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Validation of the clinical consensus recommendations on the management of fracture risk in postmenopausal women with type 2 diabetes

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Abstract *Background and aims:* Bone fragility is recognized as a complication of type 2 diabetes (T2D). However, the fracture risk in T2D is underestimated using the classical assessment tools. An expert panel suggested the diagnostic approaches for the detection of T2D patients worthy of bone-active treatment. The aim of the study was to apply these algorithms to a cohort of T2D women to validate them in clinical practice.
Methods and results: The presence of T2D-specific fracture risk factors (T2D $\geq$ 10 years, $\geq$1 T2D complications, insulin or thiazolidinedione use, poor glycaemic control) was assessed at baseline in 107 postmenopausal T2D women. In all patients at baseline and in 34 patients after a median follow-up of 60.2 months we retrospectively evaluated bone mineral density and clinical and morphometric vertebral fractures. No patient was treated with bone-active drug. Following the protocols, 34 (31.8%) and 73 (68.2%) patients would have been pharmacologically and conservatively treated, respectively. Among 49 patients without both clinical fractures and major T2D-related risk factors, who would have been, therefore, conservatively followed-up without vertebral fracture assessment, only one showed a prevalent vertebral fracture (sensitivity 90%, negative predictive value 98%). The two patients who experienced an incident fracture would have been pharmacologically treated at baseline.
Conclusions: The clinical consensus recommendations showed a very good sensitivity in identifying T2D postmenopausal women at high fracture risk. Among those with treatment indication

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as many as 13% of patients experienced an incident fracture, and, conversely, among those without treatment indication no incident fractures were observed.

1. Introduction

Type 2 diabetes (T2D) and osteoporosis are both highly prevalent chronic disorders associated with severe morbidity and increased mortality. Individuals with T2D have an increased risk of bone fragility fractures compared to non-diabetic subjects. Accordingly, nowadays skeletal fragility is considered a T2D-related complication [1]. However, the true prevalence of this complication can be hard to be determined, as the increased fracture risk in patients with T2D can be anyway underestimated by conventional WHO criteria for osteoporosis [2]. Indeed, in T2D patients for any given T-score of bone mineral density (BMD) the fracture risk is increased with respect to the general population and fragility fractures may occur despite a normal or even increased BMD, thus suggesting a deterioration of bone quality rather than of bone quantity in the pathogenesis of T2D-related bone fragility.

Even the use of classical fracture risk assessment tools, such as the FRAX (the Fracture Risk Assessment algorithm) score, underestimates the risk of osteoporotic fractures in T2D [3]. To date, surrogate measures have been proposed for the improvement of FRAX performance, such as adding the lumbar spine trabecular bone score (TBS), using rheumatoid arthritis as a proxy for T2D or decreasing the actual BMD hip T-score of the diabetic patient by 0.5 units [4]. However, no single method was found to be optimal in all settings of T2D and fracture risk remained underestimated by these approaches in this kind of patients, particularly in those with long-lasting disease [5].

Based on available data, an Italian task force of experts suggested the use of the following major T2D-specific risk factors for the stratification of fracture risk in T2D patients: a disease duration above 10 years, one or more chronic T2D complications, the use of insulin or thiazolidinediones and persistent poor glycaemic control (i.e. HbA1c levels above 64 mmol/mol for at least 1 year) [6]. The scientific rationale of choosing these specific risk factors for T2D population is extensively described in the paper by Chiodini and colleagues [6]**.** Summarizing, the expert panel identified the evidence from existing systematic reviews and relevant publications (searched on PubMed, Cochrane Register and EMBASE until April 2020), supplemented by their multi-disciplinary expertise [6].

The same expert panel defined that the fracture risk in T2D patients should firstly rely on the presence or absence of a previous fragility fracture and on the individual risk profile, with the inclusion of the above T2D-specific risk factors [6]. Accordingly, a diagnostic approach was suggested on the basis of the presence or the absence of a prevalent fragility fracture (Fig. 1). The flowchart allows to identify the different clinical situations for which the use of bone-active drugs is suggested [6], in addition to lifestyle intervention, medical nutrition therapy, weight-bearing exercises and prevention of falls, which represent the basis of the therapy of T2D and T2D-related bone involvement [1].

The aim of the present study was to validate the clinical consensus recommendations on the assessment and management of fracture risk in patients with T2D established by the Italian multidisciplinary expert panel [6], and in particular to assess, on the basis of such diagnostic approaches, whether T2D patients who would have been treated were really at high risk of fracture and, conversely, those who would have been conservatively followed up were really at low risk of fracture.

2. Methods

The present study is the continuation of a previous protocol aimed to evaluate bone involvement in diabetic postmenopausal female subjects with T2D and its relationship with cortisol secretion and sensitivity [7]. The recruitment and the data collection started in September 2011 and ended in April 2021 with the analysis of the retrospective data as soon as the expert panel perspective has been published [6]. Patients were selected on the basis of the following criteria: age 50–80 years, postmenopausal status, T2D diagnosis after 30 years of age, body mass index (BMI) 19–40 kg/m^2, glycosylated haemoglobin (HbA1c) $\leq$64 mmol/mol at the time of recruitment.

The exclusion criteria at study entry were the following: insulin therapy during the first 2 years of the disease (in the attempt to exclude primitive insulin deficiency due to a possibly hidden form of autoimmune diabetes), history of ketoacidosis or hypoglycaemia in the past 6 months before enrolment, an ongoing treatment with drugs known to influence bone metabolism (e.g. glucocorticoids, antidepressants, anticonvulsants, thiazolidinediones, sodium–glucose cotransporter inhibitors, acarbose), a recent treatment with bone-active drugs (teriparatide or denosumab in the past 2 years and bisphosphonate or strontium ranelate in the past 5 years), endocrine diseases (e.g. hyperthyroidism, primary hyperparathyroidism, hypercortisolism, idiopathic hypercalciuria, hyperandrogenism) or other diseases or conditions known to influence bone metabolism (e.g. rheumatoid arthritis, connective tissue diseases, malabsorption, intestinal bowel diseases, chronic liver disease, malignant neoplasia, alcoholism, depression, chronic obstructive pulmonary disease, multiple sclerosis or other severe motor

