± 2.51	0.334
Platelet count, $\times 10^9$/L	196.79 ± 65.31	193.25 ± 63.97	197.63 ± 67.04	203.79 ± 64.41	0.012
Red blood cell count, $\times 10^{12}$/L	4.38 ± 0.82	4.54 ± 0.83	4.32 ± 0.82	4.13 ± 0.67	< 0.001
Hemoglobin, g/L	132.44 ± 24.68	137.48 ± 25.58	130.33 ± 24.24	124.42 ± 20.23	< 0.001
hs-CRP, mg/L	6.34 ± 18.32	6.18 ± 19.42	6.46 ± 16.78	6.47 ± 18.69	0.931
Lumbar spine T-score	-0.18 ± 1.75	1.17 ± 1.28	-0.72 ± 1	-2.37 ± 0.95	< 0.001
Total hip T-score	-0.22 ± 1.27	0.75 ± 0.93	-0.64 ± 0.75	-1.73 ± 0.86	< 0.001
Femoral neck T-score	-0.35 ± 1.28	0.57 ± 1	-0.77 ± 0.84	-1.74 ± 0.87	< 0.001

Variable	Total	Normal BMD	Osteopenia	Osteoporosis	P value
Ward’s triangle T-score	-0.4 ± 1.53	0.79 ± 1.14	-0.98 ± 0.95	-2.1 ± 0.97	< 0.001
Hypertension, n (%)	1606 (62.54)	711 (62.48)	590 (60.82)	305 (66.30)	0.135
Coronary heart disease, n (%)	510 (19.86)	206 (18.10)	183 (18.87)	121 (26.30)	0.001
Cerebral infarction, n (%)	476 (18.54)	182 (15.99)	184 (18.97)	110 (23.91)	0.001
Fatty liver, n (%)	1312 (51.09)	670 (58.88)	484 (49.90)	158 (34.35)	< 0.001
Calcium carbonate use, n (%)	991 (38.59)	79 (6.94)	598 (61.65)	314 (68.26)	< 0.001
Active vitamin D use, n (%)	737 (28.70)	28 (2.46)	406 (41.86)	303 (65.87)	< 0.001
Alendronate use, n (%)	15 (0.58)	5 (0.44)	9 (0.93)	1 (0.22)	0.178
Statin or fibrate use, n (%)	1643 (63.98)	702 (61.69)	642 (66.19)	299 (65.00)	0.088
Ezetimibe use, n (%)	98 (3.82)	49 (4.31)	34 (3.51)	15 (3.26)	0.501

Table note

Data are presented as mean ± standard deviation, median (interquartile range), or n (%), as appropriate. Differences among the normal BMD, osteopenia, and osteoporosis groups were assessed using one-way analysis of variance for normally distributed continuous variables, the Kruskal–Wallis test for skewed continuous variables, and the chi-square test or Fisher’s exact test for categorical variables. BMD status was classified according to T-score criteria. A two-sided P value < 0.05 was considered statistically significant.

Abbreviations

BMD, bone mineral density; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; ALP, alkaline phosphatase; Ca, calcium; P, phosphorus; UA, uric acid; TP, total protein; ALB, albumin; PAB, prealbumin; GLOB, globulin; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; PLT, platelet count; RBC, red blood cell count; HGB, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; CHD, coronary heart disease.

Table 2

Correlations between lipid parameters and site-specific T-scores

Lipid parameter	Ward's triangle T-score	Femoral neck T-score	Total hip T-score	Lumbar spine T-score
TG	0.13(0.09, 0.18) P < 0.001	0.13 (0.08, 0.17) P < 0.001	0.14 (0.09, 0.18) P < 0.001	0.10 (0.06, 0.15) P < 0.001
TC	0.03 (-0.01, 0.07) P = 0.12	0.04 (0.01, 0.08) P = 0.03	0.03 (-0.01, 0.06) P = 0.19	-0.05 (-0.08, -0.01) P = 0.01
HDL-C	-0.25 (-0.28, -0.21) P < 0.001	-0.23 (-0.26, -0.19) P < 0.001	-0.26 (-0.29, -0.22) P < 0.001	-0.30 (-0.33, -0.26) P < 0.001
LDL-C	0.05 (0.01, 0.09) P = 0.01	0.06 (0.02, 0.10) P < 0.001	0.04 (0.01, 0.08) P = 0.03	-0.02 (-0.06, 0.02) P = 0.31
ApoA1	-0.15 (-0.18, -0.11) P < 0.001	-0.15 (-0.19, -0.11) P < 0.001	-0.16 (-0.20, -0.12) P < 0.001	-0.24 (-0.27, -0.20) P < 0.001
ApoB	0.08 (0.04, 0.12) P < 0.001	0.07 (0.03, 0.11) P < 0.001	0.06 (0.02, 0.09) P < 0.001	-0.01 (-0.04, 0.03) P = 0.79
ApoA1/ApoB ratio	-0.11 (-0.15, -0.07) P < 0.001	-0.10 (-0.14, -0.06) P < 0.001	-0.10 (-0.14, -0.06) P < 0.001	-0.09 (-0.13, -0.05) P < 0.001

