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Review

Bone Health in the Elderly with Type 2 Diabetes Mellitus–A Systematic Review

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Abstract

Type 2 diabetes mellitus (T2DM) and osteoporosis are two major public health concerns worldwide, contributing to morbidity and mortality in the elderly. Aging is one of the most significant risk factors for low bone mass, bone fragility, and fractures. Among the several

comorbidities that affect the elderly with diabetes, increased fracture risk is a relatively recently discovered complication. Generally, individuals with T2DM exhibit higher bone mineral density, which complicates the assessment of fracture risk. Despite the growing evidence for an association between T2DM and increased fracture risk, especially among the elderly, the underlying mechanism has not yet been fully uncovered, and proper evaluation of bone health in individuals with T2DM remains a challenge. The present review includes 125 articles investigating the effects of T2DM on bone health in the elderly. A systematic literature search was performed in PubMed, Embase, and CINAHL for articles containing terms corresponding to 'elderly' and 'type 2 diabetes mellitus' along with 'bone fracture', 'osteoporosis', or 'bone turnover'. Articles investigating the effects of T2DM and disease severity, duration, or complications on bone parameters – i.e. fracture risk, structure, and turnover – were selected for inclusion in the present review. Overall, the evidence indicated reduced bone turnover in individuals with T2DM, accompanied by an increased bone mineral density (BMD) and an inefficient distribution of bone mass with accumulated trabecular bone and diminished cortical bone. These structural alterations in bone tissues result in bone fragility and overall increased fracture risk in elderly individuals with T2DM. However, measurement of BMD does not adequately predict the increased fracture risk in T2DM. Therefore, identification and application of more precise predictors of fracture risk in individuals with T2DM are required. Furthermore, a better understanding of the pathophysiological mechanisms involved may assist in developing effective treatments of bone disease in individuals with diabetes. The present review introduces current candidates for improved measures of bone quality and fracture risk along with the current knowledge on the pathophysiology of diabetic bones.

Keywords
Elderly; bone; diabetes mellitus; bone structure; bone turnover; fractures

1. Introduction

The average human lifespan has increased by 5.5 years over the last 16 years [1]. Currently, the average life expectancy in Europe and the United States of America is 80.9 years and 78.7 years, respectively, with the highest life expectancy reported in women [2, 3]. Consequently, the need for effective prevention and treatment of chronic aging-related diseases has increased. Type 2 diabetes mellitus (type 2 DM; T2DM) and osteoporosis are two common metabolic diseases among the elderly [4, 5].

Increasing age is a significant risk factor for osteoporosis, as evidenced by the exponential increase in hip fracture incidence with age [6]. The World Health Organization has defined the following diagnostic criterion for osteoporosis: bone mineral density (BMD) of ≥2.5 SD below the average value for young, healthy women, i.e., a BMD T-score ≤ −2.5 [6, 7]. The T-score is derived from areal BMD (aBMD) measured using Dual-energy X-ray Absorptiometry (DXA) at the lumbar spine, femoral neck, or total hip. However, in a prospective study from 2004 conducted with elderly men and women aged ≥55 years, it was reported that only 21% and 44% of all non-

vertebral fractures in men and women, respectively, occurred with an aBMD T-score below −2.5 [8]. Therefore, there must be several important risk factors for fractures other than a relative reduction in the aBMD.

T2DM is a chronic metabolic disorder that arises due to insulin resistance and a relative insulin deficiency, resulting in elevated blood glucose levels [9]. The risk of T2DM is reported to increase with age [10]. Neither the Fracture Risk Assessment Tool (FRAX) nor aBMD sufficiently predict fracture risk in T2DM [11, 12]. In fact, fracture risk is underestimated in T2DM, corroborating the hypothesis that bone quality is affected by T2DM [12, 13]. T2DM is associated with an increased fracture risk despite consistent findings of unaffected or elevated aBMD [13-16]. Diabetic bones are characterized by a state of low bone turnover, which potentially leads to impaired bone quality [17, 18]. Evidence suggests that T2DM is an independent risk factor for bone fragility and fractures as it exerts an effect on bone metabolism and aggravates the age-related impairment of bone quality [17]. Therefore, bone health in the elderly with T2DM requires increased attention and improved assessment. However, the utility of aBMD as a clinical indicator of osteoporosis and fracture risk has significant limitations. Complementary tools are increasingly being used to assess the association of diabetes to bone fragility and fractures in the elderly. In addition, a higher aBMD T-score intervention threshold has been proposed for diabetic patients [19].

The present systematic review summarizes the current knowledge regarding bone health in the elderly with T2DM through discussion of structural and biochemical bone measurements as well as fracture risk.

The aim of the present review is to present the current knowledge on the effects of T2DM on bone, identify associated risk factors and confounders, and identify knowledge gaps in the field.

2. Materials and Methods

A systematic literature search was performed in accordance with the PRISMA guidelines [20, 21] in the following three databases: PubMed, Embase, and CINAHL. The search strings were optimized through database-specific evaluation of the search terms. Search terms were used only if they influenced the number of articles yielded by the search. Each database has its own form of bibliographic indexing (for example, MeSH-terms in PubMed), and these indexing terms were identified for each database and added to the respective search strings. The search strings were made to yield articles satisfying the following three criteria: (1) contained a term representing “type 2 diabetes” in the title or abstract, (2) contained a term representing “elderly” in the title or abstract (or in the ‘age group’ category for CinAHL), and (3) contained a term representing “bone disease”, “fracture”, or “ bone turnover” in the title or abstract. The final literature search was performed on 29th October, 2019.

Table S1 lists the search terms used in the PubMed search. Table S2 provides the exact search strings. The initial search yielded 1,548 results. After removing duplicate articles, 1,204 articles remained. Two reviewers (RV and ZAM) independently assessed abstracts and subsequently full-text articles for eligibility according to the inclusion criteria. Disagreements were resolved through discussion.

Figure 1 illustrates the exclusion process described ahead. First, articles which were not available in English, German, Spanish, Italian, French, Norwegian, Danish, or Swedish were excluded. Next, articles reporting studies that were not human *in-vivo* studies were excluded.

