Self-reported low-energy fractures and associated risk factors in people with diabetes: A national population-based study

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ABSTRACT

Aims: Clinical risk factors and bone mineral densitometry underestimate low-energy fracture (LEF) risk in people with diabetes. We aim to estimate the prevalence of LEF in diabetics, compare with nondiabetics; and evaluate possible predictors of LEF in people with diabetes.

Methods: Cross-sectional, population-based study in Portuguese subjects over 40 years-old. Estimates computed as weighted proportions/means, considering sample design. Multivariate logistic regression models to evaluate the association of diabetes and LEF; and predictors of LEF in diabetics.

Results: 7675 subjects were analysed, of which 1173 reported diabetes. Diabetics were older (mean age 66.0 ± 11.49y), more frequently reported osteoporosis and falls in the previous 12 months (32.4% vs. 22.9%). Prevalence of self-reported LEF was 16.2% (95% CI:13.68–19.13) among diabetics (vs. 13.3%, 95% CI:12.14–14.57, in nondiabetics); OR for the association diabetes and LEF:1.26, 95% CI:1.01–1.58, p = 0.045 (in women, adjusted OR:1.41, 95% CI:1.05–1.89, p = 0.02). Thirty percent of diabetics reported at least one major LEF and 70% in other sites. In diabetics, LEF was independently associated with self-reported osteoporosis and falls in the previous 12 months.

Conclusion: People with diabetes reported more falls and had higher prevalence of self-reported LEF. Self-reported osteoporosis and falls were associated with LEF in diabetics. Our findings emphasize the need for fracture and falls preventive measures in diabetics.

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1. Introduction

Diabetes mellitus is an increasingly prevalent disease, which can reach 15% of the population in some regions worldwide [1,2]. Besides the well-known micro- and macrovascular complications [2], people with diabetes can also have skeletal disorders including low-energy fractures (LEF). Both Type 1 (T1DM) and Type 2 diabetes (T2DM) have been associated with

increased risk of LEF [3,4]. LEF are those occurring from a fall from a standing height or less, without major trauma [5]. There were an estimated nine million osteoporotic fractures worldwide in 2000 and they were more prevalent in Europe. All fractures – hip, vertebral, non-vertebral - are associated with significant morbidity [6] and increase in health care costs since they may result in hospitalization, loss of independence, depression, chronic pain and ultimately death [7,8].

Fractures are relatively common in older adults [9]. As the population ages and the prevalence of diabetes increases, it is expected that the occurrence of fractures will increase. The identification of those at risk for early fracture-preventive interventions is imperative.

In clinical practice, bone mineral densitometry (BMD) levels at osteoporotic thresholds and fragility fracture risk assessment tools such as the World Health Organization Fracture Risk Assessment Tool (FRAX) are used to decide when to initiate fracture preventive treatment (i.e., bisphosphonates, raloxifene, calcium supplements). However, these tools underestimate the risk of fracture in people with diabetes [10,11]. Specifically, T2DM has been associated with higher risk of LEF despite normal to increased BMD levels [12]. The reason for this discordant increase is not entirely clear. T2DM may affect bone turnover and result in decreased bone remodelling with normal or even increased BMD, but low bone quality. Moreover, complications of T2DM including retinopathy, neuropathy and autonomic dysfunction may contribute to bone fracture by increasing the risk of falls [13,14]. In T1DM, the vast majority of studies indicate a decline in BMD, especially at the hip, compared to individuals without diabetes. Regarding fracture risk, many studies to date have shown an increased risk of fracture in T1DM that is not fully predicted by the BMD level. Studies in rats suggest that alterations in both the mechanical and intrinsic bone properties may explain these differences [15,12].

This article presents a population-based study on the risk of LEF in patients with diabetes. Fractures are associated with low quality of life and increased health care costs. Understanding the public health burden of LEF will create awareness among clinicians and health policy makers to address this matter. Moreover, it is important to understand the distribution pattern of low energy fractures in people with diabetes and their impact at the population level, as well as to study their causes and predictive factors to adjust preventive measures. Our aim is to describe the frequency of LEF in the Portuguese population with diabetes, compared to those without diabetes, and evaluate risk factors associated with LEF in the subpopulation with diabetes.

2.   Subjects, materials and methods

We conducted a national, cross-sectional and population-based study. EpiReumaPt is a national health survey that was designed to study the prevalence of rheumatologic diseases in Portugal. It consists of a total of 10 661 adults over 18 years-old who at time of recruitment were noninstitutionalized and living in private households in the Mainland and the Islands (Azores and Madeira). Exclusion criteria were: residents in hospitals, nursing homes and military institutions or prisons, and individuals unable to speak Portuguese or unable to complete the questionnaires [16]. Participants were selected through a process of multistage random sampling and the sample was stratified according to the Portuguese Nomenclature of Territorial Units for Statistics (NUTS II, seven territorial units) and the size of the population. It is representative of the Portuguese population and the study protocol as well as its methodological details have been previously published [16,17]. Our study population was composed of a subset of this cohort consisting of adults over 40 years of age. Sociodemographic and clinical data were collected between September 2011 and December 2013, by face-to-face interviews.

