# Ischemic heart disease is associated with vertebral fractures in patients with type 2 diabetes mellitus

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## ABSTRACT

**Aims/Introduction:** Discordant results about the relationship between diabetes complications and the risk of fragility fractures have been reported. Our aims were to analyze the factors related to morphometric vertebral fractures (VFs) in patients with type 2 diabetes mellitus, and to explore the association between the presence of VFs and the main cardiovascular risk factors.

**Materials and Methods:** We carried out a cross-sectional study including 123 patients with type 2 diabetes mellitus, and in 72 of these patients we recorded data about the risk factors for VFs and comorbidities of diabetes including diabetes-related microvascular disease and cardiovascular disease.

**Results:** In the crude analysis, diabetic retinopathy (odds ratio [OR] 4.09, 95% confidence interval [CI] 1.01–12.5), ischemic heart disease (OR 5.02, 95% CI 1.1–9.7) and waist circumference (OR 1.06, 95% CI 1.006–1.114) were related to VFs. In the full model (adjusted for age, sex, body mass index), ischemic heart disease was the only determinant of VF (OR 3.33, CI 1.02–10.91, $P = 0.047$); whereas diabetic retinopathy did not reached significance (OR 2.27, CI 0.71–7.27, $P = 0.16$).

**Conclusions:** In summary, ischemic heart disease is associated with an increased risk of VFs in type 2 diabetes mellitus. (J Diabetes Invest, doi: 10.1111/jdi.12034, 2013)

**KEY WORDS: Ischemic heart disease, Type 2 diabetes mellitus, Vertebral fractures**

## INTRODUCTION

Diabetes mellitus and osteoporotic fractures are major causes of morbidity and mortality worldwide. Recent studies have shown that type 1 and type 2 diabetes mellitus are associated with an increased risk of hip fractures and other non-vertebral fractures[1]. In type 2 diabetes mellitus, fracture risk is known to increase approximately 1.5-fold at the hip, proximal humerus and forearm[2,3]. However, the data on VFs in type 2 diabetes mellitus are not uniform[4]. Discrepancies between studies might be due to the fact that most of VFs are asymptomatic and difficult to identify in routine clinical practice. Thus, most of the studies, but not all, have been made considering clinical fractures[4]. Furthermore, discordant results about the relationship between diabetes complications and risk of fragility fractures have also been reported[4,5].

The mechanisms whereby diabetes increases fracture risk include impaired bone quality and diabetes-related comorbidity, such retinopathy and peripheral neuropathy, which might increase the risk of falling. They include impaired bone quality and diabetes-related comorbidity, such retinopathy and peripheral neuropathy, which might increase the risk of falling. There are several factors that could explain poor bone quality in diabetes. Hyperglycemia leads to non-enzymatic glycosylation of bone proteins, such as type I collagen, which impairs bone quality. The accumulation of AGEs in bone has been associated with deterioration of biomechanical properties[6], and the concentrations of pentosidine, a well-known AGE, in bone are negatively associated with bone strength[6] and hip fractures[7]. Serum pentosidine levels have also been described to be positively associated with VFs in type 2 diabetes mellitus women independent of BMD[5], and esRAGE levels were related to VFs in type 2 diabetes mellitus in both sexes[8]. Another potential factor could be the effects on cytokine and adipokine levels as a result of obesity and higher visceral fat. There are several results that confirm the effects of cytokines and adipokines in bone. Inflammatory cytokines levels are elevated in obesity and stimulate osteoclastic activity[9]. Adipokine levels have been shown not only to modulate BMD and risk of fracture[10], but also to display several adverse effects on the cardiovascular system[11]. Thiazolidinedione treatment has also been linked to low bone mass and fractures[12]. Finally, several studies have shown an increased risk of falls as a result of visual impairment, neuropa-

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thy and foot problems[13]. Falls are a well-established risk factor for hip fractures in older people, but their role in VFs and younger people are less clear[14].