Subsequently, case reports, case series, posters, conference abstracts, reviews (without meta-analysis), letters to the editor, commentaries, expert opinions, and consensus statements were excluded. Finally, the remaining abstracts and articles were assessed to identify relevant study populations, exposures, and outcomes. Articles were included only if at least one subset of the study population had T2DM, satisfied the age criterion (see below), and was examined for relevant bone-related outcomes (see below). The age criterion was as follows: mean age ≥ 55 years, minimum age ≥ 50 years, or postmenopausal. Exposures were considered relevant if the study involved one of the following: 1) comparison of T2DM with non-diabetic subjects, 2) analysis of the effects of glycemic control (e.g., hemoglobin A1c [HbA1c] or fasting plasma glucose [FPG]), 3) assessment of the effects of insulin resistance (e.g., through homeostatic model assessment [HOMA]), 4) investigation of the effects of prevalent diabetic complications (e.g., neuropathy), or 5) assessment of the effects of diabetes duration. Outcomes were considered relevant if the study involved: 1) any measure of fracture risk, 2) any measure of bone structural integrity (such as BMD, trabecular bone score [TBS], and bone material strength index [BMSi]), or 3) bone biochemical markers. Bone markers included osteocalcin (OC), sclerostin, carboxy-terminal collagen crosslinks (CTX), N-terminal propeptide of type 1 procollagen (P1NP), and osteoprotegerin, among others. Measurements of parathyroid hormone (PTH), vitamin D, and alkaline phosphatase (ALP) levels in articles were noted, although articles were not considered for inclusion if no other bone markers were measured. Finally, inaccessible full-text articles were excluded, as the categories of data considered relevant for extraction could not be reliably obtained from abstracts. Conference abstracts were excluded for the same reason. Articles were regarded as inaccessible if there were no links to the articles in the utilized databases; authors were not contacted. Eleven additional articles eligible for inclusion were identified in the reference lists of the examined articles and were included in the final review.

Two authors, RV and ZAM, extracted data from all the included articles; articles involving bone structural parameters were examined by author RV, while articles involving biochemical or fracture-related parameters were examined by author ZAM.

Data related to the following were extracted**:** 1) author name, 2) study sample size, 3) population characteristics (age, nationality/geographic information, sex, disease status, other relevant information), 4) investigation performed or main outcome parameter (for example, DXA-scan/aBMD), 5) adjustment parameters used in the main statistical analyses, and 6) major findings, including significance levels and effect sizes.

The extracted data for biochemical, structural, and fracture-related outcomes are presented in Table 1, Table 2, and Table 3, respectively. If solely the baseline characteristics from a study population were extracted for review, the study in question was characterized as cross-sectional, regardless of the true nature of the study.

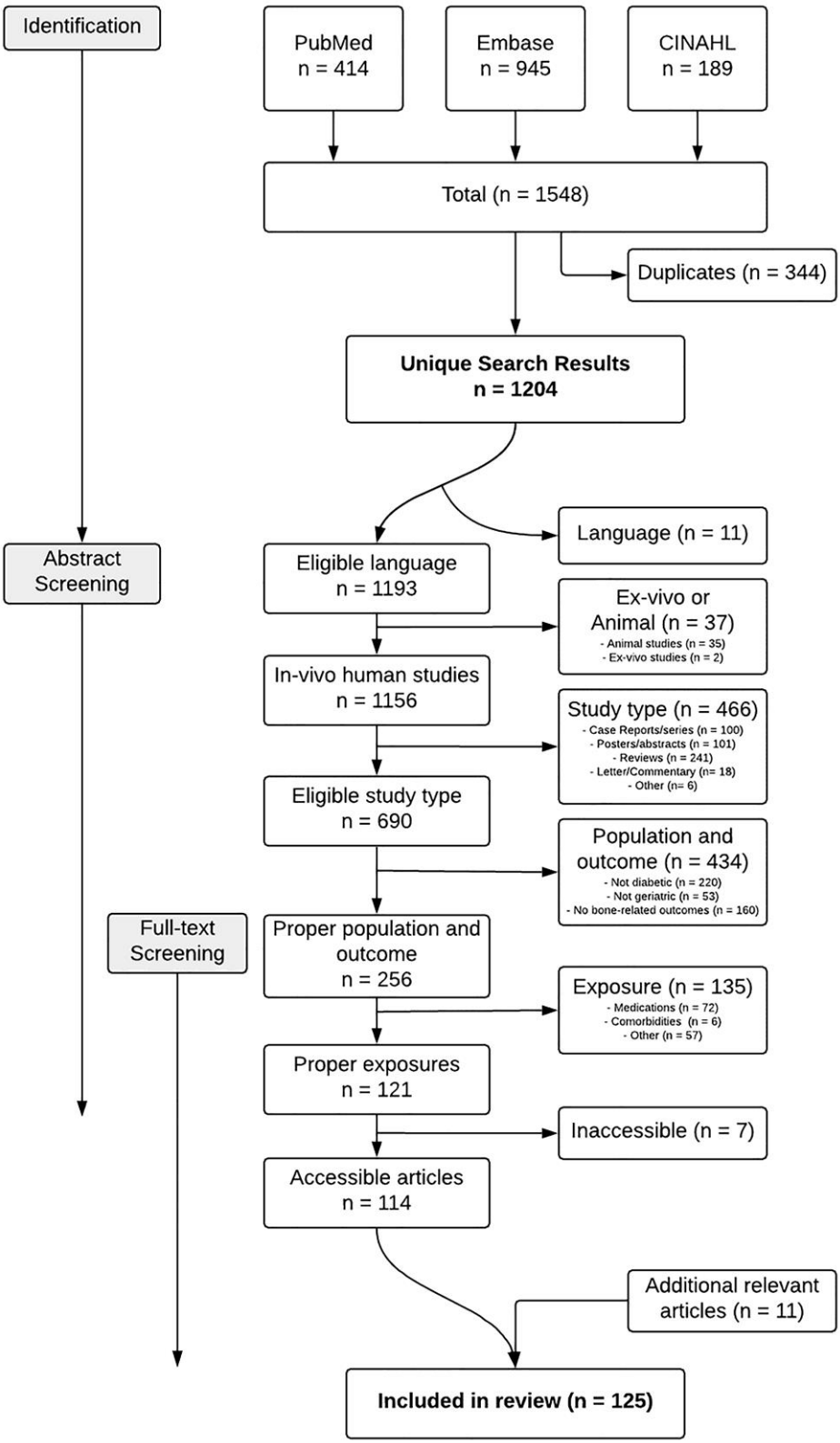

Figure 1 Appraisal/exclusion process.

3. Results

A total of 125 articles satisfied the inclusion criteria and were included in the present review. Among the included articles, 78 articles investigated bone structural changes associated with T2DM, 61 articles investigated fracture risk, and 28 articles investigated bone biochemical markers.

3.1 T2DM and Biochemical Markers of Bone Health

Among the 28 articles investigating the relationship between T2DM or related parameters and bone biochemical markers (Table 1), 7 articles included only men and 11 included only women as their study subjects. In the remaining 10 articles, the average proportion of women was 55% (not weighted according to study size). In the studies reporting age, the mean ages were averaged (not weighted according to study size) to 58 years.

Only two studies reported no association between T2DM and related parameters (duration, complications, or severity) and bone biochemical markers [22, 23]. The most commonly studied markers were OC, sclerostin, CTX, and P1NP. OC and P1NP are markers of osteoblast function and bone formation, while CTX and NTX (N-terminal telopeptide) are collagen degradation products and, therefore, bone resorption markers [24]. Levels of undercarboxylated OC (ucOC) are associated with increased fracture risk [25]. Sclerostin is an inhibitor of osteoblasts and, consequently, bone formation [24].