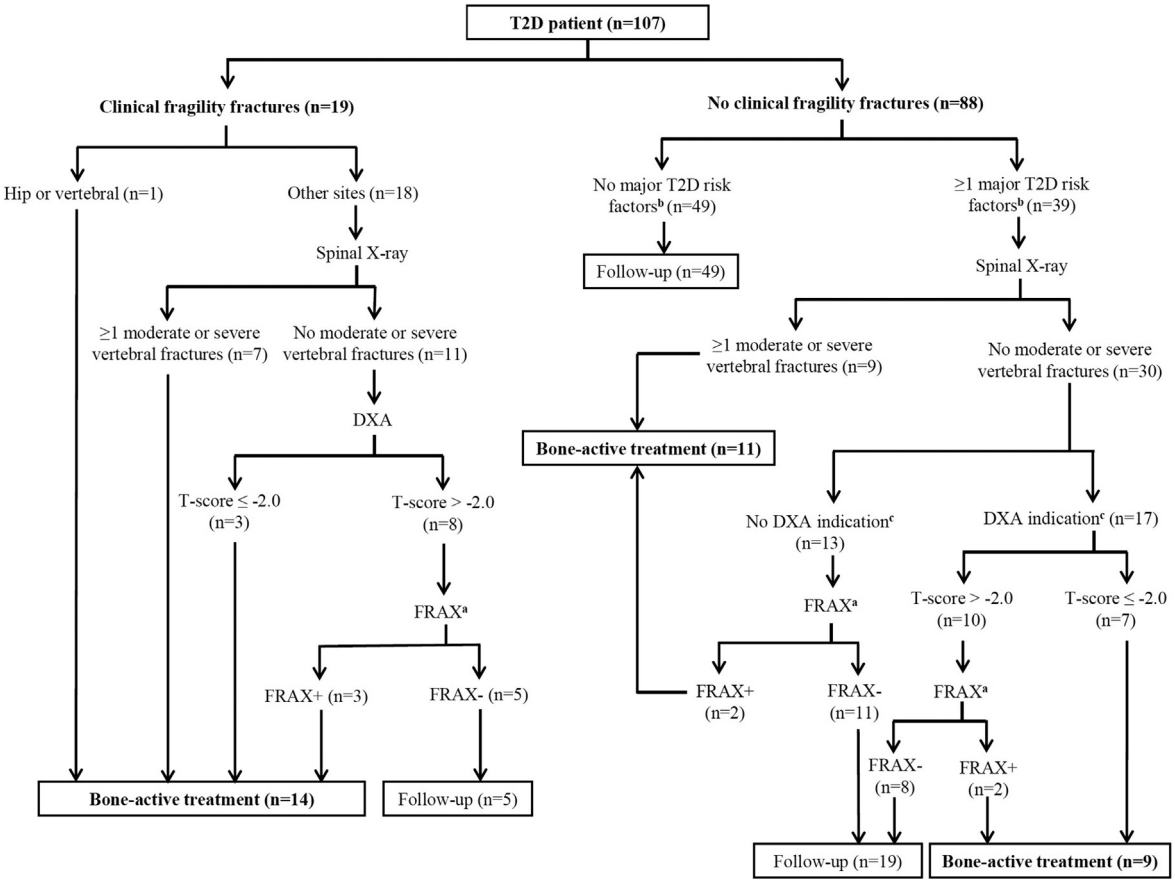

Figure 1 The diagnostic approach suggested by the expert panel for the evaluation and management of bone fragility in T2D patients, depending on the presence or absence of a prevalent clinical fragility fracture (modified from Chiodini et al. [6]). Numbers in the brackets indicate the number of patients of our sample in each clinical situation.
DXA: Dual X-Ray Absorptiometry. FRAX: Fracture Risk Assessment algorithm. T2D: type 2 diabetes.
[a]FRAX criteria to be calculated without bone mineral density and with rheumatoid arthritis as surrogate risk factor of diabetes (FRAX+, patients who fulfil the National Osteoporosis Foundation criteria for treatment: 20% ten years risk of major fragility fractures and 3% ten years risk of hip fracture); [b]major T2D risk factors for fracture: (1) diabetes duration >10 years, (2) insulin and/or thiazolidinedione treatment, (3) chronic diabetes complications, (4) glycosylated haemoglobin levels above 64 mmol/mol for at least 1 year; [c]DXA analysis to be performed in females ≥65 years or males ≥75 years, according to the International Society of Clinical Densitometry indications for DXA [12].

impairment, a history of severe vitamin D deficiency), presence of proliferative or laser-treated retinopathy, overt diabetic nephropathy (macroalbuminuria >300 mg/24-h or chronic kidney disease), severe macroangiopathy (history of myocardial infarction, coronary artery bypass graft surgery, percutaneous transluminal coronary, carotid, femoral or femoral-popliteus angioplasty).

Eventually, at baseline our sample included 107 Caucasian postmenopausal female subjects with T2D. At the basal evaluation the presence of previous fragility fracture and of the major T2D-specific fracture risk factors according to the guidelines [6] was ascertained by the clinical history and by the review of the medical reports.

In keeping with the expert panel [6], if requested by the flow-chart, the FRAX score was calculated without BMD and with rheumatoid arthritis as surrogate risk factor of diabetes [8]. The T2D patients were considered FRAX positive (FRAX+) if they fulfilled the National Osteoporosis Foundation criteria for treatment: 20% ten years risk of major fragility Fracture and 3% ten years risk of hip Fracture [9].

At the baseline and then after a minimum follow-up of 18 months data on BMD and on the presence of morphometric vertebral fractures (VFx) were retrospectively collected. Dual energy X-ray absorptiometry (DXA) scan was carried out to measure BMD (Hologic Discovery or Horizon A, Waltham, MA, USA) at lumbar spine (LS; in vivo precision 1.7%), total femur (FT; in vivo precision 1.7%), and femoral neck (FN; in vivo precision 1.8%), whereas VFx assessment (VFA) by DXA [10] or a conventional spinal radiograph in lateral and anteroposterior projection with standardized technique were used to detect morphometric VFx using the semiquantitative assessment previously described by Genant [11]. Two trained physicians, blinded to BMD and biochemical data, independently reviewed the images, discussing questionable cases to agree on a diagnosis. According to the interdisciplinary expert panel [6], only moderate and severe VFx were included in the analysis.