The aim of the present study was to analyze the factors related to morphometric VFs in patients with type 2 diabetes mellitus. To address this issue, the relationship between the classic risk factors of VFs and the observed prevalent VFs were determined. Likewise, the association between the presence of VFs and the main cardiovascular disorders linked to type 2 diabetes mellitus was analyzed.

## METHODS

### Study Participants

The present cross-sectional study included 123 patients with type 2 diabetes mellitus (mean age 55 ± 7 years), with the diagnosis of diabetes according to the American Diabetes Association criteria (2003). From January 2006 to December 2007, we consecutively recruited patients who had been referred to outpatient endocrinology at the University Hospital San Cecilio (Granada, Spain) from community clinics for treatment of diabetes. A total of 51 patients were excluded from analysis because of lack of data (good-quality spine radiographs, ophthalmological evaluation and dual energy X-ray absorptiometry), renal or hepatic dysfunction and thiazolidinedione treatment. All patients were Caucasian, ambulatory, had normal values of serum calcium and phosphorus, and had neither renal, hepatic, gastrointestinal or thyroid diseases nor other secondary causes for low BMD. All patients were on medication for diabetes, including metformin, sulfonylureas, insulin or a combination of these drugs. None of the patients had been treated with calcium supplements, vitamin D preparations, hormone therapy, antiresorptive therapy, thiazides, steroids or other medications that might affect bone mass.

Detailed medical histories were carried out in order to identify classic risk factors of VFs (age, sex, BMD, previous fragility fracture, smoking and BMI). We also recorded data about the comorbidities including: hypertension, hyperlipidemia, diabetes duration, diabetes-related microvascular disease (retinopathy, nephropathy and neuropathy) and cardiovascular disease (cerebrovascular disease, peripheral arterial disease and ischemic heart disease). We defined ischemic heart disease as: previous myocardial infarction, diagnosed stable or unstable angina, or coronary revascularization surgery assessed in the medical history.

The study was carried out with the approval of the ethical committee of the San Cecilio University Hospital, and conformed to the relevant ethical guidelines for human and animal research. Written informed consent was obtained from all participants.

### BMD Measurements and Spine Radiographs

DXA was carried out in all patients at LS (L2–L4) and femoral regions (FN and TH). BMD was determined by DXA (Hologic QDR 4500; Hologic, Whatman, MA, USA; variation coefficient <1%). We used the World Health Organization criteria for osteopenia and osteoporosis.

The presence of prevalent VFs was evaluated in lateral-view conventional X-rays of the thoracic and lumbar spine (T4–L5). The anterior, central and posterior heights of each vertebral body were measured. A vertebral fracture was diagnosed if at least one of three height measurements along the length of the same vertebrae had decreased by >20% compared with the nearest uncompressed vertebral body. Traumatic VFs were excluded by medical history. The severity of vertebral deformities was graded according to Genant's criteria as follows: mild, a reduction of 20–25%; moderate, a reduction of 25–40%; severe, a reduction of more than 40%. Only moderate and severe fractures were considered for analysis. Two independent investigators who were blinded to each other's readings analyzed the radiographs. The kappa statistic was used to adjust rates of simple agreement for chance. We used the definitions of Landis and Koch[15] to describe agreement: $\kappa$ = 0–0.20, slight; $\kappa$ = 0.21–0.40, fair; $\kappa$ = 0.41–0.60, moderate; $\kappa$ = 0.61–0.80, substantial; and $\kappa$ = 0.81–1.0, almost perfect. Simple agreement was 89% among reviewers, and kappa values were perfect (0.81–1).

### Other Parameters

Height, weight and waist circumference were measured at baseline according to standard procedures. Weight was measured to the nearest 100 g using digital electronic scales. Height and waist circumference were measured to the nearest 1 mm using a stadiometer and a metal anthropometric tape, respectively. BMI in kg/m$^2$ was calculated as weight divided by the square of height in meters. Serum total, HDL and LDL cholesterol, and TGs were measured at baseline. Dyslipemia was defined as follows: LDL ≥130 mg/dL, TGs ≥150 mg/dL, HDL <40 mg/dL in women and <50 mg/dL in men, or current treatment with statins.