Several studies reported lower levels of CTX or NTX in individuals with T2DM [26-34], those with diabetes-related retinal complications [35], or those with increasingly pathological levels of glycemic markers [31, 36]. Other studies reported no association between these markers and diabetes [23, 36-40]. Zhou et al. reported an increased urinary NTX secretion in individuals with T2DM [41], whereas Ardawi et al. observed reduced urinary NTX secretion in these individuals [34].

Several studies reported suppressed OC levels in individuals with T2DM [26, 27, 29-32, 34, 37-39, 41-45]. Suppressed OC levels have also been reported in association with higher levels of FPG, fasting plasma insulin (FPI), HbA1c, or HOMA-IR (HOMA–insulin resistance) or with lower levels of HOMA-β (HOMA – beta-cell function) [26, 31, 42-44, 46, 47]. Xia et al. compared different groups of individuals with T2DM and reported decreased OC levels in the group with microalbuminuria; the OC levels were observed to be further decreased in the group with macroalbuminuria [48].

Yeap et al. reported that the ratio of ucOC to total OC was higher in individuals with T2DM compared to those without DM [29]. Iki et al. observed that this ratio increased with higher levels of FPG, FPI, HOMA-IR, and HbA1c [44]. Few studies reported no association between OC and T2DM [22, 23, 33]. Bulló et al. reported positive associations of baseline OC levels with FPI, HOMA-IR, and HOMA-β, although changes in OC levels over a period of two years (during a diet-intervention randomized controlled trial) could not predict FPG or FPI levels [47].

Similarly, P1NP was observed to be reduced in individuals with T2DM [26-30, 34, 37, 39, 49], those with diabetes-related retinal complications [35], and those with higher levels of FPG, FPI, HbA1c, or HOMA-IR or lower levels of HOMA-β [36, 49]. Few studies reported no effects of T2DM on P1NP levels [36, 38].

Among the six studies investigating sclerostin, two studies reported increased levels of sclerostin in individuals with T2DM [33, 34]. In addition, García-Martín et al. reported an association between sclerostin levels and the duration of T2DM [33]. Three studies reported no

correlation between T2DM or HbA1c and sclerostin levels [22, 38, 46]. Only one study reported lower levels of sclerostin in individuals with T2DM or in those with higher levels of FPG or FPI [42].

Rianon et al. studied the effect of DM duration and reported no association with OC or sclerostin levels [46]. Rasul et al. reported an association between prevalent polyneuropathy and higher levels of CTX, P1NP, and OC in men but not in women [50]. Maagensen et al. and Chailurkit et al. investigated the effect of an oral glucose load and reported that the suppression of CTX was attenuated in individuals with T2DM [37, 40]. Moreover, Maagensen et al. observed that the suppression of OC and P1NP was unaffected in individuals with T2DM, and Chailurkit et al. observed the suppression of osteoprotegerin to be unaffected by T2DM [37, 40].

Most of the studies investigating levels of vitamin D, PTH, calcitonin, or ALP reported no significant differences between individuals with DM and those without DM [23, 26, 28, 31-33, 35, 36, 41, 48, 50, 51]. However, decreased vitamin D levels in individuals with T2DM were reported in three studies [32, 36, 38], whereas increased levels were reported in one [30]. Four studies observed no effect of DM on vitamin D levels [26, 28, 31, 51]. Three studies reported lower PTH levels in individuals with T2DM [30, 31, 34, 39], whereas in this population PTH levels were reported to be higher in one study [48] and unaffected in seven studies [23, 26, 28, 32, 36, 41, 51] compared to individuals without DM.

3.2 T2DM and Structural Changes in Bone Tissue

Among the 78 articles that reported outcomes related to bone structure (Table 2), 12 included only men and 30 included only women as their study subjects. In the remaining 36 articles, the average proportion of women was 58% (not weighted according to study size). In the studies reporting age, the mean ages were averaged to 65 years (not weighted according to study size).

There was considerable variation among the articles in regard to the measures of bone structure used, with a variety of measures for BMD, bone composition, and bone microarchitecture.

The most prevalent among the methods and outcome parameters in the examined articles was DXA/aBMD (N = 64), followed by Quantitative Computed Tomography (QCT) or High-Resolution peripheral QCT (HRpQCT) (N = 9), Quantitative UltraSound (QUS) (N = 10), and MRI (N = 3), respectively.

Among the 78 studies involving structural bone measurements, 66 studies reported the effects of T2DM or glycemic control on aBMD, primarily obtained by DXA-scan of total hip, femoral neck, or lumbar spine. In 50 studies, higher aBMD at one or more sites was observed in association with prevalent T2DM or with worse glycemic control in individuals with T2DM. Higher aBMD was observed at all measured sites in 16 studies. Nine studies reported no difference in aBMD, while five studies reported lower aBMD in individuals with T2DM compared to those without T2DM (details below).

A few studies reported no difference in aBMD between individuals with and without T2DM [26, 33, 52-58]. Although these study populations were dissimilar in terms of nationalities and sex, all of these studies were adjusted for multiple variables–always including BMI. On the other hand, the studies reporting a difference were more heterogeneous in terms of statistical analyses, and a number of results were based on unadjusted data, although the majority of the studies were adjusted for BMI and other factors (Table 2).

Five studies, four of which included Chinese men and women as study subjects, reported reduced aBMD in correlation with T2DM or higher HbA1c levels [41, 48, 59, 60]. Sert et al., in their study conducted on Turkish men and women, reported that T2DM was associated with reduced aBMD at the lumbar spine in men, whereas higher femoral aBMD was reported in both men and women [61]. The mean BMI values were in the range of 25.1–26.1 in three studies with Chinese subjects [48, 59, 60], and Zhou et al. reported reduced aBMD only in those subjects which had BMI < 25 kg/m^2 [41]. These findings may indicate that T2DM is associated with increased BMD only in the presence of high BMI. However, six other studies conducted on Asian populations did report increased aBMD in subjects with T2DM with mean BMI ranging from 22.0 to 25.6 [30, 39, 62-65].

A higher trabecular bone score (TBS) reflects denser trabeculae and a more fracture-resistant microarchitecture [66]. TBS is estimated from DXA and has been reported to be associated with osteoporotic fracture risk, independently of aBMD and clinical risk factors [67, 68]. Studies have reported lower TBS in subjects with T2DM compared to those with prediabetes and those with normal glucose metabolism [39, 58, 69, 70]. Especially lumbar spine TBS appears to be reduced in T2DM [58, 69, 71]. This is consistent with the findings of a meta-analysis conducted by Ho-Pham et al., which concluded that individuals with T2DM exhibit lower TBS compared to those without DM [72].

Leslie et al. reported an accentuated risk of incident major osteoporotic fracture after adjusting for BMD, whereas the risk was partially attenuated when adjusting for trabecular bone score (TBS) [71]. This supports the conclusion that BMD is insufficient as a prognostic tool for predicting fracture rates in individuals with T2DM. TBS may thus serve as an easily obtainable yet powerful addition to any predictive model for fracture risk in T2DM.

