

Research Article

# Association of Diabetic Retinopathy Severity with Bone Mineral Density and Fragility Fracture Risk in Adults with Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Received: 14.06.26, Revised: 20.08.26, Accepted: 18.10.26

## ABSTRACT

**Background:** Type 2 diabetes mellitus is associated with increased skeletal fragility despite relatively preserved bone mineral density (BMD). Diabetic retinopathy may indicate systemic complications associated with skeletal vulnerability. Retinal microvascular injury and altered skeletal metabolism may share mechanisms involving hyperglycemia, inflammation, and vascular dysfunction.

**Objective:** To examine associations between retinopathy severity, site-specific BMD, and incident fragility fractures in adults with type 2 diabetes.

**Methods:** This multicenter prospective cohort included 170 adults recruited in three tertiary care hospitals of Pakistan between March 2025 and April 2026. Retinopathy was classified as absent, mild-to-moderate nonproliferative, or severe nonproliferative/proliferative disease. BMD was measured using dual-energy X-ray absorptiometry. Multivariable linear regression assessed BMD associations; fractures were assessed during follow-up using incidence rates and exploratory Cox regression.

**Results:** Participants included 80 men and 90 women; 55 had no retinopathy, 74 had mild-to-moderate disease, and 41 had advanced disease. Mean femoral neck BMD declined across groups ( $0.843 \pm 0.076$ ,  $0.785 \pm 0.072$ , and  $0.746 \pm 0.076$  g/cm<sup>2</sup>, respectively;  $p < 0.001$ ). After adjustment, advanced retinopathy was associated with lower femoral neck BMD ( $B = -0.102$  g/cm<sup>2</sup>; 95% confidence interval,  $-0.140$  to  $-0.064$ ). Twelve fragility fractures occurred over 164.08 person-years. Fracture incidence was highest in advanced retinopathy (156.9 per 1,000 person-years), but the unadjusted hazard ratio was imprecise (4.30; 95% confidence interval, 0.87-21.30;  $p = 0.074$ ).

**Conclusion:** Greater retinopathy severity was associated with lower BMD, whereas evidence for increased incident fracture risk remained inconclusive. Larger cohorts with extended follow-up are needed.

**Keywords:** Type 2 Diabetes Mellitus, Diabetic Retinopathy, Bone Mineral Density, Fragility Fractures, Osteoporosis, and Microvascular Complications.

## INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is a chronic metabolic condition that is linked with progressive microvascular and macrovascular complications, which have a significant impact on long-term morbidity<sup>1</sup>. In addition to its known impact on the cardiovascular, renal and nervous systems, T2DM is now known to be a significant factor in skeletal health. Though

many people with T2DM have normal or high bone mineral density (BMD), they are nonetheless at risk for fragility fractures. This mismatch indicates that traditional assessment of bone density by densitometry might not fully capture the increased fragility of bones and changes in bone quality and strength associated with diabetes disease<sup>3,4</sup>.

A major microvascular complication of T2DM, DR is a result of the long-term metabolic damage, endothelial dysfunction, and microvascular dysfunction associated with T2DM. There is growing evidence that diabetic microvascular complications are also linked with skeletal deterioration and fracture susceptibility<sup>5</sup>. In a large population based cohort study, there was a strong association between diabetic microvascular disease and osteoporosis and osteoporotic fractures. Likewise, another study of adults with diabetes found an inverse relationship between femoral BMD and DR, suggesting a link between microvascular damage to the retina and bone abnormalities. But it is not clear how well the progression of retinopathy is correlated with the degree of bone loss and the likelihood of fracture<sup>6</sup>.

There may be several related mechanisms involved in this relationship. Longstanding hyperglycemia leads to AGEs, oxidative stress, chronic inflammation and disturbances in bone remodeling that may impair the integrity of collagen and bone microarchitecture. These changes may affect skeletal strength without any decrease in the measurable BMD<sup>7</sup>. In addition, retinopathy can lead to visual dysfunction, which can contribute to a risk of falling and increased fracture risk; peripheral neuropathy can lead to a fall risk and diabetic kidney disease can lead to mineral metabolism disturbances, which can also lead to fracture risk. Therefore, the presence and severity of retinopathy could be a reflection of a general burden of diabetes-related complications relating to skeletal health<sup>8</sup>.