2.1.   Variables definitions

The outcome variable was defined as the proportion of participants who reported at least one LEF (based on a positive response to "did you ever suffer a fracture from minimal trauma, for instance a fall on the street or at home, a fall from your height?"), overall and specified by site of fracture. Diabetes mellitus status was defined by self-report (based on a positive response to "did any doctor tell you that you suffer from Diabetes?"). The following variables were also collected by patient self-report: gender; sociodemographic and anthropometric data; presence of comorbid conditions (cardiovascular, gastrointestinal, neurologic, psychiatric, oncologic, thyroid/parathyroid and rheumatologic), osteoporosis, rheumatoid arthritis; use of corticosteroids (defined as a positive response to "in the previous year, did you take corticosteroids for more than 3 months, in a dose equal or higher than 5 mg of prednisolone/equivalent per day?"); parental history of hip fracture; current cigarette smoking (yes/no), alcoholic habits (daily/occasionally/never in descriptive analysis and yes/no in regression models) and regular practice of exercise (yes/no). Body Mass Index (BMI), in kg/m^2, was calculated as weight (in kg) divided by height (in m) squared. BMI was described by group according to the Centers for Disease Control and Prevention criteria, but used as a continuous variable in regression models. We used the self-reported occurrence of falls in the previous 12 months (yes/no) as a proxy of a pattern of recurrent falls [18].

2.2.   Statistical analysis

In descriptive analysis, continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as count/percentages. All estimates were computed as weighted proportions/means, taking sampling design into account. Statistical analysis was also done considering sample design.

First of all, we performed a descriptive analysis of the Portuguese population over 40 years-old and compared subjects with diabetes and subjects without diabetes regarding sociodemographic and clinical variables, using univariate analysis and Chi2 test.

Secondly, we estimated the prevalence of LEF in each subgroup (people with and without diabetes) and then performed multivariate logistic regression to predict the risk of LEF in subjects with diabetes.

Thirdly, we performed a subpopulation analysis of Portuguese people over 40 years-old with diabetes who have information on the LEF status. We used descriptive analysis to describe this subpopulation regarding the distribution of LEF by age and sex and the site of LEF by age group. Continuing with analysing only the subpopulation of subjects with diabetes and LEF information, we used univariate analysis to compare sociodemographic and clinical variables between subjects with and without LEF. We then performed logistic stepwise regression models with forward elimination to assess predictors of LEF risk in this subgroup. Covariates had <10% of missing values and the outcome variable (LEF) <5% (2.56%), thus the analysis was done using complete case analysis. Significance level was set at 0.05. All analysis was performed using STATA IC V 14.2 (StataCorp. 2015).

2.3. Ethical issues

EpiReumaPt was performed according to the principles of the Declaration of Helsinki and approved by the National Committee for Data Protection and by the NOVA Medical School Ethics Committee. All participants provided informed consent [16].

3. Results

A total of 7675 subjects over 40 years-old from the EpiReumaPT national survey were analysed (Fig. 1). Mean age was 59.4 ± 12.49 years-old and fourteen percent (13.9%, 95% Confidence Interval (CI): 12.69–15.17) reported having diabetes.

3.1. Sociodemographic and clinical characteristics of subjects over 40 years-old with and without diabetes

Subjects with diabetes (n = 1173) were older than those without diabetes (mean age was 66.0 ± 11.49 vs. 58.2 ± 12.28 years-old, p < 0.001), with 69.5% being 60 years-old or older. Fifty-six percent were female. They reported a higher burden of

cardiovascular risk factors and 81.4% were overweight or obese (vs. 61.3% in the nondiabetic, p < 0.001). They were more likely to report osteoporosis (20.4% vs. 15.4%, p = 0.007) or a rheumatologic disorder (48.4% vs. 32.7%, p < 0.001). Alcohol consumption was high, but lower than in nondiabetic (51.8% vs. 61.3%, p = 0.001). One third (32.4%) reported at least one fall in the previous 12 months (vs. 22.9% in people without diabetes, p < 0.001). Table 1 shows the sociodemographic and clinical characteristics of the Portuguese population over 40 years-old, with and without diabetes.

3.2. Prevalence of self-reported low-energy fractures in subjects with diabetes compared to subjects without diabetes

Of the 1173 subjects with diabetes, we had LEF information of 1143 subjects. Using the weighted estimation of prevalence according to study design, the estimated prevalence of self-reported LEF among the subjects with diabetes was 16.2% (95% CI: 13.68–19.13, n = 203), compared to 13.3% (95% CI: 12.14–14.57, n = 931) in those without diabetes (p = 0.045). We found a positive association between self-reported diabetes and LEF (crude OR: 1.26, 95% CI: 1.01–1.58, p = 0.045; in women, adjusted OR controlling for age, NUTS II and regular exercise: 1.41, 95% CI: 1.05–1.89, p = 0.02; in men, adjusted OR: 0.86, 95% CI: 0.57–1.31, p = 0.481; p-value for the interaction between diabetes and gender: 0.008).