Table note

Data are presented as correlation coefficient r (95% confidence interval) and P value. Correlations between lipid parameters and site-specific T-scores were assessed using Pearson or Spearman correlation analysis, as appropriate. A two-sided P value < 0.05 was considered statistically significant.

Abbreviations

TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.

Table 3

Association between HDL-C and lumbar spine T-score in stepwise multivariable linear regression models

Variables	Crude	Model 1	Model 2	Model 3	Model 4
β (95% CI) P value	-1.92 (-2.15, -1.68) <0.001	-1.18(-1.40, -0.96) <0.001	-0.99(-1.27, -0.72) <0.001	-0.95 (-1.41, -0.49) <0.001	-0.79(-1.22, -0.35) <0.001
Table notes					
Model 1 was adjusted for age and sex.					
Model 2 was further adjusted for BMI, current smoking, and current drinking.					
Model 3 was further adjusted for HbA1c, fasting plasma glucose, eGFR, uric acid, albumin, hemoglobin, fatty liver, hypertension, and statin or fibrate use.					
Model 4 was further adjusted for calcium carbonate use and active vitamin D use.					

Table 4

Association between HDL-C and site-specific T-scores in the fully adjusted model

Outcome	β	95%CI	P value
Lumbar spine T-score	-0.79	(-1.22, -0.35)	<0.001
Total hip T-score	-0.41	(-0.72, -0.10)	0.01
Femoral neck T-score	-0.44	(-0.77, -0.10)	0.01
Ward’s triangle T-score	-0.50	(-0.87, -0.11)	0.01
Table notes			
Estimates were derived from the fully adjusted model, including age, sex, BMI, current smoking, current drinking, HbA1c, fasting plasma glucose, eGFR, uric acid, albumin, hemoglobin, fatty liver, hypertension, statin or fibrate use, calcium carbonate use, and active vitamin D use.			