Due to the retrospective design of the study, no patient was treated with bone-active drug. Those patients who

developed during the follow-up one of the exclusion criteria were excluded from the follow-up analysis.

The BMD at the follow-up was considered increased or decreased if the BMD variations were respectively higher or lower than the least significant change (LSC) in at least one skeletal site. Least significant change was calculated by multiplying the precision error of each skeletal site by 2.77 [12].

Finally, the incidence of clinical fragility fractures during the follow-up was recorded and confirmed by the review of the medical reports.

The study was designed to answer the following questions: if the protocol would have been retrospectively applied to our sample of patients:

i. How many T2D patients with clinical fractures would have been pharmacologically treated?
ii. How many T2D patients without clinical fractures would have been pharmacologically treated?
iii. How many T2D patients with asymptomatic VFx would not have been pharmacologically treated and how many patients without both clinical and morphometric VFx would have been pharmacologically treated?
iv. How many T2D patients with at least 1 major T2D-related risk factor for fracture, but without both clinical and morphometric VFx would have been either pharmacologically or conservatively treated on the basis of the FRAX score and/or BMD levels?
v. How many T2D patients experienced a fragility fracture during the follow-up and who of them would have been pharmacologically treated?

Statistical analysis was performed by SPSS version 24.0 statistical package (SPSS Inc, Chicago, IL). The results were expressed as mean ± standard deviation (SD) with range in parentheses or absolute number with percentage in parentheses. The normality of distribution was tested by Kolmogorov–Smirnov test. The comparison of continuous variables between groups were performed using Student's t-test or Mann–Whitney U test as appropriate. Categorical variables were compared by $\chi 2$ test or Fisher Exact test, as appropriate. A pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) was obtained according to the random effect method proposed by Der Simonian and Laird [13].

P-values of less than 0.05 were considered significant.

3. Results

3.1. General overview

Following the flow-chart depicted in Fig. 1, in our sample of 107 T2D patients, 34 (31.8%) and 73 (68.2%) would have been pharmacologically and conservatively treated, respectively. The characteristics of the whole sample and the comparison between the characteristics of T2D patients who would have been pharmacologically treated and those of patients who would have been conservatively followed-up are reported in Table 1. As compared with patients who would not have been pharmacologically treated, T2D subjects who would have been treated were older, had a lower BMD at the femur and had a higher prevalence of morphometric VFx, low BMD (T-score ≤ -2.0 in at least one skeletal site) and, as expected, of insulin treatment, T2D duration above 10 years, neuropathy, at least one T2D-related chronic complication and at least one major T2D-related risk factor for fracture. In patients who would have been pharmacologically treated the BMD at the spine tended to be lower than in patients who would not have been pharmacologically treated, despite not reaching the statistical significance. The two groups were not statistically different as far as BMI, HbA1c levels, prevalence of retinopathy and nephropathy, even though these T2D chronic complications were 3-4-fold more frequent in patients who would have been pharmacologically treated.

3.1.1. How many T2D patients with clinical fractures would have been pharmacologically treated?

Following the flow-chart depicted in Fig. 1, among clinically fractured patients (19 out of 107, 17.8%), we would have pharmacologically treated one patient with hip fracture and, among the 18 patients with a clinical non-hip and non-vertebral (i.e. humerus or wrist) fracture, we would have treated 7 patients with at least one moderate or severe VFx, 3 patients without VFx but with BMD T-score ≤ -2.0, and 3 patients without VFx and without BMD T-score ≤ -2.0 but with FRAX+. Overall 14 out of 19 patients (73.7%) with clinical fractures would have been pharmacologically treated.

On the other hand, 5 patients (26.3%) with a non-hip nor vertebral clinical fragility fracture would not have been treated since they did not show morphometric, asymptomatic VFx, had a BMD T-score above −2.0 and were at low risk by FRAX score. Among these patients, in keeping with a low-risk fracture profile in spite of the presence of a prevalent fracture, no one had T2D complications, no one was on insulin treatment and only one showed a T2D duration above 10 years.

The comparison between the clinical characteristics of T2D patients with clinical fractures and those without clinical fractures is reported in Table 2.

As compared to patients without clinical fractures, T2D patients with clinical fractures showed a lower BMD at the FN and an increased prevalence of asymptomatic moderate or severe VFx, retinopathy, nephropathy and neuropathy. Moreover, as expected, the prevalence of patients with at least one T2D-related chronic complication was increased in clinically fractured patients than in patients without clinical fractures. Age, BMI, HbA1c levels, spine BMD and the prevalence of T2D duration above 10 years, insulin treated subjects and patients with at least one major T2D-related risk factor for fracture were comparable between the two groups.

The comparison between the clinical characteristics of T2D patients with clinical and/or asymptomatic VFx and those without fractures is reported in Table 3.

Table 1 Characteristics of T2D patients and comparison between those who would have been pharmacologically treated and those who would have been conservatively followed-up.

Parameters	All T2D patients (n = 107)	T2D patients who would have been pharmacologically treated (n = 34)	T2D patients who would not have been pharmacologically treated (n = 73)	*p*
Age (years)	65.6 ± 7.3 (52–80)	68.5 ± 7.1 (53–80)	64.3 ± 7.0 (52–80)	0.005
BMI (kg/m^2)	29.6 ± 4.8 (21.0–40.0)	30.1 ± 4.3 (21.0–40.0)	29.4 ± 5.1 (21.3–40.0)	0.485
HbA1c (mmol/mol)	51 ± 8 (31–64)	53 ± 8 (40–64)	50 ± 8 (31–64)	0.113
Patients with asymptomatic VFx (moderate or severe)	17 (15.9)	16 (47.1)	1 (1.4)	<0.0001
Patients with T2D duration ≥ 10 years	45 (42.1)	26 (76.5)	19 (26.0)	<0.0001
Patients on insulin treatment	20 (18.7)	10 (29.4)	10 (13.7)	0.05
Patients with retinopathy	5 (4.7)	3 (8.8)	2 (2.7)	0.182
Patients with nephropathy	6 (5.6)	4 (11.8)	2 (2.7)	0.079
Patients with neuropathy	4 (3.7)	4 (11.8)	0 (0.0)	0.009
Patients with at least one T2D chronic complication[a]	9 (8.4)	6 (17.6)	3 (4.1)	0.028
Patients with at least 1 major T2D-related risk factor for Fx[b]	51 (47.7)	31 (91.2)	20 (27.4)	<0.0001
Patients with BMD T-score ≤ −2.0	34 (31.8)	20 (58.8)	14 (19.2)	<0.0001
LS BMD (T-score)	−0.84 ± 1.44 (−5.30–2.90)	−1.21 ± 1.45 (−3.60 −1.50)	−0.67 ± 1.41 (−5.30 −2.90)	0.068
FN BMD (T-score)	−1.11 ± 1.06 (−3.40–1.40)	−1.65 ± 0.92 (−3.20 −0.70)	−0.85 ± 1.03 (−3.40 −1.40)	<0.0001