Previous studies have investigated the relationship between microvascular diabetic complications and bone measures, but data on the direct association of graded retinopathy severity and site-specific BMD as well as incident fragility fracture are scarce<sup>9</sup>. The knowledge of these relationships could be used to better identify those with diabetes who need thorough skeletal risk assessment. The present study was thus aimed to assess the relationship between severity of DR and BMD and risk of fragility fracture in adult T2DM population while adjusting for various demographic, metabolic and clinical parameters<sup>10</sup>.

## **MATERIALS AND METHODS**

### **Study Design and Setting**

A multicenter, prospective observational cohort study was undertaken to examine the association of diabetic retinopathy (DR) severity with bone mineral density (BMD) and

subsequent fragility fractures among adults with type 2 diabetes mellitus (T2DM). This study was carried out from March 2025 to April 2026 in three tertiary care hospitals of Pakistan namely Department of Biochemistry, Gujranwala medical college, Gujranwala; Department of Biochemistry, Amna Inayat medical college, Sheikhupura and Department of Medicine, Shaheed Mohtarma benazir Bhutto general hospital, Quetta. The initial clinical and diagnostic assessments were performed from March-April 2025, with a prospective surveillance period of up to 12 months. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations were followed to guide the methodological approach and the reporting.

### **Study Population and Sampling**

The participants were adults with known T2DM, who were recruited using consecutive, nonprobability sampling with 170 adults participating. Participants were eligible if they were able to have comprehensive retinal examination and dual-energy X-ray absorptiometry (DXA) and were 50 years or older, or post menopause for women. Patients with malignancy-related bone disease, a recent fracture as a result of high-energy trauma, or disease that hindered the ability to obtain reliable retinal imaging or DXA interpretation were excluded. Diabetic kidney disease, peripheral neuropathy, history of fragility fracture or other co-morbidities were not exclusion criteria to account for the clinical diversity of the diabetic population. These were recorded and taken into account in subsequent analysis. Baseline comparisons and assessment of prospective fracture were performed for all 170 participants enrolled in the study.

### **Diabetic Retinopathy (DR) Assessment**

Retinal microvascular involvement was assessed using a full ophthalmic examination including fundus assessment with dilation and retinal photography. Retinopathy was initially judged as absent, mild, moderate, severe NPDR or proliferative DR (PDR) as per the International Clinical Diabetic Retinopathy Disease Severity Scale.<sup>7</sup> If there was disparity between the retinal findings in both eyes, the eye with the more advanced retinal findings was used for the classification. For the main analyses, participants were classified into three groups: no DR, mild to moderate NPDR and severe NPDR/PDR. This grouping allowed for assessment of skeletal outcome with sufficient

numbers within each analytic category of increasing degree of microvascular involvement in the retina.

#### **Bone mineral density assessment.**

DXA was performed to measure bone mineral density at three sites: lumbar spine (L1–L4); femoral neck; and total hip. Absolute BMD measurements were expressed in grams per square centimeter ( $\text{g}/\text{cm}^2$ ), accompanied by the corresponding site-specific T-scores. Densitometric data were interpreted according to the recommendations of International Society for Clinical Densitometry. Skeletal status was defined as normal (T score  $\geq -1.0$ ), low bone mass (T score between  $-1.0$  and  $-2.5$ , excluding both limits) and osteoporosis (T score  $\leq -2.5$ ). The overall densitometric classification was based on the lowest technically acceptable T-score at any of the diagnostic sites evaluated. Femoral neck BMD was considered as the primary skeletal measurement, lumbar spine and total hip BMD were considered as secondary measurements. Scans with significant positioning errors and degenerative changes or other artefacts that could potentially affect the validity of the measurement were not site-specific interpreted.