3.3. Subpopulation analysis of subjects over 40 years-old with diabetes

3.3.1. Characterization of low-energy fractures in subjects over 40 years-old with diabetes, by age group, sex and fracture site

Analysing the subjects with diabetes with LEF information, self-reported LEF were more frequent in the southern regions of Portugal, compared to the Centre and North. A higher frequency of LEF was reported by women, overall and by age strata (Fig. 2). There seems to be a bimodal prevalence of
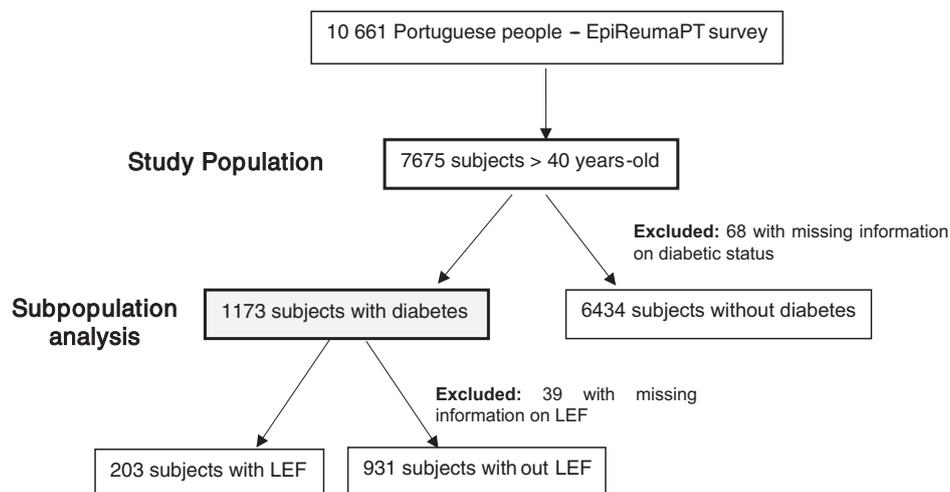
Abbreviations: LEF, Low-energy fracture.

Fig. 1 – Flowchart of the study population. Abbreviations: **LEF, Low-energy fracture.**

Table 1 – Sociodemographic and clinical data of the Portuguese population over 40 years-old and between those with and without diabetes.

	Total (n = 7675) n (%)	Diabetic (n = 1173) n (%)	Nondiabetic (n = 6434) n (%)	p-value
Age strata (years)				p < 0.001
41–49	1882 (30.2)	83 (9.7)	1793 (33.9)	
50–59	1851 (25.4)	222 (20.8)	1611 (25.7)	
60–69	1884 (23.1)	373 (35.0)	1495 (21.4)	
70–79	1500 (15.7)	371 (26.6)	1109 (14.0)	
≥80	558 (5.6)	124 (7.9)	426 (5.0)	
Sex				0.641
Female	4803 (54.5)	736 (55.8)	4023 (54.5)	
Male	7675 (45.5)	437 (44.2)	2411 (45.5)	
NUTS II region				0.283
North	2251 (33.5)	361 (35.0)	1868 (33.5)	
Centre	1515 (24.3)	239 (25.3)	1265 (24.4)	
Lisbon	1615 (26.0)	204 (22.2)	1400 (26.1)	
Alentejo	527 (8.0)	90 (9.5)	434 (7.8)	
Algarve	271 (3.9)	40 (3.3)	228 (4.0)	
Azores	693 (2.0)	121 (2.4)	562 (1.9)	
Madeira	803 (2.3)	118 (2.2)	677 (2.3)	
BMI group (kg/m^2)				<0.001
Underweight (<18.5)	67 (1.0)	4 (0.27)	62 (1.1)	
Normal weight (18.5–24.9)	2385 (34.7)	187 (18.3)	2178 (37.6)	
Overweight (25–29.9)	2974 (41.6)	446 (38.8)	2509 (41.6)	
Obesity (30–39.9)	1653 (21.4)	393 (39.6)	1241 (18.7)	
Morbid obesity (≥40)	101 (1.3)	35 (2.99)	65 (1.0)	
Comorbidities				
Hypertension	3224 (38.4)	784 (67.8)	2408 (33.5)	<0.001
High cholesterol	3089 (38.4)	694 (57.8)	2367 (35.2)	<0.001
Hyperuricemia	650 (8.5)	183 (18.1)	460 (7.0)	<0.001
Cardiac disorders	1275 (15.7)	352 (30.9)	909 (12.7)	<0.001
Gastrointestinal disorders	1649 (21.6)	306 (26.5)	1327 (21.0)	0.015
Neurologic disorders	381 (4.7)	98 (10.8)	280 (3.7)	<0.001
Psychiatric disorders	1357 (17.0)	256 (21.1)	1090 (16.4)	0.014
Cancer	409 (5.1)	76 (6.2)	330 (5.0)	0.266
Thyroid/parathyroid disorders	817 (9.1)	152 (11.0)	660 (8.9)	0.053
Rheumatologic disorders	2852 (35.2)	582 (48.4)	2241 (32.7)	<0.001
Osteoporosis	1397 (16.0)	236 (20.4)	1150 (15.4)	0.007
Fragility fracture risk factors and lifestyle habits				
Rheumatoid Arthritis	365 (4.1)	77 (6.8)	286 (3.8)	<0.001
Family history of FF	556 (8.2)	70 (7.3)	480 (8.3)	0.396
Corticosteroid treatment	171 (2.2)	24 (2.8)	144 (2.1)	0.334
Alcoholic habits (yes/no)				<0.001
Daily	1840 (29.6)	282 (28.3)	1540 (29.4)	
Occasionally	2318 (30.6)	247 (23.5)	2055 (31.9)	
Never	3503 (39.8)	640 (48.2)	2829 (38.7)	
Current smoking	1144 (18.4)	83 (8.7)	1051 (19.6)	<0.001
Regular exercise	2237 (30.4)	244 (22.5)	1979 (32.0)	<0.001
Falls in previous 12M (yes/no)	1905 (24.1)	364 (32.4)	1521 (22.9)	<0.001