Blood pressure was measured in a standardized manner. After participants sat quietly for at least 5 min, blood pressure was measured twice using a standard mercury sphygmomanometer (12 cm long, 35 cm wide). The mean of the two values was used for analysis. We defined hypertension values as ≥140/90 mmHg and/or antihypertensive treatment.

All participants were referred to an ophthalmologist for evaluation of the presence of diabetic retinopathy. Briefly, a comprehensive dilated fundus examination to detect diabetic retinopathy by indirect ophthalmoscopy was carried out. Diabetic retinopathy was clinically graded in accordance with the International Clinical Diabetic Retinopathy guidelines. For statistical analysis, patients were categorized as with or without retinopathy. Criteria for diagnosis of diabetic neuropathy were a positive electrodiagnostic study or a DNS score ≥ 1. Diabetic nephropathy was diagnosed if albuminuria excretion was persistently above 30 mg/day.

### Statistical Analysis

Data were recorded and analyzed with SPSS version 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics, including means, frequencies and percentages, were used to describe the study population and examine differences between groups. Data were expressed as mean ± SD. A *P*-value <0.05 was considered to be significant. Mean values in groups were compared by parametric statistics or non-parametric statistics depending on the distribution of the variable of interest. Pearson's standard linear regression analysis (normal distribution) or Spearman's test (non-normal distribution) were used for correlation studies. The association among qualitative variables was realized by means of the $\chi^2$-test. Logistic regression analysis was carried out in type 2 diabetes mellitus patients to establish the key determinants of VFs.

## RESULTS

The clinical characteristics for the study group are shown in Table 1. Prevalent VFs were detected in 20 of 72 patients (27.8%; 95% CI 17.8–37.6).

When we compared patients with and without VFs (Table 2), diabetic retinopathy and ischemic heart disease were more prevalent in patients with VFs (retinopathy 65 % vs 38.5%, $\chi^2 = 4.09$, $P = 0.043$; ischemic heart disease 55% vs 26.9%, $\chi^2 = 5.02$, $P = 0.025$). Furthermore, patients with VFs had higher waist circumference (VFs 110.8 ± 11.76 cm vs no VFs 103.9± 11.18 cm, $P = 0.024$).

No significant differences were observed between the other analyzed parameters and the presence of VFs (age, sex, BMD, previous fragility fracture, falls, smoking, BMI, arterial hypertension, dyslipidemia, microalbuminuria). The percentage of patients treated with statins, insulin or oral hypoglycaemic drugs in patients with or without VFs showed no difference. No relationship was observed between the presence of diabetic

**Table 1** | Characteristics of study participants

| No. participants | 72 | Range |
|---|---|---|
| Age (years) | 57.8 ± 6.4 | 35–65 |
| Males/females | 38/34 | |
| Weight (kg) | 81.8 ± 15.8 | 50.2–144 |
| Height (m) | 1.61 ± 0.08 | 1.62–1.78 |
| BMI | 31.2 ± 5.6 | 19.1–54.9 |
| BMD LS (g/cm$^2$) | | |
| All | 0.95 ± 0.14 | 0.59–1.30 |
| Women | 0.93 ± 0.15 | 0.67–1.25 |
| Men | 0.96 ± 0.13 | 0.59–1.30 |
| T score LS | −1.33 ± 1.30 | −4.8–1.7 |
| BMD FN (g/cm2) | 0.81 ± 0.12 | 0.55–1.16 |
| T score FN | −0.59 ± 1.00 | −2.7–2.8 |
| BMD TH (g/cm2) | 0.90 ± 0.14 | 0.57–1.25 |
| T score TH | −0.60 ± 0.99 | −3.1–1.4 |
| Osteoporosis criteria | 15 (20.8%) | |
| Vertebral fractures | | |
| All | 20 (27.8%) | |
| Males/Females | 14/6 | |

Data expressed as *n*, *n* (%) or mean ± standard deviation. BMD, bone mineral density; BMI, body mass index; FN, femoral neck; LS, lumbar spine; TH, total hip.