#### **Clinical and Biochemical Assessment**

Demographic data, anthropometric measures, diabetes history, past low-trauma fracture, falls, peripheral neuropathy, and current glucose-lowering therapy was collected for baseline. The variables recorded were age, sex, body mass index (BMI), duration of diabetes and insulin therapy. Body mass index was calculated by dividing body weight in kilograms by the square of height in meters ( $\text{kg}/\text{m}^2$ ). Glycemic status was assessed by glycated hemoglobin (HbA1c) while kidney function was assessed by estimated glomerular filtration rate (eGFR). Insulin exposure was documented, as a proxy for treatment history and diabetes related clinical characteristics. These variables were selected as potential confounders because they have known or suspected associations with retinal microvascular abnormalities and they also have known or suspected associations with skeletal health. Therefore, models were adjusted for relevant clinical and biochemical measurements which might affect the relationship between DR severity and BMD.

#### **Evaluation and Ascertainment of Fragility Fractures**

Participants were then followed-up prospectively for up to 12 months after

baseline. An incident fracture was defined as a fracture that occurred after a low-energy fall (defined as a fall from standing height or less). Fractures were detected by clinical follow-up, review of hospital records and radiography. Fractures from major trauma, malignant bone disease or other pathological bone problems were not deemed eligible outcomes. The date and anatomical location of each confirmed event were recorded. The first qualifying fracture in the follow-up period was the only fracture included in the primary time-to-event analysis. Observation time was measured from baseline assessment to first fragility fracture, end of observation period or last participant contact, whichever came first. Person-time was accrued for those who did not have fractures recorded until the last available follow-up assessment.

#### **Study Outcomes**

The main outcome was the correlation between the DR severity at baseline and the femoral neck BMD. Secondary outcomes were differences in lumbar spine and total hip BMD by retinopathy category, differences in prevalence of normal BMD, low bone mass and osteoporosis, and incident fragility fractures during prospective follow-up. Baseline skeletal measurements and subsequent fracture events were assessed separately to separate cross-sectional associations with bone density and the prospective association between retinal disease severity and fracture events.

#### **Statistical Analysis**

The statistical procedures used were determined by the characteristics of measurement and distribution of the variables in the study. Means and standard deviations were used to present continuous data, while categorical characteristics were presented in frequencies and percentages. One-way analysis of variance (ANOVA) was used for continuous measures and Pearson's chi-square test was used for categorical variables to compare the three DR severity categories. When the assumptions of conventional tests were not met, appropriate nonparametric/exact methods were applied. Multivariable linear regression was used to assess associations among retinopathy severity and BMD at individual skeletal sites adjusted for age, sex, BMI, duration of diabetes, HbA1c, eGFR, and recruiting center. Results were reported as  $\beta$  values and 95% confidence intervals (CIs) for the regressions.

Fragility fracture incidence rate was determined as the number of fractures per 1,000 person-years of follow-up. Kaplan–Meier estimates of fracture-free survival were performed and log rank differences between retinopathy categories were evaluated. Unadjusted hazard ratios (HRs) and 95% CIs for incident fragility fracture were estimated for exploratory Cox proportional hazards regression, with participants without DR as the reference category. Since the number of fracture events observed was small ( $n = 12$ ), multivariable models of fracture were not fitted to avoid overfitting and imprecise estimation of the effect of the variables. All hypothesis tests were two-sided, with statistical significance defined as  $p < 0.05$ .

### Ethical Considerations

The investigation was carried out in compliance with the ethical principles established in the Declaration of Helsinki and in compliance with specific research requirements of the institutions. Ethical clearance was sought from the institutional review committee and written informed consent from all the participants prior to recruitment. The confidentiality of personal data and protection of clinical data related to the study were respected during the investigation.