The estimated percentages were obtained considering study design. Reported p-values are from univariate analysis. **Abbreviations:** BMI, body mass index; NUTS II, Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); FF, fragility fracture; M, months.

LEF with higher prevalence in the 40–49 years-old group and then increasing with age >60 years-old. The mean number of self-reported LEF was 1.8 ± 1.70 (95% CI: 1.34–2.21).

Ninety-three percent reported the site of fracture. LEF of the distal forearm was the most prevalent (13.9%, 95% CI: 9.26–20.28, n = 31), followed by hip (5.2%, 95% CI: 2.54–10.49, n = 10) and vertebral fractures (3.2%, 95% CI: 1.35–7.59, n = 8). Thirty percent (30.2%, 95% CI: 25.80–35.0) reported at

least one major LEF (hip, vertebral or distal forearm) and 70% (95% CI: 65.39–74.36) reported at least one LEF in other anatomical location (Table 2).

3.3.2. Risk factors associated with low-energy fractures in subjects over 40 years-old with diabetes

In the subpopulation with diabetes, subjects with self-reported LEF, compared to subjects without fractures, were
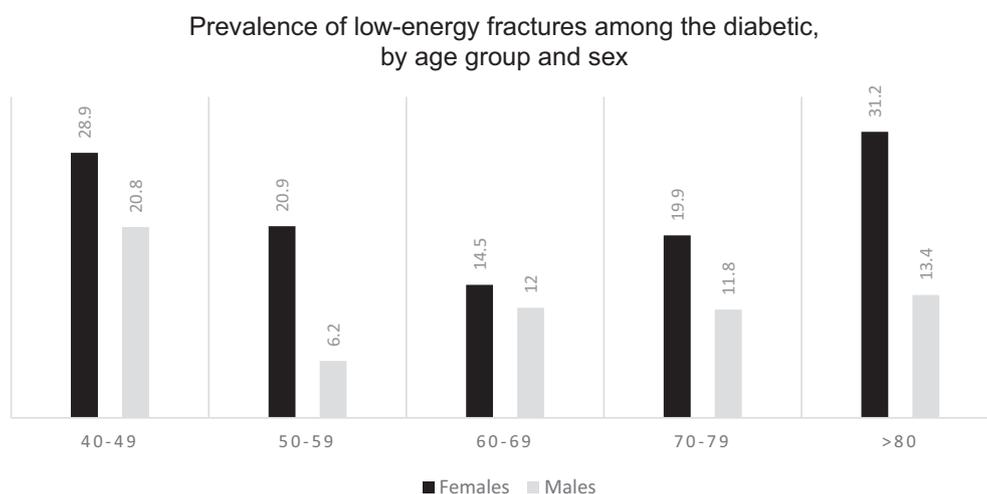
Fig. 2 – Prevalence of self-reported low-energy fractures in people over 40 years-old with diabetes, by age and sex. Estimated percentages were obtained taking study design into account. Total n in each age group: 40–49, n = 83; 50–59, n = 222; 60–69, n = 373; 70–79, n = 371; ≥80, n = 124.

Table 2 – Distribution of self-reported low-energy fractures in people over 40 years-old with diabetes, by age and site of fracture.

Age strata (years)	Hip n (%)	Distal forearm n (%)	Vertebral n (%)	Other n (%)
40–49 (n = 83)	1 (4.6)	4 (13.7)	0	14 (82.3)
50–59 (n = 222)	0	6 (18.6)	1 (2.8)	24 (72.1)
60–69 (n = 373)	3 (9.1)	9 (14.1)	0	44 (74.9)
70–79 (n = 371)	3 (3.7)	9 (10.5)	5 (6.8)	50 (78.8)
≥80 (n = 124)	3 (8.3)	3 (13.8)	2 (8.2)	21 (72.9)

more likely to report psychiatric disorders (28.3% vs 20%, p = 0.047), endocrine (thyroid/parathyroid) disorders (17.1% vs 10%, p = 0.011), osteoporosis (33.7% vs. 17.6%, p < 0.001) and the occurrence of at least one fall in the previous 12 months (44.5% vs. 29.9%, p = 0.004) (Table 3). In the subpopulation of subjects with diabetes, among the traditional clinical risk factors for fragility fractures (included in the FRAX score [19]), only female gender was found to be significantly associated with self-reported LEF (p = 0.005), but it did not remain statistically significant after adjusting for covariates (Table 4). The occurrence of falls in the previous 12 months was associated with a 72% increase in the odds of self-reported LEF, after adjusting for other variables, and self-reported osteoporosis was associated with an increase to the double in the odds of LEF (Table 4).