**Table 2** | Clinical characteristics in type 2 diabetes mellitus with and without vertebral fractures

| | VFs | No VFs | *P* |
|---|---|---|---|
| No. participants | 20 | 52 | |
| Age (years) | 59.2 ± 5.4 | 58.2 ± 6.8 | $P = 0.17$ |
| Men (%) | 36.8 | 63.2 | $\chi^2 = 2\ 3.24$; $P = 0.69$ |
| Women (%) | 17.6 | 82.4 | $\chi^2 = 2.04$; $P = 0.121$ |
| BMI | 32.1 ± 4.4 | 30.9 ± 6.1 | $P = 0.41$ |
| $HbA_{1c}$ | 7.6 ± 1.3 | 8.2 ± 1.9 | $P = 0.28$ |
| Duration of diabetes | 14.2 ± 6.9 | 13.7 ± 7.7 | $P = 0.79$ |
| BMD LS (g/cm$^2$) | 0.96 ± 0.15 | 0.95 ± 0.13 | $P = 0.94$ |
| BMD FN (g/cm$^2$) | 0.89 ± 0.14 | 0.91 ± 0.19 | $P = 0.37$ |
| Falls (%) | 5 | 7.7 | $\chi^2 = 0.162$; $P = 0.69$ |
| Previous fracture(%) | 5 | 9.6 | $\chi^2 = 0.40$; $P = 0.53$ |
| Dyslipemia (%) | 19 (95) | 47 (90.4) | $\chi^2 = 0.34$; $P =$ p 0.55 |
| Insulin, *n* (%) | 15 (75) | 31 (60.8) | $\chi^2 = 1.27$; $P = 0.26$ |
| Metformin, *n* (%) | 9 (45) | 21 (41.2) | $\chi^2 = 1.18$; $P = 0.77$ |
| SUs, *n* (%) | 1 (5) | 7 (13.7) | $\chi^2 = 0.48$; $P = 0.82$ |
| Metformin + SUs, *n* (%) | 5 (25) | 12 (23.5) | $\chi^2 = 0.38$; $P = 0.56$ |
| Statins, *n* (%) | 14 (70) | 34 (66.7) | $\chi^2 = 0.07$; $P = 0.79$ |
| Retinopathy, *n* (%) | 13 (65) | 20 (38.5) | $\chi^2 = 4.09$; $*P = 0.043$ |
| Ischemic heart disease, *n* (%) | 11 (55) | 14 (26.9) | $\chi^2 = 5.02$; $*P = 0.025$ |
| Neuropathy, *n* (%) | 13 (65) | 25 (48) | $\chi^2 = 2.31$; $P = 0.13$ |
| Nephropathy, *n* (%) | 9 (45) | 15 (28.9) | $\chi^2 = 2.13$; $P = 0.14$ |
| Cerebrovascular disease, *n* (%) | 5 (25) | 11 (15.3) | $\chi^2 = 0.23$; $P = 0.89$ |
| Peripheral artery disease, *n* (%) | 2 (10) | 7 (9.7) | $\chi^2 = 0.16$; $P = 0.69$ |
| Abdominal circumference (cm) | 110.8 ± 11.8 | 103.9 ± 11.2 | $*P = 0.024$ |

Data expressed as *n*, *n* (%) or mean ± standard deviation. Unpaired *t*-test, Comparisons of categorical variables were made using $\chi^2$- test, BMD, bone mineral density; BMI, body mass index, $HbA_{1c}$, glycated hemoglobin; FN, femoral neck; LS, lumbar spine; SUs, sulfonylureas; TH, total hip, VFs, vertebral fractures. $*P < 0.05$.