### RESULTS

#### Baseline Demographic and Clinical Characteristics

A total of 170 adults with type 2 diabetes mellitus (T2DM) were included in the study, comprising 80 males (47.1%) and 90 females (52.9%), with a mean age of  $60.96 \pm 5.81$

years. The participants were selected from three centers, Gujranwala Medical College ( $n = 58$ ), Amna Inayat Medical College ( $n = 52$ ) and Shaheed Mohtarma Benazir Bhutto General Hospital ( $n = 60$ ). According to the eye examination, 55 participants (32.4%) did not have any diabetic retinopathy (DR), 74 (43.5%) had mild to moderate nonproliferative diabetic retinopathy (NPDR), and 41 (24.1%) had severe NPDR or PDR.

Among participants without DR, 27 (49.1%) were male and 28 (50.9%) were female. There were 35 males (47.3%) and 39 females (52.7%) in the mild to moderate NPDR group, and 18 males (43.9%) and 23 females (56.1%) in the severe NPDR/PDR group. There was no significant difference in sex distribution between the different retinopathy categories ( $p = 0.879$ ). Retinopathy severity was associated with age ( $p = 0.001$ ), diabetes duration ( $p < 0.001$ ), glycated hemoglobin (HbA1c) ( $p < 0.001$ ) and estimated glomerular filtration rate (eGFR) ( $p < 0.001$ ). Advanced retinopathy was also associated with a higher prevalence of peripheral neuropathy ( $p = 0.002$ ), history of falls ( $p = 0.044$ ) and insulin use ( $p = 0.005$ ). There was no significant difference of previous fragility fracture between severe NPDR/PDR (26.8%) and no DR (9.1%) ( $p = 0.060$ ).

Tables 1 provides baseline characteristics. Continuous variables are reported as mean  $\pm$  standard deviation (SD) and analyzed by one-way analysis of variance, while categorical variables are reported as numbers and percentages and analyzed by Pearson's chi-square test. Body mass index (BMI) and all other clinical parameters were compared among all three retinopathy groups.

Table 1. Baseline demographic, clinical, and biochemical characteristics according to diabetic retinopathy severity

| Characteristic                     | No DR (n = 55)    | Mild/moderate NPDR (n = 74) | Severe NPDR/PDR (n = 41) | p-value |
|------------------------------------|-------------------|-----------------------------|--------------------------|---------|
| Age, years                         | $58.89 \pm 5.05$  | $61.15 \pm 6.03$            | $63.41 \pm 5.45$         | 0.001   |
| Sex, n (%)                         |                   |                             |                          | 0.879   |
| Male                               | 27 (49.1)         | 35 (47.3)                   | 18 (43.9)                | —       |
| Female                             | 28 (50.9)         | 39 (52.7)                   | 23 (56.1)                | —       |
| BMI, kg/m <sup>2</sup>             | $27.83 \pm 3.17$  | $27.16 \pm 3.21$            | $26.76 \pm 3.19$         | 0.248   |
| Diabetes duration, years           | $7.44 \pm 3.84$   | $11.26 \pm 4.07$            | $12.93 \pm 3.83$         | <0.001  |
| HbA1c, %                           | $7.34 \pm 1.01$   | $8.12 \pm 1.17$             | $8.49 \pm 1.11$          | <0.001  |
| eGFR, mL/min/1.73 m <sup>2</sup>   | $82.00 \pm 12.29$ | $76.83 \pm 14.16$           | $66.50 \pm 18.53$        | <0.001  |
| Peripheral neuropathy, n (%)       | 7 (12.7)          | 18 (24.3)                   | 18 (43.9)                | 0.002   |
| Previous fragility fracture, n (%) | 5 (9.1)           | 11 (14.9)                   | 11 (26.8)                | 0.060   |

|                          |           |           |           |       |
|--------------------------|-----------|-----------|-----------|-------|
| History of falls, n (%)  | 8 (14.5)  | 18 (24.3) | 15 (36.6) | 0.044 |
| Insulin treatment, n (%) | 14 (25.5) | 29 (39.2) | 24 (58.5) | 0.005 |