Data are mean ± SD with range in parentheses or absolute number with percentage in parentheses. T2D: type 2 diabetes. BMI: body mass index. HbA1c: glycosylated haemoglobin. BMD: bone mineral density; LS: lumbar spine. FN: femoral neck. VFx: vertebral fracture (moderate or severe). Fx: fracture.

[a] Patients with at least one out of nephropathy, retinopathy and neuropathy.

[b] Patients with at least one out of a disease duration above 10 years, the presence of one or more chronic T2D complications, the use of insulin and persistent poor glycaemic control (i.e. HbA1c levels above 64 mmol/mol for at least 1 year).

As compared to patients without fractures, patients with clinical and/or morphometric moderate or severe VFx showed an increased prevalence of nephropathy and neuropathy. Moreover, they also showed a higher prevalence of subjects with insulin treatment, with a T2D duration longer than 10 years, with at least one major T2D-

Table 2 Comparisons between the clinical characteristics of T2D patients with clinical fractures and those without clinical fractures.

Parameters	T2D patients with clinical Fx (n = 19)	T2D subjects without clinical Fx (n = 88)	*p*
Age (years)	66.5 ± 7.9 (54–77)	65.5 ± 7.2 (52–80)	0.587
BMI (kg/m^2)	29.8 ± 3.9 (24.2–40.0)	29.6 ± 5.0 (21.0–40.0)	0.877
HbA1c (mmol/mol)	52 ± 8 (40–64)	51 ± 8 (31–64)	0.625
Patients with asymptomatic VFx (moderate or severe)	7 (36.8)	10 (11.4)	0.006
Patients with T2D duration ≥ 10 years	9 (47.4)	36 (40.9)	0.605
Patients on insulin treatment	4 (21.1)	16 (18.2)	0.752
Patients with retinopathy	3 (15.8)	2 (2.3)	0.038
Patients with nephropathy	4 (21.1)	2 (2.3)	0.009
Patients with neuropathy	4 (21.1)	0 (0.0)	0.001
Patients with at least one T2D chronic complication[a]	6 (31.6)	3 (3.4)	0.001
Patients with at least 1 major T2D-related risk factor for Fx[b]	12 (63.2)	39 (44.3)	0.136
Patients with BMD T-score ≤ −2.0	9 (47.4)	25 (28.4)	0.107
LS BMD (T-score)	−1.18 ± 1.47 (−3.20–1-50)	−0.76 ± 1.43 (−5.30–2.90)	0.255
FN BMD (T-score)	−1.56 ± 0.89 (−3.20–0.30)	−1.01 ± 1.07 (−3.40–1.40)	0.038

Data are mean ± SD with range in parentheses or absolute number with percentage in parentheses.
T2D: type 2 diabetes. BMI: body mass index. HbA1c: glycosylated haemoglobin. VFx: vertebral fracture. Fx: fracture. BMD: bone mineral density. LS: lumbar spine. FN: femoral neck.

[a] Patients with at least one out of nephropathy, retinopathy and neuropathy.

[b] Patients with at least one out of a disease duration above 10 years, the presence of one or more chronic T2D complications, the use of insulin and persistent poor glycaemic control (i.e. HbA1c levels above 64 mmol/mol for at least 1 year).

Table 3 Comparisons between the clinical characteristics of T2D patients with clinical and/or asymptomatic vertebral fracture and those of T2D patients without fractures.

Parameters	T2D patients with clinical Fx and/or asymptomatic VFx (n = 29)	T2D patients without clinical Fx and asymptomatic VFx (n = 78)	*p*
Age (years)	65.8 ± 8.0 (52–77)	65.6 ± 7.1 (52–80)	0.899
BMI (kg/m^2)	30.1 ± 3.8 (23.3–40.0)	29.5 ± 5.2 (21.0–40.0)	0.535
HbA1c (mmol/mol)	52 ± 7 (40–64)	50 ± 9 (31–64)	0.257
Patients with asymptomatic VFx (moderate or severe)	17 (58.6)	0 (0.0)	<0.0001
Patients with T2D duration ≥ 10 years	17 (58.6)	28 (35.9)	0.034
Patients on insulin treatment	9 (31.0)	11 (14.1)	0.046
Patients with retinopathy	3 (10.3)	2 (2.6)	0.122
Patients with nephropathy	4 (13.8)	2 (2.6)	0.045
Patients with neuropathy	4 (13.8)	0 (0.0)	0.005
Patients with at least one T2D chronic complication[a]	6 (20.7)	3 (3.8)	0.011
Patients with at least 1 major T2D-related risk factor for Fx[b]	21 (72.4)	30 (38.5)	0.002
Patients with BMD T-score ≤ −2.0	11 (37.9)	23 (29.5)	0.404
LS BMD (T-score)	−0.89 ± 1.36 (−3.20–1.50)	−0.82 ± 1.48 (−5.30–2.90)	0.140
FN BMD (T-score)	−1.36 ± 0.89 (−3.20–0.70)	−1.01 ± 1.11 (−3.40–1.40)	0.169

Data are mean ± SD with range in parentheses or absolute number with percentage in parentheses.
T2D: type 2 diabetes. BMI: body mass index. HbA1c: glycosylated haemoglobin. VFx: vertebral fracture. Fx: fracture. BMD: bone mineral density. LS: lumbar spine. FN: femoral neck.
[a] Patients with at least one out of nephropathy, retinopathy and neuropathy.
[b] Patients with at least one out of a disease duration above 10 years, the presence of one or more chronic T2D complications, the use of insulin and persistent poor glycaemic control (i.e. HbA1c levels above 64 mmol/mol for at least 1 year).

related risk factor for fracture and with at least one T2D chronic complication. Age, BMI, BMD and HbA1c levels were comparable between the two groups.