**Table 3** | Associations between retinopathy, coronary heart disease, waist circumference and vertebral fractures

| | OR | 95% CI | *P*-value |
|---|---|---|---|
| Retinopathy | | | |
| Crude | 4.09 | (1.01–12.5) | 0.043 |
| Adjusted for age and sex | 2.97 | (1.01–8.7) | 0.047 |
| Full model | 2.27 | (0.71–7.27) | $P = 0.16$ |
| Ischemic heart disease | | | |
| Crude | 5.02 | (1.1–9.7) | 0.025 |
| Adjusted for age and sex | 3.31 | (1.13–9.7) | 0.029 |
| Full model | 3.33 | (1.02–10.91) | 0.047 |
| Waist circumference | | | |
| Crude | 1.058 | 1.006–1.114 | 0.029 |
| Adjusted for age and sex | 1.052 | 0.997–1.11 | 0.66 |
| Full model | 1.063 | 0.967–1.169 | 0.20 |

Full model: adjusted for age, sex, retinopathy, ischemic heart disease and body mass index.

neuropathy, cerebrovascular disease or peripheral arterial disease and the presence of VFs.

Logistic regression analysis was carried out in type 2 diabetes mellitus to establish the key determinants of VFs (Table 3). In the crude analysis, diabetic retinopathy (OR 4.09, 95% CI 1.01–12.5), ischemic heart disease (OR 5.02, 95% CI 1.1–9.7) and waist circumference (OR 1.06, 95% CI 1.006–1.114) were related to VFs. After adjustment for age and sex, diabetic retinopathy (OR 2.97, 95% CI 1.01–8.7) and ischemic heart disease (OR 3.33, 95% CI 1.13-9.7) remained significantly related to the presence of VFs, but not waist circumference (OR 1.052, 95% CI 0.997–1.11; $P = 0.66$). In the full model, ischemic heart disease was the only determinant of vertebral fracture after adjustment for age, sex and other factors (OR 3.33, 95% CI 1.02–10.91, $P = 0.047$), whereas diabetic retinopathy did not reach significance (OR 2.27, 95% CI 0.71–7.27, $P = 0.16$; Table 3). However, ischemic heart disease as a predictor of VFs lost statistical significance when waist circumference was included in the analysis instead of BMI.

## DISCUSSION

The present data suggest that in type 2 diabetes mellitus patients, morphometric VFs are associated with ischemic heart disease, diabetic retinopathy and abdominal circumference; although after adjustment for age, sex and BMI, only ischemic heart disease remained as an independent factor. Furthermore, when abdominal circumference was included in the model, the relationship between ischemic heart disease and VFs disappeared.

Other diabetes-related factors, such as diabetes duration, glycated hemoglobin levels or type of antidiabetic drugs, were not related to the presence of VFs. There have been reported discordant results regarding diabetes treatment and fractures. Insulin treatment has been associated with higher fracture risk in some[16,17], but not all studies[18,19], mainly in relation to the higher risk of hypoglycemia and falls. Furthermore, data evidence of metformin and fracture risk is also conflicting[17,19]. The present results are in accordance with those previous studies showing no difference in fracture risk according to diabetes treatment. However, typical risk factors for VFs (age, sex, BMD, previous fragility fracture, falls, smoking, BMI) were not predictive of higher fracture risk in this group of patients.

There are scarce data about the relationship between diabetic-specific complications and fracture risk. Previous studies have shown no differences in diabetic retinopathy and nephropathy according to presence or absence of VFs[8,20,21]. Other authors reported an increased risk of fracture in diabetic patients with retinopathy[22]. In the present study, prevalent VFs were significantly related to the presence of diabetic retinopathy. This association did not persist after multivariate analysis, possibly influenced by sample size. Another possibility is that ischemic heart disease could reflect the presence of microvascular damage, including retinopathy. The presence of diabetic retinopathy might indicate severe diabetic microvascular disease that causes a decrease in blood flow to the bone, and impaired bone quality and strength, raising the risk of fracture. No relationship was observed with nephropathy and neuropathy, which coincides with previous results[8,20]. Neuropathy has been linked to fractures because of an increase in foot problems and falls[23]. Maybe in our population, which was relatively young and with no increase of falls, those factors were not relevant in the risk of VFs.