#### Association Between Diabetic Retinopathy Severity and Bone Mineral Density

Bone mineral density (BMD) was found to decline step by step as the DR levels increased at all three skeletal sites. Mean femoral neck BMD was highest among participants without DR ( $0.843 \pm 0.076$  g/cm<sup>2</sup>), followed by those with mild-to-moderate NPDR ( $0.785 \pm 0.072$  g/cm<sup>2</sup>) and severe NPDR/PDR ( $0.746 \pm 0.076$  g/cm<sup>2</sup>;  $p < 0.001$ ). Similarly, mean BMD was  $0.925 \pm 0.072$  g/cm<sup>2</sup> in non-retinopathy group and  $0.825 \pm 0.077$  g/cm<sup>2</sup> in severe NPDR/PDR group ( $P < 0.001$ ) at the total hip. Lumbar spine BMD also decreased significantly, from  $1.053 \pm 0.085$  g/cm<sup>2</sup> to  $0.932 \pm 0.088$  g/cm<sup>2</sup> across the corresponding categories ( $p < 0.001$ ).

Based on lowest valid diagnostic t-score from the lumbar spine, femoral neck or total hip, 30 participants (17.6%) were classified as having

normal BMD, 131 (77.1%) were classified as having low bone mass and nine (5.3%) were classified as having osteoporosis. The proportion classified as having osteoporosis increased with retinopathy severity, from 0% among participants without DR to 4.1% among those with mild-to-moderate NPDR and 14.6% among those with severe NPDR/PDR. There was a significant difference in distribution of densitometric categories between retinopathy groups ( $p < 0.001$ ).

Specific BMD values and densitometric classification by site are included in Table 2. The continuous measurements were expressed as mean  $\pm$  SD and compared by one-way analysis of variance. A conditional Monte Carlo exact test was used to test for differences in the overall distribution of densitometric categories.

Table 2. Bone mineral density measurements and densitometric classification according to diabetic retinopathy severity

| Parameter                           | No DR (n = 55)    | Mild/moderate NPDR (n = 74) | Severe NPDR/PDR (n = 41) | p-value |
|-------------------------------------|-------------------|-----------------------------|--------------------------|---------|
| Femoral neck BMD, g/cm <sup>2</sup> | $0.843 \pm 0.076$ | $0.785 \pm 0.072$           | $0.746 \pm 0.076$        | <0.001  |
| Total hip BMD, g/cm <sup>2</sup>    | $0.925 \pm 0.072$ | $0.863 \pm 0.067$           | $0.825 \pm 0.077$        | <0.001  |
| Lumbar spine BMD, g/cm <sup>2</sup> | $1.053 \pm 0.085$ | $0.982 \pm 0.078$           | $0.932 \pm 0.088$        | <0.001  |
| Densitometric classification, n (%) |                   |                             |                          | <0.001  |
| Normal BMD                          | 17 (30.9)         | 10 (13.5)                   | 3 (7.3)                  | —       |
| Low bone mass                       | 38 (69.1)         | 61 (82.4)                   | 32 (78.0)                | —       |
| Osteoporosis                        | 0 (0.0)           | 3 (4.1)                     | 6 (14.6)                 | —       |

#### Multivariable Association between Diabetic Retinopathy Severity and Bone Mineral Density

Multivariable linear regression demonstrated that diabetic retinopathy severity remained significantly associated with lower BMD after adjustment for age, sex, BMI, diabetes duration, HbA1c, eGFR, and recruitment center. Three regression models were created to analyze the effect of retinopathy on femoral neck, total hip, and lumbar spine BMD, respectively, using the non retinopathy group as a reference. The regression coefficients ( $\beta$ ) reflect mean differences in BMD, with negative values indicating a decrease in BMD in comparison with the reference group. The

effect estimates are reported with their 95% confidence intervals (CIs).