3.1.2. How many T2D patients without clinical fractures would have been pharmacologically treated?

Following the flow-chart depicted in Fig. 1, among the 88 patients without clinical fractures, we would have pharmacologically treated 20 patients (22.7%): 9 patients with at least one morphometric moderate or severe VFx, 8 patients without morphometric VFx s but with a BMD T-score ≤ −2.0, 3 patients without a morphometric VFx but with a FRAX score suggesting a high fracture risk regardless of BMD. On the other hand, 68 patients (77.3%) would have been conservatively followed-up: 49 patients without a major T2D-related risk factor for fracture, 10 patients with at least 1 major T2D-related risk factor for fracture but without VFx and with a negative FRAX score regardless of BMD and 9 patients with BMD T-score above −2.0 and with a FRAX score suggesting low fracture risk.

3.1.3. How many T2D patients with asymptomatic VFx would not have been pharmacologically treated and how many patients without both clinical and morphometric VFx would have been pharmacologically treated?

The application of the flow-chart depicted in Fig. 1 selects those patients for vertebral X-ray based on their fracture risk profile. Since in our study the spinal radiographs have been performed in all patients, regardless of basal fracture risk, we were able to verify the algorithm's reliability in identifying patients worthy of bone-active treatment due to the presence of asymptomatic morphometric VFx. Among the overall group of 73 patients without treatment indication, only 1 moderate morphometric VFx was present at the spinal evaluation. In other words, in our sample, among patients with asymptomatic VFx (17 out of 107, 15.9%), following the flow-chart depicted in Fig. 1, 16 would have been pharmacologically treated (94.1%) and only one would have not been pharmacologically treated because of the absence of previous clinical fractures and of major T2D-related risk factors and, thus, of indication to VFx assessment according to the diagnostic approach proposed by the expert panel [6].

Conversely, among the group of 78 patients without both clinical and morphometric VFx, 11 patients (14.1%) received anyway the treatment indication, according to the presence of at least one major T2D-related risk factors and a T-score ≤ -2.0 (n = 7) or a FRAX+ (n = 4).

3.1.4. How many T2D patients with at least 1 major T2D-related risk factor for fracture, but without both clinical and morphometric VFx would have been pharmacologically or conservatively treated on the basis of the FRAX score and/or BMD levels?

Among the 30 patients without both clinical and morphometric VFx but with at least 1 major T2D-related risk factor for fracture, 13 were younger than 65 years of age and then did not met the ISCD (International Society of Clinical Densitometry) indication for performing a DXA exam [12]. Among these latter, 11 patients were at low fracture risk based on the FRAX score and, thus, would be

conservatively treated, while 2 patients, who were found to be at high risk for fracture on the basis of the FRAX score, would have been pharmacologically treated.

On the other hand, among the same 30 patients, 17 were older than 65 years of age and then had the ISCD indication for performing a DXA exam [12]. Among these latter, 7 patients showing a BMD T-score equal or below −2.0 and 2 patients showing a BMD T-score above −2.0 but a high risk of fracture on the basis of the FRAX score, would be pharmacologically treated. Eight patients, showing both a BMD above −2.0 and a low fracture risk by FRAX score, would have been conservatively treated.

The comparisons between the clinical characteristics of T2D patients without both clinical fractures and major T2D-related risk factors and T2D patients without clinical fractures but with at least one major T2D-related risk factor for fracture is reported in Table 4.

As compared with patients without both clinical fractures and major T2D-related risk factors, patients without clinical fractures but with ≥1 major T2D-related risk factor for fracture showed an increased prevalence of asymptomatic VFx and, as expected, an increased prevalence of T2D duration above 10 years and insulin treatment. No statistically significant differences were found as far as age, BMI, HbA1c levels, BMD at both spine and femur and prevalence of T2D-related chronic complications and T-score ≤ −2.0. Importantly, among the 49 patients without both clinical fractures and major T2D-related risk factors, who would have been, therefore, conservatively followed up, only one subject (2.0%, sensitivity 90%, negative predictive value NPV 98%), in fact, showed a prevalent VFx. On the other hand, among the 39 patients without clinical fractures but with at least 1 major T2D-related risk factors 9 subjects (23.1%, specificity 61.5%) showed a VFx and then they would have been pharmacologically treated, but 11 out of the remaining 30 would have received anyway the treatment indication, according to the BMD T-score or to the FRAX score.

3.1.5. How many T2D patients experienced a fragility fracture during the follow-up and who of them would have been pharmacologically treated?

Among the 107 patients evaluated at baseline, 16 patients were excluded from the longitudinal arm of the study because of the development in the course of follow-up of one of exclusion criteria provided by the protocol (hyperthyroidism, n = 3; primary hyperparathyroidism, n = 3, hypercortisolism, n = 4, malignant neoplasia, n = 6). Among the remaining cases, 36 patients were lost at the follow-up and 21 patients refused to join the longitudinal arm. Eventually, a follow-up was available for 34 patients. The median follow-up was of 60.2 months (range 18−108).

Following the flow-chart depicted in Fig. 1, 15 out of these 34 T2D patients would have been pharmacologically treated: one patient had a prevalent clinical VFx, 3 patients reported a previous clinical non-vertebral and non-hip fragility fracture associated with another factor which justified the treatment indication (one had a moderate morphometric VFx, one a BMD T-score ≤ -2.0 and one a FRAX score suggesting a high fracture risk), 7 patients had at least one major T2D-related risk factor and at least one morphometric VFx and finally 4 had at least one major T2D-related risk factor and a BMD T-score ≤ −2.0.

Table 4 Comparisons between the clinical characteristics of T2D patients without both clinical fractures and major T2D-related risk factors and those of T2D patients without clinical fractures but with at least one major T2D-related risk factor for fracture.