The data show that prevalent VFs are significantly related to the presence of ischemic heart disease. To our knowledge, this is the first time that the association between ischemic heart disease and VFs in type 2 diabetes mellitus has been reported. Atherosclerotic vascular disease is significantly more prevalent in patients with osteoporosis[24], and several common pathophysiological pathways have been suggested. Cardiovascular diseases have been described as a risk factor for hip fracture both in women and men in most[25], but not all studies[26], and ischemic heart disease has been described as a risk factor for hip fracture[25]. Of interest, there was no association between cerebrovascular disease or peripheral artery disease and VFs, although the low number of patients with those diseases might have influenced the results.

In the present study, waist circumference was significantly greater in type 2 diabetes mellitus patients with VFs compared with type 2 diabetes mellitus patients without VFs. To our knowledge, no data have been published about the role of waist circumference as a risk factor for VFs in Western type 2 diabetes mellitus patients. There is growing evidence of the relationship between fat mass and bone, and recent reports suggest that specific fat compartments (subcutaneous vs visceral fat) also differ in their impact on bone[26]. The evidence regarding the association between visceral fat and BMD is mixed[27–29]. In patients with diabetes and metabolic syndrome, waist circumference showed a positive association with higher BMD at all

sites in both sexes[30]. However, the relationship between visceral adiposity and fracture incidence has shown conflicting results. Waist-to-hip ratio has been described as being positively related to fracture incidence in non-diabetic males[31]. However, Yamaguchi *et al.* recently reported that visceral fat was inversely associated with the presence of VFs in type 2 diabetes mellitus Japanese men, but not in women[30]. We found that waist circumference was significantly greater in type 2 diabetes mellitus patients with VFs compared with type 2 diabetes mellitus patients without VFs. The degree of obesity in Asians is known to be different from those in Caucasians, which can explain in part our different results.

Waist circumference is a component of metabolic syndrome and an accessible measure of visceral fat. Increased secretion of cytokines from visceral fat might alter bone quality[9]. An association between adipokine levels and cardiovascular disease has also been described, so increased secretion of cytokines and adipokines from visceral fat could explain in part the relationship between atherosclerosis and osteoporosis. In addition, the relationship between ischemic heart disease, abdominal circumference and VFs in the present study could indicate that visceral obesity had negative effects not only in the heart, but also on bone.

The present study had some limitations. First, the sample was not large enough to make definite conclusions. Second, we only analyzed patients who were referred to San Cecilio University Hospital for the evaluation and treatment of diabetes. Therefore, the patients enrolled in the study might have relatively more severe diabetes and might not be representative of the entire population of diabetic patients, but this fact allowed us to study type 2 diabetes mellitus patients with a higher prevalence of micro- and macrovascular diabetes-related complications. Consequently, assessment of larger numbers of patients is necessary to determine the usefulness of retinopathy and ischemic heart disease for predicting the risk of VFs in the entire population of type 2 diabetes mellitus patients. Although the antecedent of fall was recorded in the medical history, detailed data on the risk of falls were not recorded, but the role of falls in VF risk in younger people is not well established. One strength of the present study was the radiographic evaluation for the presence of VFs in all patients, which reduced the possibility that subclinical VFs were missed.

In summary, the present study showed that VFs in type 2 diabetes mellitus patients are significantly associated with the presence of ischemic heart disease, diabetic retinopathy and abdominal circumference. The strongest relationship was observed between ischemic heart disease and VFs. The classic risk factors for VFs were not predictive of higher fracture risk in this group of patients. Visceral obesity and its implications could be a common link between osteoporosis and atherosclerosis. Future prospective studies are required to clarify the role of vascular complications in the assessment of fracture risk in type 2 diabetes mellitus patients.

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