4. Discussion

In the Portuguese population over 40 years-old, the estimated prevalence of self-reported diabetes mellitus was 13.9% and the prevalence of self-reported osteoporosis was 16%, which is in agreement with previous national estimates [20,21]. Subjects with diabetes were older, had more comorbidities and reported falling more often than those without diabetes.

The prevalence of self-reported LEF was higher in people with diabetes, among which LEF were independently associated with self-reported osteoporosis and falls in the previous year.

The estimated prevalence of self-reported LEF was higher in subjects with diabetes, compared to those without (16.2% vs. 13.3%). There are multiple studies reporting the frequency of LEF in the overall at-risk population, regardless of their diabetic status [22–24]. For instance, in a French cohort of 671 postmenopausal women [23], followed for a median of 11.2 (IQR 1.1 years), the percentage of women with LEF at the end of the study was 20%. In a Canadian population-based cohort study [22] of 7689 participants 50 years-old or older followed for a mean of 14 years, 21.7% presented a LEF at the end of the study. However, most studies focusing specifically on patients with diabetes or the relation between diabetes and LEF report incidence rates, which impairs a comparison of our results with previous studies. There are two cross-sectional studies [25,26] on prevalent vertebral fractures but these were in hospital- or clinic-based cohorts and not population-based studies. Yet, there is extensive evidence of a positive and independent association between diabetes and overall fracture risk, with a greater effect in women, like in our study, but varying results by site of fracture [2–4,27].

Table 3 – Sociodemographic and clinical data of Portuguese people over 40 years-old with diabetes, with and without low-energy fractures.

	Low-energy fracture (n = 203)	No low-energy fracture (n = 931)	p-value
Age strata (years)			0.080
40–49 (n = 83)	17 (15.2)	66 (9.2)	
50–59 (n = 219)	33 (18.3)	186 (22.3)	
60–69 (n = 368)	57 (28.8)	311 (35.9)	
70–79 (n = 351)	67 (26.7)	284 (26.1)	
≥80 (n = 113)	29 (11.0)	84 (6.5)	
Sex			0.005
Female	152 (66.9)	555 (52.2)	
Male	51 (33.1)	376 (47.7)	
NUTS II Region			0.452
North	62 (35.0)	285 (35.7)	
Centre	33 (20.7)	190 (26.0)	
Lisbon	43 (22.4)	155 (20.8)	
Alentejo	21 (12.8)	68 (9.3)	
Algarve	9 (5.2)	31 (3.1)	
Azores	15 (1.7)	104 (2.7)	
Madeira	20 (2.4)	98 (2.3)	
BMI group (kg/m^2)			0.797
Underweight (<18.5)	1 (0.7)	3 (0.2)	
Normal weight (18.5–24.9)	31 (19.6)	149 (18.1)	
Overweight (25–29.9)	66 (36.9)	368 (40.2)	
Obesity (30–39.9)	78 (40.8)	303 (38.3)	
Morbid obesity (≥40)	5 (2.0)	28 (3.2)	
Comorbidities			
Cardiac disorders	71 (27.3)	259 (35.0)	0.109
Gastrointestinal disorders	67 (30.6)	227 (26.3)	0.357
Neurologic disorders	22 (12.0)	71 (8.7)	0.326
Psychiatric disorders	59 (28.3)	186 (20.0)	0.047
Cancer	22 (8.3)	48 (5.5)	0.175
Thyroid/parathyroid disorders	36 (17.1)	110 (10.0)	0.011
Rheumatologic disorders	123 (52.8)	437 (46.3)	0.203
Osteoporosis	69 (33.7)	163 (17.6)	<0.001
Fragility fracture risk factors and lifestyle habits			
Rheumatoid Arthritis	16 (9.8)	61 (6.6)	0.317
Family history of fragility fracture	17 (9.9)	51 (6.6)	0.260
Corticosteroid treatment	5 (3.2)	19 (2.7)	0.771
Alcoholic habits (yes/no)			0.248
Daily	36 (22.7)	236 (30.1)	
Occasionally	40 (24.8)	201 (23.9)	
Never	126 (52.5)	492 (46.0)	
Current smoking	15 (10.2)	67 (8.8)	0.655
Regular exercise	39 (20.0)	203 (24.2)	0.326
Falls in previous 12M (yes/no)	81 (44.5)	279 (29.9)	0.004
0	114 (55.5)	636 (70.1)	ref
1	37 (18.7)	131 (13.9)	0.032
≥2	44 (25.8)	148 (16.0)	0.016
Hearing loss	98 (43.8)	434 (41.3)	0.607
Vision loss	178 (86.2)	754 (81.4)	0.184
Imbalance	111 (51.9)	422 (46.9)	0.333

The estimated percentages were obtained considering study design. Reported p-values are from univariate analysis. **Abbreviations:** BMI, body mass index; NUTS II, Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); M, months.

Among the subjects with diabetes, self-reported LEF expectedly increased with age in adults 60 years or older. As for the high percentage of LEF between 40 and 49 years-old, it could be hypothesized that the effect of diabetes on fracture risk may be particularly important in middle-aged adults, while in older adults, other elements may add to fracture risk, such as age-related alterations in bone architecture, comorbidities, diabetic complications and increased fall risk. Holmberg et al. [28], showed that diabetes was one of the risk factors most strongly associated with LEF in a prospective

Table 4 – Crude and adjusted analysis for the association between risk factors for low-energy fractures and self-reported low-energy fractures among people over 40 years-old with diabetes.