It is not possible to distinguish between trabecular and cortical BMD using DXA. Cortical bone density is a major determinant of bone strength. QCT and HRpQCT enable the assessment of bone architecture at the trabecular and cortical sites using volumetric BMD (vBMD) and the prediction of bone fragility and fracture risk [73, 74]. vBMD was measured in nine of the included studies.

Several studies reported vBMD differences, such as higher spine vBMD [75] and radial and tibial trabecular vBMD [28, 76, 77] in subjects with T2DM compared to those without DM. A few studies reported higher aBMD in T2DM without observing any difference in vBMD [78-80]. One study reported lower vBMD at the spine in individuals with T2DM compared to those without DM [81]. De Waard et al. observed no association between HRpQCT measures of vBMD and T2DM or prediabetes, although they reported an association between HbA1c > 7% (53 mmol/mol) and higher cortical porosity at the distal radius in individuals with T2DM [79].

Several studies reported higher cortical porosity [77, 79] and lower cortical thickness [79, 82] and vBMD [76, 79] in individuals with T2DM. Nakamura et al. observed higher trabecular vBMD (measured by QUS) in individuals with T2DM after the age of 60 compared to individuals without DM [82]. A few studies reported no difference in cortical thickness (Table 2), while one study reported lower cortical porosity in individuals with T2DM [36].

A study that employed MRI detected higher bone marrow fat content in T2DM, which correlated inversely to hip aBMD [78]. Another study employing MRI reported increased spacing within the trabecular bone network in subjects with T2DM [83]. A prospective cohort study with two years of follow-up did not report any differences in the evolution of trabecular bone microarchitecture in elderly women with T2DM compared to elderly women without DM [84].

All the included studies were observational apart from one study, which was a randomized controlled trial [52]. The latter investigated whether bone health could benefit from intensive glycemic control, but no difference in aBMD was observed at any site following intensive or standard glycemic control with a median intervention time at examination of 2.2 years [52].

In contrast to these findings in individuals with T2DM, a study conducted by Napoli et al. in 2019 examined aBMD in individuals without DM and observed no association with insulin sensitivity assessed through HOMA-IR [85]. This may indicate a dose- and time-dependent effect of insulin resistance on bone quality, which becomes apparent only after the development of T2DM.

In summary, the studies included in the present review were substantially heterogeneous in terms of bone structural outcome measures, sex-distribution, and demographics. Increased aBMD was reported in both men and women with T2DM. Most of the included studies reported a positive association of aBMD with higher glucose or HbA1c levels, whereas a few studies reported a negative association with DM duration even after adjusting for age. However, it is not possible to distinguish between trabecular and cortical bone architecture using aBMD, which is only one component of bone quality. The vBMD measurements in the included studies indicated a greater trabecular bone volume and increased cortical porosity in elderly persons with T2DM. However, there is no clear consensus on which bone site is the most affected by diabetes-related structural changes. Therefore, the elderly with DM may have impaired bone quality which cannot be assessed properly using routine diagnostic methods, i.e. DXA BMD and T-score thresholds.

3.3 Changes in Bone Structure over Time in T2DM

Although there is an apparent association between prevalent T2DM and higher aBMD, a study conducted by Jang et al. reported that subjects with diabetes duration > five years had approximately the same adjusted femoral neck aBMD (0.738 ±0.004 g/cm^2) as subjects without T2DM, which was in turn lower than that of subjects with shorter diabetes duration (0.773 ±0.004 g/cm^2) after adjusting for age, body mass index (BMI), and other factors [86]. Leslie et al. observed that BMD loss was 0.0018 g/cm^2/year greater in individuals with T2DM compared to normal-weight individuals without DM (age-adjusted) [87]. A study conducted by Xu et al. reported a crude odds ratio (OR) of 2.06 for osteoporosis with diabetes duration > 20 years compared to duration < 10 years, although this effect was fully attenuated after adjusting for age, BMI, and a variety of other factors [88]. In addition, Xu et al. reported an adjusted OR of 1.63 for osteoporosis in association with poor glycemic control (HbA1c ≥ 7.5%) in males but not in females [88].

In contrast, Shan et al. reported a smaller aBMD decrease at the lumbar spine with increasing age in individuals with T2DM compared to those without DM; in addition, a less pronounced increase in osteoporosis prevalence was observed with increasing age [64].

Taken together, these findings appear to suggest an increase in the rate of bone loss with age. However, it is difficult to reconcile this finding with reduced bone turnover and increased BMD. Rather, it may be that an increased mineral loss is present only in a subset of individuals with T2DM, possibly in those with the highest severity and longest duration of the disease, allowing for several years of mineral accumulation prior to the acceleration of mineral loss at a late stage.

3.4 T2DM and Risk of Fracture

Among the 61 articles investigating the effects of T2DM on fracture risk (Table 3), 6 included only men, and 16 included only women as their study subjects. In the remaining 39 articles, the average proportion of women was 55% (not weighted according to study size). In the studies reporting age, the mean ages were averaged to 70 years (not weighted according to study size).

Most articles (N = 49) reported an increased risk of fracture in at least one location associated with the presence of diabetes or diabetes-related parameters. A total of 13 studies reported no association of fracture risk with T2DM [32, 75, 89-92], HbA1c levels [38, 62, 80, 93-96], fasting plasma glucose [38, 62], HOMA indices [90], or diabetes duration [32, 62, 80, 95]. Five of these studies reported no associations in any of the analyses performed [32, 38, 75, 89, 93]. Six studies reported reduced fracture risk in at least one location associated with the presence of diabetes [51, 81, 95, 97-99] or higher HbA1c levels [97]; four of these studies were relatively small (the largest with n = 5,931) case-control studies investigating fracture prevalence [51, 81, 95, 99], whereas the remaining two were retrospective cohort studies investigating fracture incidence [97, 98].

All the studies included in the present review were observational apart from one randomized controlled trial which reported no effect of intensive glycemic control on fracture risk compared to standard glycemic control [52].

Several studies reported an increase in hip fracture prevalence or incidence with the presence of T2DM (N = 22) [14, 31, 65, 100-118], higher levels of HbA1c in individuals with T2DM (cut-offs varying among the studies) (N = 6) [91, 107, 119-122], higher fasting plasma glucose in individuals with T2DM (N = 1) [120], complications of diabetes (N = 5) [94, 102, 107, 109, 121], or duration of diabetes (N = 8) [14, 107, 110, 114, 115, 118, 120, 121]. de Liefde et al. reported no association between T2DM and hip fracture, although they did observe an increased risk of hip fracture associated with diabetes treated with antidiabetic drugs [123]. Among the studies which reported association of T2DM with an increased risk of hip fracture, most presented an OR, a hazard ratio (HR), a relative risk (RR), or an incidence rate ratio (IRR). Most of the effect sizes reported here (OR/HR/RR/IRR) were in the range of 1.30–1.80. The largest studies were conducted by Hothersall et al. (n = 3,840,841) and Hippisley-Cox et al. (n = 3,142,673), which in women reported HRs of 1.05 (95% confidence interval [CI] of 1.01–1.10) and 1.57 (95% CI 1.45–1.69), respectively [110, 112]. A meta-analysis of 12 articles (combined n = 764,282), which included several of the studies examined in the present review [31, 32, 89, 113-115, 118, 123], conducted by Dytfeld et al. assessed hip fracture risk and revealed an increased risk with an OR of 1.30 (95% CI 1.07–1.57) [104]. Only one study reported a reduced risk of hip fracture associated with T2DM; however, this association was observed only in the subgroup comprising males not receiving antidiabetic medications [124].