The adjusted mean differences in femoral neck BMD compared to those who were not DR were  $-0.061$  g/cm<sup>2</sup> (95% CI,  $-0.090$  to  $-0.031$ ,  $p < 0.001$ ) for those with mild-to-moderate NPDR and  $-0.102$  g/cm<sup>2</sup> (95% CI,  $-0.140$  to  $-0.064$ ,  $p < 0.001$ ) for those with severe NPDR/PDR. Similar relationships were seen at the TH and LS. Severe NPDR/PDR was associated with an adjusted total hip BMD difference of  $-0.115$  g/cm<sup>2</sup> (95% CI,  $-0.152$  to  $-0.077$ ;  $p < 0.001$ ) and a lumbar spine BMD difference of  $-0.133$  g/cm<sup>2</sup> (95% CI,  $-0.176$  to  $-0.090$ ;  $p < 0.001$ ). Mild-to-moderate NPDR was also independently associated with lower total hip BMD (adjusted  $\beta = -0.071$  g/cm<sup>2</sup>; 95% CI,  $-0.100$  to  $-0.043$ ;  $p$

< 0.001) and lumbar spine BMD (adjusted  $\beta$  =  $-0.077$  g/cm<sup>2</sup>; 95% CI,  $-0.110$  to  $-0.044$ ;  $p$  < 0.001). The magnitude of the negative associations was consistently greater among

participants with severe NPDR/PDR, indicating a graded relationship between retinopathy severity and reduced BMD across all skeletal sites (Table 3).

Table 3. Multivariable-adjusted association between diabetic retinopathy severity and site-specific bone mineral density

| Skeletal site and retinopathy category | Adjusted $\beta$ (g/cm <sup>2</sup> ) | 95% CI           | p-value |
|----------------------------------------|---------------------------------------|------------------|---------|
| Femoral neck BMD                       |                                       |                  |         |
| No DR                                  | Reference                             | —                | —       |
| Mild/moderate NPDR                     | −0.061                                | −0.090 to −0.031 | <0.001  |
| Severe NPDR/PDR                        | −0.102                                | −0.140 to −0.064 | <0.001  |
| Total hip BMD                          |                                       |                  |         |
| No DR                                  | Reference                             | —                | —       |
| Mild/moderate NPDR                     | −0.071                                | −0.100 to −0.043 | <0.001  |
| Severe NPDR/PDR                        | −0.115                                | −0.152 to −0.077 | <0.001  |
| Lumbar spine BMD                       |                                       |                  |         |
| No DR                                  | Reference                             | —                | —       |
| Mild/moderate NPDR                     | −0.077                                | −0.110 to −0.044 | <0.001  |
| Severe NPDR/PDR                        | −0.133                                | −0.176 to −0.090 | <0.001  |

#### Incidence of Fragility Fractures and Time-to-Event Analysis

Over the 12-month follow-up, 166 participants (97.6%) completed follow-up or the fracture endpoint, and four (2.4%) were lost to follow-up. There were 12 participants (7.1%) who had incident fragility fractures in the cohort, with an overall incidence rate of 73.1 fractures per 1000 person years. Incident fracture rates were determined by the first fracture that met the fragility fracture criteria while on the follow-up period, with participants censored at the first fracture, last contact or end of study.

There was a progressive increase in the number of participants with an incident fragility fracture with retinopathy severity. There were two fractures among subjects without DR, four among those with mild-to-moderate NPDR and six among those with severe NPDR/PDR. The corresponding incidence rates were 37.0, 55.7 and 156.9 fractures per 1,000 person-years, respectively. Of the 12 incident fractures, 3 were hip, 2 were clinical spine, 5 were distal forearm and 2 were proximal humerus.