	Crude OR [95% CI]	p-value	Adjusted OR[*] [95% CI]	p-value
Age (years)	1.00 [0.98–1.02]	0.982	0.99 [0.97–1.02]	0.600
Sex (Female)	1.85 [1.20–2.83]	0.005	1.52 [0.97–2.38]	0.065
Body mass index (Kg/m^2)	0.98 [0.94–1.03]	0.404	0.99 [0.95–1.04]	0.788
Rheumatoid Arthritis	1.53 [0.67–3.52]	0.317	1.10 [0.52–2.34]	0.803
Family (parent) history of fragility fracture	1.55 [0.72–3.35]	0.260	1.28 [0.60–2.76]	0.524
Corticosteroid treatment	1.18 [0.39–3.51]	0.771	1.03 [0.36–2.96]	0.963
Alcoholic habits	0.77 [0.52–1.16]	0.209	0.95 [0.59–1.52]	0.822
Current smoking	1.18 [0.56–2.49]	0.655	1.40 [0.66–2.98]	0.381
Osteoporosis	2.39 [1.49–3.84]	0.000	2.03 [1.25–3.29]	0.004
Falls in previous 12M (yes)	1.88 [1.23–2.88]	0.004	1.72 [1.14–2.61]	0.010

All variables were adjusted for age, sex, NUTS II, osteoporosis (p < 0.05) and falls in the previous 12 months (p < 0.05), except for:
Age – only adjusted for sex, NUTS II, osteoporosis and falls in previous 12 months;
Sex – only adjusted for age, NUTS II, osteoporosis and falls in the previous 12 months;
Osteoporosis - only adjusted for age, sex and NUTS II and falls in the previous 12 months;
Falls in the previous 12 months – only adjusted for age, sex, NUTS II and osteoporosis.
Covariates tested and eliminated: psychiatric disorders, thyroid/parathyroid disorders.
Abbreviations: NUTS II, Nomenclature of Territorial Units for Statistics (North, Centre, Alentejo, Algarve, Lisbon, Madeira and the Azores); M, months; 95% CI, 95% Confidence Interval.
[*] Adjusted analysis was performed using logistic regression models and taking the study design into account, i.e. using weighted estimations. We considered an alpha error of 0.1 for selection of variables from univariate analysis and then used an alpha error of 0.05 in the adjusted analysis, forcing age, sex and NUTS II in every model.

study of 33 000 men and women in middle age (range 27–62 years). Moreover, it was previously shown that the relationship between diabetes and hip fracture may be stronger at a younger age (<65 years) [1,8,10].

Our findings have a high impact in clinical practice and public health. Among patients with diabetes, approximately one third indicated at least one major LEF and more than two thirds in other locations, which is in accordance with previous studies reporting that non-hip non-vertebral fractures accounted for more than two thirds of all fragility fractures [22,29]. Although harder to study because they may not involve hospitalization, non-major LEF have significant implications on the individual and health care costs burden. In a prospective physicians practice-based multinational study of 51 491 women 55 years old or older at risk of osteoporosis followed for a year, there were 1898 fragility fractures, of which 93% were at sites other than hip implicating a greater total amount of health resources than hip fractures [29]. Furthermore, LEF have been associated with low quality of life [6]. Specifically in patients with diabetes, there is a lack of epidemiological evidence on fractures besides major osteoporotic fractures, although T2DM has been associated with fractures at multiple sites [27].

In the subgroup of subjects with diabetes, self-reported osteoporosis and the occurrence of falls in the previous year were the only factors independently associated with overall self-reported LEF. Formiga et al. [30] showed that a significant number of patients with late stage T2DM who experience a fall complicated by hip fracture have a history of recurrent falling in the previous year (OR 1.13, 95% CI 1.01–1.27). On the other hand, our results differ from existing evidence showing that typical risk factors can predict fracture to some extent in people with diabetes [31]. In one nested-case control study of diabetic patients [32], age and alcohol-related diagnosis increased

the odds of fracture, although both low and high-energy fractures were included. In another study on vertebral fractures in T2DM patients [25], those with vertebral fractures were older than those without, with no significant differences in BMD at any site, biochemical parameters, or the percentage of people with T2DM complications, habitual smoking, or alcohol consumption between those with and without vertebral fractures in either sex. However, these different results may be due to different study designs and populations.

Despite not being able to determine whether falls were just a marker of increased LEF risk or have a direct contribution to fracture occurrence, it is a clinical predictor easy to assess and these results show that it could increase awareness for diabetic patients at higher risk for fracture. Supporting this, falls are a known risk factor for fragility fractures [3]. In the French cohort of 671 postmenopausal women - the OFLEY cohort [23], followed for a median of 11.2 (IQR 1.1 years), there was a significant difference in reported falls in the past year between those with a LEF and those without (45.5% vs 30.2%), similar to our study. In addition, the likelihood of suffering a fall increases with increasing age (>65 years) and the emergency of T2DM [27,33]. In previous studies, older persons with T2DM were found to be at an increased risk of falling compared with healthy adults of a similar age [33–35]. Patients with diabetes have gait disturbances associated with microvascular complications, high BMI and the use of various medications, which may contribute to the increased fall risk [13,36].