Vertebral fracture risk was reported to be associated with diabetes in six studies [30, 34, 62, 96, 105, 125], among which five studies investigated prevalent fractures using x-ray imaging [30, 34, 62, 96, 125]. Majumdar et al. studied incident fractures by means of hospital discharge notes and reported an increased risk with a study sample of n = 57,938 [105]. Yamamoto et al. reported a higher prevalence of vertebral fracture (evaluated using x-ray) in women with T2DM, while a lower prevalence was reported in men with T2DM (although no statistical analysis was performed) [30]. Viégas et al. reported an increased prevalence of vertebral fracture associated with longer

diabetes duration and with the presence of retinopathy; the increase was not observed for nephropathy and peripheral diabetic neuropathy [125]. Only two of the studies reported ORs [62, 96]. Kilpadi et al. reported an OR of 2.86 (95% CI 1.56–5.34), and Yamamoto et al. reported an OR of 1.86 (95% CI 1.11–3.12) for women and 4.73 (95% CI 2.19–10.20) for men; however, both of these studies had a relatively small sample size (n = 296 and n = 996, respectively) [62, 96]. In contrast, eight studies reported no association of vertebral fracture risk with diabetes [14, 32, 75, 89, 103, 111] or glycemic control [38, 62]. Among these eight studies, six studies investigated prevalent fractures [32, 38, 62, 75, 89, 111] and four studies investigated incident fractures [14, 32, 75, 103], most by means of x-ray assessment, although two studies relied on self-reported data [38, 111]. A meta-analysis by Dytfeld et al. of seven studies (combined n = 107,514), which included four of the above-stated studies [14, 32, 62, 89], investigated vertebral fracture risk and did not observe this to be increased (OR = 1.13 [95% CI 0.94–1.37]) [104]. No studies reported a reduced risk specifically of vertebral fracture in individuals with T2DM.

Many articles investigated the overall risk of fracture or risk of clusters of fracture types, such as non-vertebral fractures, osteoporotic fractures (OPF), major osteoporotic fractures (MOPF), and non-hip non-vertebral fractures (NHNVF). The majority of these articles reported an increased risk associated with diabetes [14, 69, 71, 80, 102, 105, 108, 111-113, 123, 126-130], with glycemia in individuals with T2DM (higher levels of HbA1c or FPG, with cut-offs varying among studies) [69, 90, 128], with longer disease duration [92, 105, 123, 131], or with diabetic complications [92, 102]. Few articles reported no increased risk of overall or clustered fracture types [38, 51, 81, 89, 93, 95, 97, 99, 103]. In the articles that reported an effect on the overall risk of clustered fracture types, effect sizes (ORs or HRs) were around 1.20 [102, 108, 112]. Kachroo et al. observed that each 1 standard deviation (SD) increase in HbA1c or FPG levels was associated with an HR of 1.38–1.39 for osteoporotic fractures and an HR of 1.45–1.48 for major osteoporotic fractures [90].

Reporting of fracture risk in locations other than the hip or vertebrae was less common (data presented in Table 3).

In summary, there appears to be a general trend toward an increased risk of hip and overall fractures in elderly individuals with T2DM compared to individuals without T2DM. This finding is consistent with the conclusion of a literature review conducted by Rasmussen et al. [132]. The severity of DM, measured in terms of glycemic control, diabetes duration, and complications, also appears to be a risk factor for fractures. The evidence for increased risk of vertebral fractures is inconsistent, although all the studies included in the present review reported either no effect or an increased risk of fracture in this location. However, the observed increase in fracture risk may also be mediated, at least in part, by an increased risk of falls due to hypoglycemia and peripheral neuropathy.

3.5 Bone Health and Hypoglycemia

Although hyperglycemia appears to be a risk factor for fractures, some studies reported an increased risk of fractures associated with hypoglycemia or with lower levels of HbA1c compared to higher HbA1c levels [119, 125, 133-135], whereas only two studies reported no deleterious effect of hypoglycemia [120, 121]. However, Chiang et al. observed that visit-to-visit variation of FPG was a predictor of hip fracture, indicating an effect mediated by increased hypoglycemia risk [120]. Kachroo et al. quantified the increased risk associated with hypoglycemia and reported an

OR of 2.16 (95% CI 1.74–2.67) for any fracture [134]. Viégas et al. observed that normal postprandial glucose in individuals with T2DM was a risk factor for vertebral fractures compared to postprandial hyperglycemia and that women with prevalent fractures had lower levels of postprandial glucose and HbA1c compared to those without prevalent fractures [125]. This may reflect an underlying increased risk of hypoglycemia in those with normal postprandial glucose levels in this particular study population. Two studies reported that the increased fracture risk was entirely or mostly associated with insulin use, suggesting an effect mediated in part by hypoglycemia [124, 129]. Another study reported that the increased fracture risk was fully attenuated after adjusting for comorbidities and falls [127]. It is a seemingly inconsistent finding that fracture groups exhibit higher HbA1c levels in some studies and lower HbA1c levels in other studies. However, this apparent contradiction may be explained by a J-shaped association mediated by hypoglycemia and falls at one end and bone fragility at the other. Indeed, Lee et al. reported just such an association with increased fracture risk at both high (> 9.5%) and low (< 6.5%) HbA1c levels [119].

3.6 Bone Health and Complications of T2DM

A few studies reported data on diabetes-related complications and bone structure. Xia et al. reported that a lower aBMD at the lumbar spine and femoral neck was correlated with albuminuria in individuals with T2DM [48]. Rasul et al. observed no differences in aBMD between individuals having T2DM with and without polyneuropathy [50]. Zhong et al. reported no association between aBMD and HbA1c levels, although it was observed that the presence of microangiopathy was associated with decreased bone mass at the lumbar spine, total hip, and femoral neck in women, while the same was not true for men [136].