Unadjusted Cox proportional hazards regression was used for exploratory time-to-event analyses, with the participants without DR as the reference group. Mild-to-moderate NPDR was associated with a hazard ratio (HR) of 1.51 (95% CI, 0.28–8.27;  $p$  = 0.632), whereas severe NPDR/PDR was associated with an HR of 4.30 (95% CI, 0.87–21.30;  $p$  = 0.074). The estimated fracture hazard was also higher in the group with advanced retinopathy, though neither of the comparisons was statistically significant and the confidence intervals were wide suggesting a lot of uncertainty. A comparison of the fracture-free survival across retinopathy categories overall was also not statistically significant (log rank  $p$  = 0.080). Because the number of incident fracture events was small ( $n$  = 12), multivariable Cox regression was not performed, as this approach may yield unstable estimates. Table 4 shows follow-up characteristics, fracture incidence, anatomical fracture distribution, and exploratory hazard estimates.

Table 4. Incidence of fragility fractures, follow-up characteristics, and exploratory fracture risk according to diabetic retinopathy severity

| Parameter                          | No DR (n = 55) | Mild/moderate NPDR (n = 74) | Severe NPDR/PDR (n = 41) | Overall (N = 170) |
|------------------------------------|----------------|-----------------------------|--------------------------|-------------------|
| Total follow-up, person-years      | 54.08          | 71.75                       | 38.25                    | 164.08            |
| Incident fragility fracture, n (%) | 2 (3.6)        | 4 (5.4)                     | 6 (14.6)                 | 12 (7.1)          |
| Incidence per 1,000 person-years   | 37.0           | 55.7                        | 156.9                    | 73.1              |
| Hip fracture, n                    | 0              | 1                           | 2                        | 3                 |

|                                |           |                  |                   |         |
|--------------------------------|-----------|------------------|-------------------|---------|
| Clinical vertebral fracture, n | 0         | 0                | 2                 | 2       |
| Distal forearm fracture, n     | 2         | 2                | 1                 | 5       |
| Proximal humerus fracture, n   | 0         | 1                | 1                 | 2       |
| Lost to follow-up, n (%)       | 1 (1.8)   | 2 (2.7)          | 1 (2.4)           | 4 (2.4) |
| Unadjusted HR (95% CI)         | Reference | 1.51 (0.28–8.27) | 4.30 (0.87–21.30) | —       |
| Cox regression p-value         | —         | 0.632            | 0.074             | —       |

## DISCUSSION

The current study proved that the higher the severity of DR, the lower the bone mineral density (BMD) in adult patients with type 2 diabetes mellitus (T2DM). There were significant differences in femoral neck, total hip and lumbar spine BMD between participants with severe nonproliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) and the retinopathy-free subjects<sup>1-5</sup>. These associations remained after accounting for demographic, metabolic, renal and clinical variables. Participants with advanced retinopathy had a greater incidence of fragility fracture; however, this was not statistically significant in the time-to-event analysis. These results indicate that the severity of the retinal microvascular disease might also help give extra information concerning the vulnerability of a person with T2DM<sup>6</sup>.

The relationship between DR and lower BMD is in line with recent studies that have shown an association between microvascular complications and skeletal loss<sup>7</sup>. Yen et al. found that people with diabetic microvascular complications (specifically retinopathy, neuropathy and diabetic kidney disease) had a higher risk of osteoporosis and major osteoporotic fracture. Likewise, Liu et al. showed an inverse correlation with DR and femoral BMD, indicating a possible correlation between microvascular damage in the retina and compromised bone health<sup>5</sup>. The current results further expand on these observations, showing a progressive decrease in BMD in each retinopathy severity category and stable relationships at all skeletal sites, even after adjusting for multiple factors<sup>8,9</sup>.