Parameters	All T2D patients without clinical Fx (n = 88)	T2D patients without clinical Fx but with ≥1 major T2D-related risk factor for Fx (n = 39)	T2D patients without both clinical Fx and major T2D-related risk factor for Fx (n = 49)	P[a]
Age (years)	65.6 ± 7.2 (52−80)	65.8 ± 7.6 (52−80)	65.2 ± 6.9 (52−80)	0.726
BMI (kg/m^2)	29.6 ± 5.0 (21.0−40.0)	29.8 ± 4.3 (21.0−39.5)	29.4 ± 5.5 (21.3−40.0)	0.737
HbA1c (mmol/mol)	51 ± 8 (31−64)	52 ± 8 (31−63)	50 ± 8 (31−64)	0.390
Patients with asymptomatic VFx (moderate or severe)	10 (11.4)	9 (23.1)	1 (2.0)	0.004
Patients with T2D duration ≥ 10 years	36 (40.9)	35 (89.7)	1 (2.0)	<0.0001
Patients on insulin treatment	16 (18.2)	14 (35.9)	2 (4.1)	<0.0001
Patients with retinopathy	2 (2.3)	2 (5.1)	0 (0.0)	0.194
Patients with nephropathy	2 (2.3)	1 (2.6)	1 (2.0)	0.693
Patients with neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	–
Patients with at least one T2D chronic complication[a]	3 (3.4)	2 (5.1)	1 (2.0)	0.582
Patients with BMD T-score ≤ −2.0	25 (28.4)	11 (28.2)	14 (28.6)	0.970
LS BMD (T-score)	−0.76 ± 1.43 (−5.30−2.90)	−0.86 ± 1.30 (−3.6−2.5)	−0.69 ± 1.54 (−5.30−2.90)	0.595
FN BMD (T-score)	−1.01 ± 1.07 (−3.40−1.40)	−1.08 ± 1.12 (−2.9−1.00)	−0.95 ± 1.04 (−3.40−1.40)	0.567

Data are mean ± SD with range in parentheses or absolute number with percentage in parentheses.
T2D: type 2 diabetes. BMI: body mass index. HbA1c: glycosylated haemoglobin. BMD: bone mineral density. LS: lumbar spine. FN: femoral neck. Fx: fracture. VFx: vertebral fracture. [a]: patients with at least one out of nephropathy, retinopathy and neuropathy.
[a] p = level of statistical significance between T2D patients without clinical Fx but with ≥1 major T2D-related risk factor for Fx (n = 39) and T2D patients without both without clinical Fx and major T2D-related risk factor for Fx (n = 49).

Table 5 BMD variations and incident fractures at follow-up in T2D patients who would have been pharmacologically treated and who would have been conservatively followed-up.

Follow-up parameters	All T2D patients evaluated at follow-up (n = 34)	T2D patients who would have been pharmacologically treated (n = 15)	T2D patients who would not have been pharmacologically treated (n = 19)	*p*
Patients with stable BMD	22 (64.7)	10 (66.7)	12 (66.7)	0.826
Patients with increased BMD	6 (17.65)	3 (20.0)	3 (11.1)	
Patients with decreased BMD	6 (17.65)	2 (13.3)	4 (22.2)	
Patients with incident fractures	2 (6.5)	2 (13.0)	0 (0.0)	0.187

Data are absolute number with percentage in parentheses. BMD: bone mineral density. T2D: type 2 diabetes.

At the follow-up evaluation 22 patients (64.7%) showed no significant BMD variations. In 6 patients (17.65%) BMD was significantly increased, whereas in the other 6 patients (17.65%) was significantly decreased. The BMD variations according to the baseline treatment indication are summarized in Table 5. It is noteworthy that in all 6 cases of BMD gain the improvement was limited to only the lumbar spine.

During the follow-up period two patients out of 34 experienced an incident fragility fracture (5.9%): one patient had a clinical VFx and one a morphometric moderate VFx. In both cases VFx involved the dorsal tract. Both patients with incident fractures would have been pharmacologically treated at baseline (Table 5) on the basis of the compresence of at least one major T2D-related factor risk (T2D duration $\geq$10 years) and a BMD T-score $\leq$ -2.0. At the follow-up evaluation one patient showed no significant BMD variations, whereas the other one experienced a significant BMD gain at the vertebral site.

Based on these data, a T2D patient with bone-active treatment indication according to the clinical recommendations established by the Italian multidisciplinary expert panel [6] tended to have a 7-fold increased risk of experiencing an incident fracture in the subsequent years (OR 7.04, 95%I.C: 0.31–158.7, p = 0.095) compared to patients without this indication, although not reaching the statistical significance probably because of the low number of incident fractures.

4. Discussion

Individuals with T2D have an increased risk of bone fragility compared to the general population and diabetic patients with fragility fractures have higher mortality rates than individuals (diabetic or not) without fractures [14–16]. Bone fragility is then increasingly recognized as a complication of T2D [1]. However, the underestimation of fracture risk in T2D using the classical assessment tools [2,4,5,17] pointed out the urgent need of clinical recommendations for the routine assessment of bone health in T2D subjects. The clinical consensus recommendations formulated by the multidisciplinary expert panel by Chiodini et al. suggested the diagnostic approach for the detection of T2D patients worthy of bone-active treatment for the fracture risk reduction [6].

This study was aimed at applying this algorithm to a well-characterized cohort of postmenopausal women with T2D in order to validate them in the clinical practice.

Following the flow-chart depicted in Fig. 1, about one third of patients would have been pharmacologically treated (Table 1). As expected, the group of subjects with treatment indication showed a higher prevalence of risk factors of fracture, both those common to the general population (advanced age, prevalent asymptomatic VFx, low femoral BMD) and those disease-specific (insulin treatment, disease duration above 10 years, T2D chronic complications considered as a whole). The lack of statistical difference in the glycaemic control between the two groups was due to the fact that, according to the inclusion criteria of our protocol, all recruited patients had a good glycaemic control.