A total of seven studies reported an increased risk of fractures associated with the presence of diabetes-related complications [92, 94, 102, 107, 109, 121, 125]. An increased risk of fractures associated with the presence of peripheral neuropathy was reported in three studies, the largest of which was conducted by Lee et al. (n = 2,798,309) [102, 107, 121]. Three smaller studies reported no effect of peripheral neuropathy on fracture risk, possibly due to insufficient sample size [62, 120, 125]. In addition, these three small studies reported no effects of nephropathy [125] or retinopathy [62, 120], whereas four studies (the largest conducted by Kabue et al.; n = 120,256) observed that the presence of retinopathy was associated with fracture risk [92, 94, 121, 125]. Reyes et al. (registry-based study) observed that T2DM with any complications (of unspecified type) presented an increase of 89% in hip fracture risk compared to T2DM without complications, which presented an increase of only 45% in hip fracture risk.

These findings suggest that all complications of diabetes, besides serving as simple proxies for disease severity, may increase fracture risk independently. However, retinopathy and peripheral neuropathy may have a special significance in increasing the risk of fractures, as the impaired vision and proprioception is expected to increase the risk of falling.

3.7 Sex-Specific Differences in Bone Health in T2DM

It is well known that men have a lower risk of osteoporosis and fractures and a higher BMD compared to women [7]. Nonetheless, sex-specific differences regarding bone mass in individuals

with T2DM have been investigated inadequately. The vast majority of studies reported increased aBMD associated with T2DM in both men and women (Table 2).

However, a number of studies included in the present review concluded that women with T2DM had a higher aBMD compared to women without DM, whereas no such difference was observed for men [30, 88, 137-139]. A cohort study conducted by Lunt et al. investigated the effect of insulin use in T2DM and reported that insulin treatment was associated with an increase in aBMD at all sites in women, whereas such an increase was observed only at the spine in men [140].

Only one study reported higher whole-body aBMD in men with T2DM and not in women with T2DM [141]. Chi et al. reported a higher aBMD in men compared to women, independently of the presence of diabetes [142]. Sert et al. observed that the difference in aBMD between subjects with T2DM and those without DM was more pronounced in men than in women [61]. The study reported that among women aged 51–60, those with T2DM exhibited higher femoral neck aBMD than controls [61]. Similarly, among men aged 51–60, those with T2DM exhibited higher femoral neck and total femur aBMD and lower lumbar spine aBMD compared to men without DM, the latter being present already after the age of 30 [61].

A study comparing men and women with and without T2DM reported that T2DM was associated with skeletal hypertrophy (measured using HRpQCT), which was attenuated at the tibial cortex in men compared to women [143].

Accounting for sex altered the strength of the association between T2DM and fracture risk in some studies [65, 98, 111, 113], although the direction of this effect was not consistent across studies. Wallander et al. reported that the risks of any fracture, hip fracture, and major osteoporotic fractures were all increased to a higher extent in women compared to men [124].

3.8 Effects of Other Subject Characteristics

Several articles examined the effects of other participant characteristics on the association between T2DM and fracture risk.

Only two studies investigated the effect of T2DM on fracture risk in individuals with osteoporosis [116, 126]. Sato et al. reported an association between T2DM and fracture risk in individuals diagnosed with osteoporosis and receiving antiosteoporotic medication [126], whereas Taylor et al. reported no association between T2DM and fracture risk in the subset of osteoporotic participants [116].

Two studies examining bone structure reported that aBMD was increased only in the obese subpopulation [137] and that obesity attenuated the increased BMD loss over time observed in individuals with long diabetes durations (> 4 years) [87]. In addition, two studies reported that the effect of T2DM on fracture risk was diminished or absent in obese individuals [115, 118]. Taken together, these results suggest a protective effect of high BMI, possibly mediated by a beneficial increase in BMD. Alternatively, there may be a protective effect of increased padding of bone tissues in obese individuals.

Nakamura et al. observed that elderly subjects with T2DM and reduced handgrip strength exhibited diminished cortical thickness but no changes in trabecular vBMD [82]. This result indicates that reduced muscle strength, or sarcopenia, is an important factor associated with cortical thinning and, consequently, with increased fracture risk.

4. Discussion

The present review provides data on bone health in the elderly with T2DM. However, as most of the studies included were epidemiological in nature, an inevitable uncertainty remains with regard to parameters such as diabetes status and type. Indeed, a few studies attempted to quantify the degree of certainty regarding the type of diabetes present in their subjects. These estimates of certainty appeared to be sufficiently high (≥97%) [87, 102]. In case of contamination of the included studies with individuals having T1DM, underestimation of BMD and overestimation of fracture risk are expected [13]. This is supported by the findings reported in two of the included studies, in which comparisons between individuals with T1DM and individuals with T2DM were also performed [53, 124]. In the study conducted by Tuominen et al., the individuals with T1DM exhibited lower aBMD values compared to those with T2DM and those without DM [53]. These findings were consistent with those of previous meta-analyses [13, 144] and were neither explained by differences in BMI nor by insulin treatment. Wallander et al. reported that fracture risks (any, hip, major osteoporotic, and ankle) were higher in individuals with T1DM compared to any subgroup of individuals with T2DM [124].

The majority of studies examining OC, P1NP, and CTX/NTX indicated suppression of bone turnover mediated by the presence, severity, and duration of T2DM. This suppression appears to be correlated with the presence and severity of diabetes. Owing to relatively small sample sizes, most of the studies reported unadjusted results and performed few subgroup analyses in general. Therefore, it is not possible to distinguish, for instance, the sex-specific effects. However, there are no clear differences between the results of studies examining one sex and those examining the other or both sexes. The insufficiency of evidence along with varying proxies for disease severity (e.g., comorbidities or glycemic control) do not allow exact conclusions regarding the specific effects of disease severity and comorbidities.

The findings regarding vitamin D and PTH suggest that the levels of vitamin D or PTH might be affected in individuals with T2DM, although the evidence is insufficient, and further research is warranted.

Reduced bone turnover may lead to the accumulation of microfractures and impaired bone quality, resulting in reduced adaptability to alterations in mechanical stress. Furthermore, reduced bone turnover is expected to lead to a relative increase in bone mineral content due to reduced BMD loss over time.

As a consequence of reduced bone turnover, it appears that individuals with T2DM do indeed exhibit a higher aBMD compared to those without DM. Studies on bone microarchitecture suggest compromised bone integrity with more trabecular bone and diminished cortical bone, which correlates highly to bone quality [145] and may indicate reduced bending strength and axial load-bearing capacity. In addition, some studies reported that T2DM was associated with a greater aBMD loss over time, possibly indicating a subgroup effect, warranting further research.

The difference in aBMD between individuals with T2DM and those without T2DM appeared to be more pronounced in women than in men, although this conclusion must be made with caution due to the considerable heterogeneity of the studies. Overall, no clear demographic variation in the effect of T2DM on bone structure was observed.

These alterations in bone structure reduce bone strength and increase fracture risk, which is observed particularly in the cases of hip and overall fracture risk. The evidence for an increased

risk of vertebral fracture presented here is inconsistent and warrants further research. However, a larger proportion of studies examining hip-related regions (total hip, femoral neck, and trochanteric region) reported increases in aBMD compared to studies examining vertebral sites. These differential aBMD alterations between skeletal regions may be related to differences in their respective cortical and trabecular compartments and might affect the site-specific fracture risk. Thus, this may represent a smaller degree of pathology in vertebral bone, which would in turn lead to a less pronounced increase in fracture risk, if any. In addition, there may be a larger effect of under-reporting in vertebral fractures, as many of these fractures do not present with any symptoms and require imaging for verification.