Figures

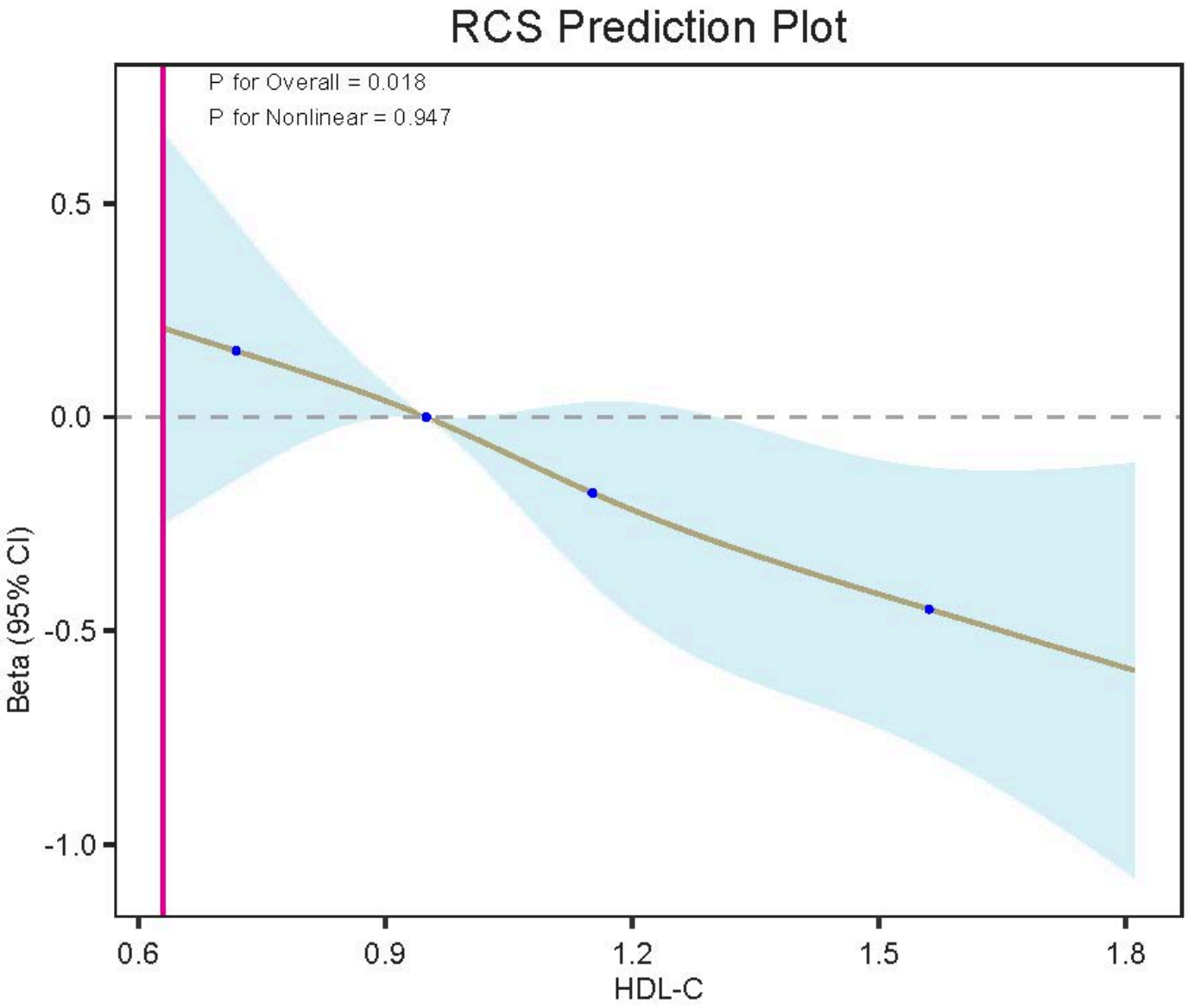


Figure 1

Restricted cubic spline analysis of the association between HDL-C and lumbar spine T-score

The restricted cubic spline model was adjusted for covariates included in Model 4. The solid line represents the estimated β coefficient, and the shaded area represents the 95% confidence interval. The dashed horizontal line indicates β = 0.

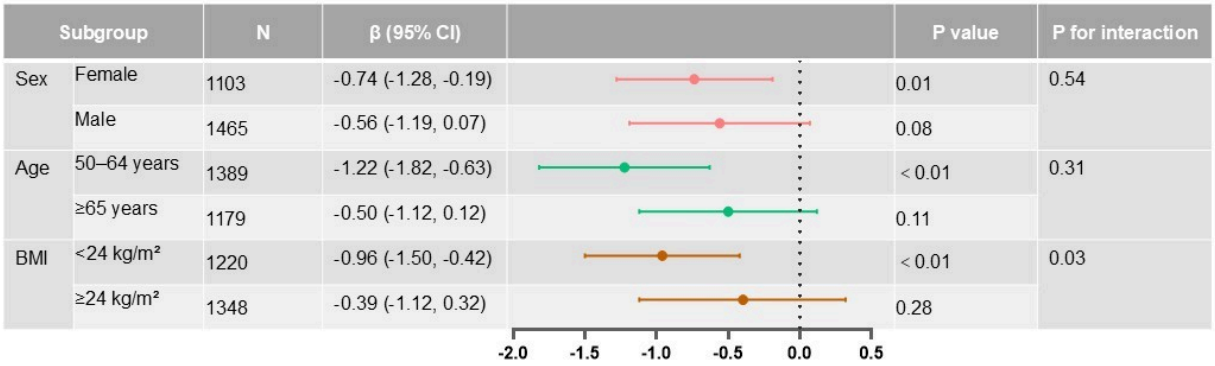


Figure 2

Subgroup analyses of the association between HDL-C and lumbar spine T-score

Subgroup analyses were performed using the fully adjusted model. The stratification variable was not included as a covariate in its corresponding subgroup model. Squares represent β coefficients, and horizontal lines represent 95% confidence intervals. The vertical dashed line indicates β = 0. P for interaction was calculated by adding a multiplicative interaction term between HDL-C and the subgroup variable to the fully adjusted model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1.docx