According to the consensus, a previous non-vertebral, non-hip clinical fracture does not represent *per se* a criterion for treatment indication [6]. Among our T2D patients with prevalent clinical fractures (who were only 19 out of 107), about three-quarters of them would have been pharmacologically treated, whereas the remaining quarter (n = 5 subjects) would have been conservatively followed-up because of the absence of other criteria for active treatment (asymptomatic VFx, BMD T-score lower than −2.0 or FRAX+). Among these 5 patients only one had a major T2D-related risk factor, in keeping with a low fracture risk profile despite the previous non-hip and non-vertebral clinical fractures.

According to the flow-chart illustrated in Fig. 1, among our T2D patients without clinical fractures, nearly a quarter of them (20 out of 88) would have pharmacologically treated: in 9 patients the treatment indication came from the radiologic identification of morphometric moderate or severe VFx, which, despite being asymptomatic, are a known risk factor of subsequent fractures [18].

Considering all fractured patients together (both those with clinical fractures and those with morphometric VFx, Table 3), fractured patients had a more advanced disease with a higher prevalence of each major T2D-related factor risk than in patients without fractures, except for the poor glycaemic control due to the same reason mentioned above. These results strengthen the choice of T2D chronic complications, insulin treatment and T2D duration >10 years as major T2D-specific risk factors for fracture.

Conversely, about a third of patients without any fractures received the treatment indication anyway on the basis of DXA and FRAX data. This suggests that, despite the limited value of DXA scan and FRAX calculation in most T2D patients [2,5,17], these tools are still useful in selected cases for treatment decision (i.e. patients with non-hip and non-vertebral fragility fractures or patients without any fragility fractures, but with at least one of the major T2D-related risk factors for fracture).

It is interesting to observe that, through the application of the algorithm proposed by the multidisciplinary expert panel to our well-studied sample of postmenopausal women with T2D [6], only one out of 17 patients with moderate or severe morphometric VFx, and then at established high risk of fracture, would not have been treated due to the lack of indication to VFx assessment and then the non-recognition of prevalent morphometric VFx.

About this, from another point of view, among T2D patients without clinical fractures the presence of at least one of the major T2D-related risk factors for fracture showed a very good sensitivity in identifying who experienced a previous asymptomatic moderate or severe VFx and then was at increased risk of subsequent fractures [18]. In other words, the application of the flow-chart depicted in Fig. 1 to our sample confirmed that the absence of both prevalent clinical fractures and major T2D-related risk factors for fracture justifies the choice of a conservative follow-up without the radiological VFx assessment (NPV 98%). This supports the assessment of the major T2D-related risk factors as the first-line, easy and inexpensive tool to define the individual fracture risk profile in T2D patients without prevalent clinical fractures.

Although on a limited fraction of patients, the follow-up data gave us the opportunity to validate the clinical consensus recommendations also in a longitudinal way.

Two incident fractures, both vertebral, occurred in our sample of 34 T2D patients evaluated at follow-up. Notwithstanding the low number of followed-up subjects and incident fractures, it must be underlined that, based on baseline data, both fractured patients would have been pharmacologically treated if the diagnostic approach suggested by the expert panel [6] had been applied at baseline.

Conversely, no incident fractures occurred in the group of patients without any indication for bone-active treatment, thus suggesting the ability of the algorithm by Chiodini and colleagues to correctly detect diabetic subjects at relatively low risk of fracture despite the underlying disease. It is possible to postulate that the increased risk of incident fracture occurrence in patients with one of the criteria for active treatment indication compared to those without this indication did not probably reach the statistical significance because of the low number of analysed subjects and fracture events.

The application of the clinical consensus recommendations proposed by the expert panel to our sample confirmed the limited role of BMD in the monitoring of fracture risk in T2D [2,17]. The BMD variation at the follow-up examination in T2D patients who would have been pharmacologically treated did not statistically differ from those observed in T2D patients who would have been conservatively followed-up. Indeed, in about two thirds of patients bone mass showed no significant variations, independent of the basal fracture risk. Moreover, paradoxically, an incident fragility morphometric VFx occurred exactly in a T2D patient who experienced a BMD gain at the lumbar site. Precisely in this regard, it is noteworthy to un++derline that the BMD improvement at the follow-up DXA scan interested the lumbar site in 6 out of 6 cases. Then it is possible to hypothesize that in T2D subjects the finding of a normal and/or improved LS BMD could not be considered a reliable index of good bone health due to the frequent association of T2D and osteoarthritis [19]. However, the finding of a BMD reduction at spine remains of clinical significance. Therefore, in our opinion, the use of BMD T-score lower than −2.0 in any skeletal site, as suggested by the expert panel [6], can be considered adequate.

This study has some limitations. First of all, as already stated before, the small number of T2D patients evaluated in the longitudinal arm prevent us to draw firm conclusions. As the patients included in the longitudinal arm were only a third of those originally enrolled, an unwanted selection bias cannot be excluded. Moreover, the variable length of follow-up can be also considered a limitation of this study because the shortest follow-up can have unavoidably underestimated the incidence of fragility fractures.

Furthermore, according to the exclusion and inclusion criteria provided by the protocol, our sample included neither some categories of T2D patients at very high risk of fracture (e.g. patients on treatment with thiazolidinediones, with advanced T2D chronic complications and with poor glycaemic control i.e. HbA1c levels above 64 mmol/mol) nor male T2D subjects and we could not estimate the long-term glycaemic control of recruited patients. However, some literature evidence suggest that a persistent poor glycaemic control (according to the algorithm, persistent HbA1c levels above 8% for at least 1 year) should be considered in clinical practice as a risk factor for fracture, irrespective from disease duration, ongoing treatment or presence of complications [6,20–22].

Finally, mild morphometric VFx were not considered in the decision-making for treatment, but this is in line with the clinical consensus recommendations [6] which excluded this kind of fractures from the assessment of fracture risk in order to reduce the possibility of incorrect classification of various vertebral deformities as VFx which could lead to unnecessary treatment prescription [23].

Nevertheless, despite these limitations, the clinical consensus recommendations established by the Italian multidisciplinary expert panel [6] performed well in our sample of postmenopausal women with T2D. Indeed, among those subjects with bone-active treatment indication as many as 13% of patients experienced an incident fracture during the follow-up, thus confirming the presence at baseline of a high fracture risk worthy of specific treatment and conversely, among those subjects without

bone-active treatment indication no incident fractures were observed.