Under-reporting is a general concern in registry studies, where both fracture rates and T2DM prevalence/incidence may be subject to error, in both cases leading to underestimation of associations.

In the present review, no statistical analyses were performed. Therefore, the heterogeneity of the studies could not be quantified, and the overall size and significance of the effects on bone health could not be estimated. Furthermore, owing to the observational nature of almost all the articles included in the present review, causality could not be determined. However, in the cases of all three areas of interest–bone structure, fracture risk, and bone turnover–clear trends were observed indicating the presence of reduced bone turnover along with altered bone distribution and a concurrent increase in fracture risk in elderly individuals with T2DM.

Fracture risk in individuals with T2DM may, however, be influenced by a variety of factors which have not or have only slightly been touched upon in the present review. These factors are discussed in the following.

None of the included articles examined the levels and the effects of advanced glycation end products (AGEs). AGEs are proteins or lipids that have become glycated as a result of exposure to sugars [146]. AGEs are more abundant in tissues in T2DM and have been shown to affect bone biomechanical properties due to cross-linking with bone proteins [147]. This process occurs more freely in low states of bone turnover, as matrix proteins are exposed to the environment for an extended time. In turn, AGEs increase oxidative stress and inflammation, besides negatively affecting bone turnover [147].

T2DM is a condition of low-grade inflammation [148, 149], a process that is closely (and possibly reversibly) linked to impaired bone turnover in several conditions [150, 151].

Besides bone fragility, an increased risk of falls would result in a consequent increase in fracture risk. Each year, approximately 30% of individuals aged over 65 years experience a fall [152], and there is evidence that fall risk is further increased in older adults with T2DM [153].

Fall risk may in turn be influenced by a variety of risk factors. De Mettelinge et al. reported polypharmacy, poor walking performance, and reduced cognitive function to be mediators of falls in diabetes [154]. Furthermore, characteristics of posture and gait have been demonstrated to be affected in individuals with T2DM and a history of falls [155].

Gait performance may be affected by disorders affecting proprioception (diabetic sensory neuropathy) [102, 107, 121], visual acuity (diabetic retinopathy) [92, 94, 121, 125], or muscle strength [82], each of which has been reported to be associated with fracture risk.

Other significant contributors to falls in the elderly in general–and perhaps in individuals with diabetes in particular–are dizziness, orthostatic hypotension, antihypertensive drug use, and concomitant cardiovascular disease [102, 127, 156, 157].

Finally, fall risk is closely associated with the risk of hypoglycemia, e.g., due to use of insulin and sulfonylureas. Indeed, almost all the included studies reported the highest increase in fracture risk among those treated with insulin, and two studies reported no residual effect when adjusting for insulin use [124, 129].

However, it is difficult to elucidate the full nature of these associations, as polypharmacy and use of insulin represent more severe cases of T2DM with longer diabetes duration and a higher comorbid load, allowing an increased impact on bone turnover and quality.

In relation to all the topics reviewed, conflicting results have been reported. This may be due to a variety of factors, including limited sample sizes and the considerable amount of both known and unknown possible confounders. Certain subject characteristics are fundamentally linked; therefore, the effects of individual characteristics are difficult to account for. This may be the case for glucose-lowering drugs and therapies for comorbidities (and the duration of treatment), which may exert direct effects on bone biochemical and biomechanical properties and also be inherently linked to the severity and duration of T2DM along with the presence of complications and, for certain drugs, hypoglycemic episodes. Other relevant confounders that were not investigated are low-grade inflammation and, in the case of NTX, renal function.

In conclusion, health problems in the elderly, particularly those with T2DM, are numerous, and the elevated risk of fractures results in increased morbidity and mortality. The increased fracture risk may present an even bigger challenge in individuals with T2DM, as Tebé et al. reported that mortality following hip fracture was higher in the elderly with T2DM compared to those without DM [100]. In this context, considering that common prediction tools underestimate fracture risk in diabetes [12], the development of more sensitive diagnostic tools for evaluating bone health in the elderly with T2DM is essential.

The use of newer bone imaging techniques, such as HRpQCT, is limited to the research setting and awaiting studies to demonstrate their clinical utility, while the use of TBS appears to be a more validated and easily accessible method for the evaluation of bone quality.

Further research exploring underlying mechanisms for diabetes-related effects on bones is required. In particular, more intervention trials are required to establish causality and determine reversibility of the effects on bone biochemical and biomechanical properties.

Table 1 Overview of findings related to biochemical markers of bone in type 2 diabetes mellitus.

Ref	Author	n =	Population Characteristics	Adjusted for	Findings
Randomized Controlled Trials					
[47]	Bulló et al.	79 (38 T2DM; 41 non-DM)	Age: Mean 68.5 Spanish Men	BMI, physical activity, intervention group, use of statins, presence of T2DM, values of the dependent variable at baseline	Subjects not taking oral antidiabetics: Baseline OC positively correlated to FPI, HOMA-IR, and HOMA-ß after 2 yr. follow-up Changes (during follow-up) in total OC associated with: - Increase in HOMA-ß (insulin production) - No effect on FPG, FPI, and HOMA-IR Changes (during follow-up) in ucOC associated with: - Decrease in HOMA-IR (insulin resistance) - No effect on FPG, FPI and HOMA-ß
Prospective Cohort Studies					
[46]	Rianon et al.	69 All w/T2DM	Age: ≥50 year Mexican American 71% women	Age groups, BMI, femoral neck BMD, serum creatinine, calcium, 25(OH)D, diabetes duration	Higher HbA1c (> 8) correlated with: - Lower OC in men ≥ 65 years - No effect on sclerostin in men. - No effect in women (nonsignificant Increase in sclerostin, p = 0.07). Longer disease duration: - No effect on sclerostin or OC
[29]	Yeap et al.	2,966 (445 T2DM; 2,521 non-DM)	Age: 70–89 Australian Men	Age, smoking, BMI, WHR, hypertension, dyslipidemia, creatinine, vitamin D, Charlson Comorbidity Index	T2DM associated with: - Lower TOC, ucOC, P1NP, and CTX - Higher ratio of ucOC to TOC For every 1 SD increase in each bone turnover marker, there was a 36–45% reduction in the risk of prevalent diabetes