Biological mechanisms by which this relationship occurs may be multifactorial. These include chronic hyperglycemia, advanced glycation end-product accumulation, oxidative stress, and inflammatory signaling, which can negatively affect collagen integrity, osteoblast activity and skeletal remodeling<sup>10</sup>. Such changes are able to affect the properties and microarchitecture of bone independently of traditional densitometric measurements. Retinal micro vascular abnormalities could be

the result of metabolic and vascular changes that also occur in the skeletal tissues. Additionally, “advanced retinopathy” participants had longer duration of diabetes, impaired renal function and peripheral neuropathy, indicating that diabetes-related comorbidities may play a role in skeletal fragility<sup>11</sup>. Another key discovery was that more patients with severe NPDR/PDR had fragility fractures. Despite the higher (albeit not significant) fracture hazard in this group, the large confidence intervals mean the results should be interpreted with caution<sup>12</sup>. However, risk of fracture is not only related to BMD, visual impairment, peripheral neuropathy, impaired balance, previous falls, and reduced bone quality all play a role in fracture susceptibility in T2DM. Schwartz et al. showed that at similar BMD values, people with T2DM had a higher risk for fracture compared to non-diabetics<sup>1</sup>. Forner and Sheu added that traditional densitometry could be failing to properly reflect diabetic fragility due to the fact that BMD alone is not sufficient to fully capture the changes in bone microarchitecture and strength that occur in the disease state<sup>2</sup>. Based on these observations, we can create a clinical model to understand the increased risk of fracture seen in our participants with advanced retinopathy<sup>13</sup>. Remarkably, for the most part, the associations between BMD remained significant after adjusting for age, sex, BMI, diabetes duration, glycemic control, and renal function, suggesting that severity of retinopathy could be a marker of a component of skeletal vulnerability that is not fully accounted for by these traditional risk factors<sup>14</sup>. However, there is potential for residual confounding, for example, due to differences in physical activity, nutritional status, vitamin D concentrations, medication use and bone turnover rates. Further, visual impairment and neuropathy can lead to fracture risk indirectly, by increasing risk of falling. Larger prospective trials, with more fine-grained functional and advanced skeletal imaging, are needed to distinguish these mechanisms<sup>15</sup>.

The clinical implications of these findings relate to the potential usefulness of integrated

assessment of complications in T2DM. Advanced retinopathy may provide a reason for thorough examination of known osteoporosis risk factors, prior fracture history, risk for falling, and indications for DXA assessment<sup>16</sup>. Adding trabecular bone score and diabetes-specific data into fracture risk assessment may offer additional information other than the conventional BMD measurements. The current results, however, do not provide sufficient evidence to regard retinopathy severity as an independent fracture predictor, and retinal grading should not supplant established fracture risk assessment methods<sup>17</sup>.

The main strengths of the study are the multicenter design, the diabetes retinopathy classification, the measurement of BMD in several skeletal sites, the adjustment for the relevant confounding factors, and the prospective recording of incident fragility fracture<sup>18</sup>. However, a few points to consider are the following limitations. The relatively small sample size and short follow-up period (12 months) limited the number of fractures observed and the precision of the estimates of time to event. Additionally, the small number of events did not allow for robust multivariable fracture modeling. Moreover, bone microarchitecture, bone turnover markers and some potential determinants of bone health were not fully evaluated<sup>19</sup>. A limitation of the observational design is that causal inferences cannot be made, and recruitment from selected clinical institutions might limit generalizability. Larger, prospective studies with longer follow-up are thus justified to find out if retinopathy severity is an independent predictor of fracture and if it adds to the predictive power of current clinical and densitometric measures<sup>20</sup>.

## CONCLUSION

Among adult type 2 diabetes mellitus patients, severity of DR was significantly associated with lower BMD at the femoral neck, total hip, and lumbar spine, after controlling for major demographic, metabolic, and renal factors. A higher observed number of fragility fractures was associated with advanced retinopathy, but this association was not statistically significant. These results suggest that the severity of DR may be used as an indicator of bone vulnerability and that a thorough bone health evaluation should be performed in patients with advanced DR.

**Funding:** This research received no external funding.

**Conflict of Interest:** The authors declare no conflicts of interest.

**Authors' Contributions:** FKC, WB, HSN, SN, HMU, and AUH contributed to the research and manuscript preparation. All authors reviewed and approved the final manuscript.

**Acknowledgments:** The authors acknowledge the cooperation and support of the participating institutions, healthcare professionals, and study participants.

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