This study has several limitations. We did not distinguish between T1DM and T2DM, which are known to have different effects on bone metabolism, BMD levels and skeleton fragility [3]. Diabetes mellitus was defined by self-report and HbA1c measurements were not included in the definition, which was the case in many previous studies. There is a proportion of diabetic patients not diagnosed that were considered

nondiabetic, leading to selection bias by misclassification of exposure. However, this non-differential bias would only lead to an underestimation of the effect. The same applies for other self-reported status. Although most variables were collected by self-report, they refer to a relatively short period of time and only people with full cognitive functions were included. Moreover, our prevalence estimates of diabetes and osteoporosis were similar to previously reported national estimates.

Since this is an observational study, causality cannot be inferred. Also, other factors that could change the effect of diabetes on fracture risk such as disease duration, glycaemic control, insulin use, hypoglycaemic episodes and presence of specific diabetic complications like neuropathy were not measured nor taken into account.

5.   Conclusion

Overall, our results show that Portuguese subjects with diabetes report more falls than those without diabetes and have a higher prevalence of self-reported LEF. Previous studies have shown that the typical risk factors for LEF do not seem to accurately predict the risk of fracture among people with diabetes. Our findings underline the need for developing specific risk prediction models for patients with diabetes to prevent underestimation of risk, especially in women.

Diabetes prevalence will continue to increase worldwide as a result of the aging of the population and the growing prevalence of metabolic syndrome, which will further contribute to the public health burden of LEF. Our results indicate that falls preventive measures [37] (i.e. exercise, environmental hazard reduction, monitoring and adjusting medications) may need to be incorporated in the care of diabetic patients to reduce LEF occurrence.

Further research on the underlying mechanisms and diabetes-specific risk factors for LEF, measurable markers of decreased bone quality and risk factors for injurious falls are necessary.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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R E F E R E N C E S

[1] Leslie WD, Morin SN, Lix LM, Majumdar SR. Does diabetes modify the effect of FRAX risk factors for predicting major osteoporotic and hip fracture? Osteoporos Int 2014;25:2817–24. https://doi.org/10.1007/s00198-014-2822-2.

[2] Moayeri A, Mohamadpour M, Mousavi S, Shirzadpour E, Mohamadpour S, Amraei M. Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis. Ther Clin Risk Manage 2017;13:455–68. https://doi.org/10.2147/TCRM.S131945.

[3] Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495–505. https://doi.org/10.1093/aje/kwm106.

[4] Jia P, Bao L, Chen H, Yuan J, Liu W, Feng F, et al. Risk of low-energy fracture in type 2 diabetes patients: a meta-analysis of observational studies. Osteoporos Int 2017;28:3113–21. https://doi.org/10.1007/s00198-017-4183-0.

[5] Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 2013;8. https://doi.org/10.1007/s11657-013-0136-1.

[6] Adachi JD, Ioannidis G, Pickard L, Berger C, Prior JC, Joseph L, et al. The association between osteoporotic fractures and health-related quality of life as measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos). Osteoporos Int 2003;14:895–904. https://doi.org/10.1007/s00198-003-1483-3.

[7] Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17:1726–33. https://doi.org/10.1007/s00198-006-0172-4.

[8] Schwartz AV. Epidemiology of fractures in type 2 diabetes. Bone 2016;82:2–8. https://doi.org/10.1016/j.bone.2015.05.032.

[9] WHO Study Group. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. 1994.

[10] Giangregorio LM, Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, et al. FRAX underestimates fracture risk in patients with diabetes. J Bone Miner Res 2012;27:301–8. https://doi.org/10.1002/jbmr.556.

[11] Schacter GI, Leslie WD. DXA-based measurements in diabetes: Can they predict fracture risk? Calcif Tissue Int 2017;100:150–64. https://doi.org/10.1007/s00223-016-0191-x.

[12] Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes - A meta-analysis. Osteoporos Int 2007;18:427–44. https://doi.org/10.1007/s00198-006-0253-4.

[13] Vestergaard P. Diabetes and bone fracture: Risk factors for old and young. Diabetologia 2014;57:2007–8. https://doi.org/10.1007/s00125-014-3338-1.

[14] Moseley KF. Type 2 diabetes and bone fractures. Curr Opin Endocrinol Diabetes Obes 2012;19:871–82. https://doi.org/10.1111/obr.12065.Variation.

[15] Khan TS, Fraser LA. Type 1 diabetes and osteoporosis: From molecular pathways to bone phenotype. J Osteoporos 2015;2015. https://doi.org/10.1155/2015/174186.

[16] Rodrigues AM, Gouveia N, Pereira L, Eusébio M, Ramiro S. EpiReumaPt – the study of Rheumatic and Musculoskeletal diseases in Portugal : a detailed view of the methodology. Acta Reum Port 2015:110–24.

[17] Branco JC, Rodrigues AM, Gouveia N, Eusébio M, Ramiro S, Machado PM, et al. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt– a national health survey. RMD Open 2016;2:e000166. https://doi.org/10.1136/rmdopen-2015-000166.