In the future, the application of the diagnostic approaches formulated by the multidisciplinary expert panel [6] in a larger sample of T2D patients with the inclusion also of subjects of both sexes and with a more severe disease (i.e. patients with proliferative or laser-treated retinopathy, overt diabetic nephropathy or severe macroangiopathy and patients with persistent HbA1c levels above 64 mmol/mol) could confirm the feasibility of the clinical consensus recommendations in the entire T2D population. Clinical trials in those T2D patients at risk for fragility fractures and deserving of bone-active treatment will then be needed to determine the actual efficacy and safety of available antiresorptive and anabolic agents in this specific setting.

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Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

[1] Paschou SA, Dede AD, Anagnostis PG, Vryonidou A, Morganstein D, Goulis DG. Type 2 diabetes and osteoporosis: a guide to optimal management. J Clin Endocrinol Metab 2017;102:3621–34. https://doi.org/10.1210/jc.2017-00042.

[2] 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.

[3] 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.

[4] 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.

[5] Leslie WD, Johansson H, McCloskey Ev, Harvey NC, Kanis JA, Hans D. Comparison of methods for improving fracture risk assessment in diabetes: the manitoba BMD registry. J Bone Miner Res 2018;33:1923–30. https://doi.org/10.1002/jbmr.3538.

[6] Chiodini I, Gaudio A, Palermo A, Napoli N, Vescini F, Falchetti A, et al. Management of bone fragility in type 2 diabetes: perspective from an interdisciplinary expert panel. Nutr Metabol Cardiovasc Dis 2021. https://doi.org/10.1016/j.numecd.2021.04.014.

[7] Zhukouskaya Vv, Eller-Vainicher C, Gaudio A, Cairoli E, Ulivieri FM, Palmieri S, et al. In postmenopausal female subjects with type 2 diabetes mellitus, vertebral fractures are independently associated with cortisol secretion and sensitivity. J Clin Endocrinol Metab 2015;100:1417–25. https://doi.org/10.1210/jc.2014-4177.

[8] FRAX n.d. https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=it (accessed February 16, 2022).

[9] Dawson-Hughes B. Commentary: a revised clinician's guide to the prevention and treatment of osteoporosis. J Clin Endocrinol Metab 2008;93:2463–5. https://doi.org/10.1210/jc.2008-0926.

[10] Zeytinoglu M, Jain RK, Vokes TJ. Vertebral fracture assessment: enhancing the diagnosis, prevention, and treatment of osteoporosis. Bone 2017;104:54–65. https://doi.org/10.1016/j.bone.2017.03.004.

[11] Genant HK, Wu, Van Kuijk Cornelis, ' Arid CY, Nevitt' MC. Vertebral fracture assessment using a semiquantitative techniquevol. 8; 1993.

[12] Shuhart CR, Yeap SS, Anderson PA, Jankowski LG, Lewiecki EM, Morse LR, et al. Executive summary of the 2019 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, periprosthetic and orthopedic bone health, transgender medicine, and pediatrics. J Clin Densitom 2019;22:453–71. https://doi.org/10.1016/j.jocd.2019.07.001.

[13] DerSimonian R, Laird N. Meta-analysis in clinical trials. Contr Clin Trials 1986;7:177–88. https://doi.org/10.1016/0197-2456(86)90046-2.

[14] Koromani F, Oei L, Shevroja E, Trajanoska K, Schoufour J, Muka T, et al. Vertebral fractures in individuals with type 2 diabetes: more than skeletal complications alone. Diabetes Care 2020;43:137–44. https://doi.org/10.2337/dc19-0925.

[15] Miyake H, Kanazawa I, Sugimoto T. Association of bone mineral density, bone turnover markers, and vertebral fractures with all-cause mortality in type 2 diabetes mellitus. Calcif Tissue Int 2018;102. https://doi.org/10.1007/s00223-017-0324-x.

[16] Tebé C, Martínez-Laguna D, Carbonell-Abella C, Reyes C, Moreno V, Diez-Perez A, et al. The association between type 2 diabetes mellitus, hip fracture, and post-hip fracture mortality: a multistate cohort analysis. Osteoporos Int 2019;30:2407–15. https://doi.org/10.1007/s00198-019-05122-3.

[17] Schwartz Av, Vittinghoff E, Bauer DC, Hillier TA, Strotmeyer ES, Ensrud KE, et al. Association of BMD and FRAX score with risk of fracture in older adults with type 2 diabetes. JAMA 2011;305:2184–92. https://doi.org/10.1001/JAMA.2011.715.

[18] Poiana C, Capatina C. Fracture risk assessment in patients with diabetes mellitus. J Clin Densitom 2017;20:432–43. https://doi.org/10.1016/j.jocd.2017.06.011.

[19] Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis. J Diabet Complicat 2016;30:944–50. https://doi.org/10.1016/j.jdiacomp.2016.02.016.

[20] Lui DTW, Lee CH, Chan YH, Chow WS, Fong CHY, Siu DCW, et al. HbA1c variability, in addition to mean HbA1c, predicts incident hip fractures in Chinese people with type 2 diabetes. Osteoporos Int 2020;31:1955–64. https://doi.org/10.1007/s00198-020-05395-z.

[21] Li C-I, Liu C-S, Lin W-Y, Meng N-H, Chen C-C, Yang S-Y, et al. Glycated hemoglobin level and risk of hip fracture in older people with type 2 diabetes: a competing risk analysis of taiwan diabetes cohort study. J Bone Miner Res 2015;30:1338–46. https://doi.org/10.1002/jbmr.2462.

[22] Wang B, Wang Z, Poundarik AA, Zaki MJ, Bockman RS, Glicksberg BS, et al. Unmasking fracture risk in type 2 diabetes: the association of longitudinal glycemic hemoglobin level and medications. J Clin Endocrinol Metab 2022;107:e1390–401. https://doi.org/10.1210/clinem/dgab882.

[23] Diacinti D, Vitali C, Gussoni G, Pisani D, Sinigaglia L, Bianchi G, et al. Misdiagnosis of vertebral fractures on local radiographic readings of the multicentre POINT (Prevalence of Osteoporosis in INTernal medicine) study. Bone 2017;101:230–5. https://doi.org/10.1016/j.bone.2017.05.008.