[18] Tchalla AE, Dufour AB, Travison TG, Habtemariam D, Iloputaife I, Manor B, et al. outcomes of falls trajectories in

older adults: The MOBILIZE Boston study with 5 years of follow-up. PLoS One 2014;9. https://doi.org/10.1371/journal.pone.0106363.

[19] McCloskey E. FRAX ® Identifying people at high risk of fracture 2009.

[20] Lucas R, Monjardino MT. O Estado da Reumatologia em Portugal. ONDOR - Obs Nac Das Doenças Reumáticas 2010;139.

[21] Observatório Nacional da Diabetes. Factos e Números - o Ano de 2014. 2015.

[22] Tran T, Bliuc D, van Geel T, Adachi JD, Berger C, van den Bergh J, et al. Population-wide impact of non-hip non-vertebral fractures on mortality. J Bone Miner Res 2017;32:1802–10.

[23] Sornay-Rendu E, Munoz F, Duboeuf F, Delmas PD. Rate of forearm bone loss is associated with an increased risk offracture independently of bone mass in postmenopausal women: The OFELY study. J Bone Miner Res 2005;20:1929–35.

[24] Holloway KL, Henry MJ, Brennan-Olsen SL, Bucki-Smith G, Nicholson GC, Korn S, et al. Non-hip and non-vertebral fractures: the neglected fracture sites. Osteoporos Int 2016;27:905–13. https://doi.org/10.1007/s00198-015-3322-8.

[25] Yamamoto M, Yamaguchi T, Yamauchi M, Kaji H, Sugimoto T. Diabetic patients have an increased risk of vertebral fractures independent of BMD or diabetic complications. J Bone Miner Res 2009;24:702–9. https://doi.org/10.1359/jbmr.081207.

[26] Kilpadi KL, ElDabaje R, Schmitz JE, Ehler B, Thames TA, Joshi AP, et al. Type 2 diabetes is associated with vertebral fractures in a sample of clinic- and hospital-based Latinos. J Immigr Minor Heal 2014;16:440–9. https://doi.org/10.1007/s10903-013-9833-5.

[27] Bonds DE, Larson JC, Schwartz AV, Strotmeyer ES, Robbins J, Rodriguez BL, et al. Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study. J Clin Endocrinol Metab 2006;91:3404–10. https://doi.org/10.1210/jc.2006-0614.

[28] Holmberg AH, Johnell O, Nilsson PM, Nilsson J, Berglund G, Đkesson K. Risk factors for fragility fracture in middle age. A prospective population-based study of 33,000 men and women. Osteoporos Int 2006;17:1065–77. https://doi.org/10.1007/s00198-006-0137-7.

[29] Ioannidis G, Flahive J, Pickard L, Papaioannou A, Chapurlat RD, De Lyon HC, et al. Non-hip, non-spine fractures drive healthcare utilization following a fracture: the Global Longitudinal study of Osteoporosis in Women (GLOW). Osteoporos Int 2013;24:59–67. https://doi.org/10.1007/s00198-012-1968-z.Non-hip.

[30] Formiga F, Chivite D, Ruiz D, Navarro M, Perez Castejon JM, Duaso E, et al. Clinical evidence of diabetes mellitus end-organ damage as risk factor for falls complicated by hip fracture: A multi-center study of 1225 patients. Diabetes Res Clin Pract 2015;109:233–7. https://doi.org/10.1016/j.diabres.2015.05.050.

[31] Melton LJ, Leibson CL, Achenbach SJ, Therneau TM, Khosla S. Fracture risk in type 2 diabetes: Update of a population-based study. J Bone Miner Res 2008;23:1334–42. https://doi.org/10.1359/jbmr.080323.

[32] Starup-Linde J, Gregersen S, Vestergaard P. Associations with fracture in patients with diabetes: a nested case-control study. BMJ Open 2016;6:e009686. https://doi.org/10.1136/bmjopen-2015-009686.

[33] Schwartz AV, Hillier TA, Sellmeyer DE, Resnick HE, Gregg E, Ensrud KE, et al. Older women with diabetes have a higher risk of falls: A prospective study. Diabetes Care 2002;25:1749–54. https://doi.org/10.2337/diacare.25.10.1749.

[34] Vinik AI, Vinik EJ, Colberg SR, Morrison S. Falls risk in older adults with type 2 diabetes. Clin Geriatr Med 2015;31:89–99. https://doi.org/10.1016/j.cger.2014.09.002.

[35] Mayne D, Stout NR, Aspray TJ. Diabetes, falls and fractures. Age Ageing 2010;39:522–5. https://doi.org/10.1093/ageing/afq081.

[36] Pijpers E, Ferreira I, De Jongh RT, Deeg DJ, Lips P, Stehouwer CDA, et al. Older individuals with diabetes have an increased risk of recurrent falls: Analysis of potential mediating factors: The Longitudinal Ageing Study Amsterdam. Age Ageing 2012;41:358–65. https://doi.org/10.1093/ageing/afr145.

[37] Al-Faisal W. Falls Prevention for Older Persons Eastern Mediterranean Regional Review, 2007.