[31]	Dobnig et al.	1,664 (583 T2DM; 1,081 non-DM)	Age: ≥70 Austrian Women Nursing home residents	Age, weight, mobility score, creatinine clearance	T2DM associated with: - Lower OC, CTX, and PTH - No effect on vitamin D HbA1c negatively correlated with OC and CTX. The slopes of the declines in OC and CTX were steeper in T2DM.
[32]	Gerdhem et al.	1,132 (74 T2DM; 1,058 non-DM)	Age: All 75 Swedish Women	Weight, p-creatinine	T2DM associated with: - Lower OC, CTX, and vitamin D - (Lower) U-DPD/crea (nonsignificant when adjusted) - No effect on bone ALP or PTH
[45]	Hannemann et al.	498 (65 T2DM; 433 non-DM)	Age: Mean 62.0 German Postmenopausal women	Unadjusted	T2DM associated with: - Lower OC
Case-control Studies					
[23]	Sahin et al.	99 (47 T2DM; 52 non-DM)	Age: Mean 60.0–61.8 Turkish Postmenopausal women	Unadjusted	T2DM not associated with: - OC, CTX, PTH or ALP
Cross-sectional Studies					
[26]	Liu et al.	775 (388 T2DM; 245 IGM; 142 NGM)	Age: >50 years (mean 73.5–76.7) Han Chinese Men	Serum creatinine, age, BMI	T2DM associated with: - Lower ß-CTX, OC, and P1NP - Unaffected ALP, 25(OH)D, and PTH FPG negatively correlated with OC
[42]	Mitchell et al.	4,713 (325 T2DM; 797 IFG; 3,591 NFG)	Age: Mean 68 Swedish Women	FPG/FPI, age, height, BMI, smoking status, physical activity, education	T2DM associated with: - Lower OC and sclerostin IFG associated with: - Lower OC FPG inversely correlated with OC and sclerostin. FPI inversely correlated with OC.

[37]	Maagensen et al.	33 (8 T2DM; 8 NAFLD + T2DM; 8 NAFLD + NGT; 9 NGT)	Age: Means 55.5, 65.0, 58.5, 54.0 Danish 45.5% women	Unadjusted	Regardless of NAFLD status, T2DM is associated with (compared to controls): - Lower OC and P1NP - No change in CTX - Attenuated suppression of CTX - No change in the suppression of OC or P1NP
[35]	Zhang et al.	408 All w/T2DM	Age: 55–70 Chinese 64.7% women	Unadjusted	Diabetic retinopathy associated with: - Lower ß-CTX - Unaltered 25(OH)D, P1NP, AZGP1, FGF21, and Osteonectin Diabetic macular edema associated with: - Lower P1NP and ß-CTX - Unaltered 25(OH)D, AZGP1, FGF21, and Osteonectin
[27]	Shou et al.	1,316 373 T2DM; 943 non-DM)	Age: ≥80 Chinese Men	Unadjusted	T2DM associated with: - Lower OC, P1NP, and ß-CTX Also found negative linear associations ($p < 0.01$) between all turnover marker levels and all measures of BMD.
[38]	Raška et al.	283 (112 T2DM; 171 non-DM)	Age: Mean 64.0–65.6 Czech Postmenopausal women	Unadjusted	T2DM associated with: - Lower OC and 25(OH)D No difference in ß-CTX, P1NP, or sclerostin
[36]	Osima et al.	443 (22 T2DM; 421 non-DM)	Age: 54–94 Norwegian Postmenopausal women	Age, fracture status.	T2DM associated with: - Lower vitamin D - No effect on P1NP, CTX, or PTH Increasing glucose associated with: - Lower P1NP and CTX Increasing insulin and insulin resistance associated with: - Lower CTX - No effect on P1NP
[39]	Iki et al.	1,683 (313 T2DM; 1,370 non-DM)	Age: 72.9 mean Japanese Men	Unadjusted	T2DM associated with: - Lower OC, P1NP, and PTH - No effect on TRACP5b or CTX

[28]	Furst et al.	35 (16 T2DM; 19 non-DM)	Age: Mean 65.4–65.6 US Citizens Postmenopausal women	Unadjusted	T2DM associated with: - Lower P1NP and CTX - No effect on ALP, PTH, or 25(OH)D
[43]	Yano et al.	1,870 (182 T2DM; 1,688 non-DM)	Age: ≥50 (mean 68.9) Japanese 58.6% women	Unadjusted	T2DM associated with: - Lower ucOC - Lower TRACP5b in women but not in men Increasing HbA1c, FPG, and insulin associated with: - Decreasing ucOC - No effect on TRACP5b Increasing HOMA-IR: - No effect on ucOC or TRACP5b
[49]	Feldbrin et al.	100 (33 T2DM + HTN; 39 HTN: 28 healthy)	Age: Mean 59.8–62.7 Israeli 55% women All: Hypertension	Unadjusted	T2DM associated with: - Lower P1NP HbA1c and FPG correlated with: - Decreasing P1NP HOMA-ß correlated with: - Increasing P1NP HOMA-IR and OPG not associated with anything
[30]	Yamamoto et al.	495 (255 T2DM; 240 non-DM)	Age: Mean 63.1–71.2 Japanese 63% women	Unadjusted	T2DM associated with: - Lower ß-CTX, OC, P1NP, and PTH - Higher ALP and vitamin D In both sexes
[48]	Xia et al.	110 (70 T2DM; 40 non-DM)	Age: Mean 74.3–78.1 Chinese Men	Unadjusted	T2DM and albuminuria associated with: - Lower OC (declining with higher albuminuria) - Higher PTH (increasing with higher albuminuria) - No effect on ALP

[50]	Rasul et al.	120 All w/T2DM	Age: Means 61–66 Austrian 40.1% women	Unadjusted	Polyneuropathy associated with: - Higher OC and CTX in men - No effect on OC or CTX in women/total - Higher P1NP in men and total - No effect on P1NP in women - No effect on ALP, vitamin D, or PTH
[44]	Iki et al.	1,597 (286 T2DM; 1,311 non-DM)	Age: Mean 73.0 Japanese Men	Age, height, weight, weekly alcohol consumption, smoking (pack-years), physical activity, milk intake, fermented soybean product intake	Fasting glucose, fasting insulin, HOMA-IR, HbA1c and T2DM prevalence inversely correlated with: - iOC (only when unadjusted for ucOC) - ucOC (also when adjusted for iOC) - Ratio of ucOC to iOC Fasting insulin inversely correlated with TRACP5b
[51]	Bulló et al.	251 (110 T2DM; 141 non-DM)	Age: Mean 67.70–67.82 Spanish 50.6% women	Unadjusted	T2DM associated with: - Higher OPG - Lower DPD - No effect on vitamin D, PTH, or bone ALP
[41]	Zhou et al.	1,579 (890 T2DM; 689 non-DM)	Age: Mean 56.1–58.5 Chinese Women	Unadjusted	T2DM associated with: - Higher urinary NTX secretion - Lower OC - No effect on PTH, ALP, or calcitonin Regardless of BMI group
[40]	Chailurkit et al.	163 (54 T2DM; 109 non-DM)	Age: 50–88 (mean 62.8–66.9) Thai Postmenopausal women	Age, BMI	T2DM associated with: - Attenuated suppression of CTX after oral glucose - No suppression of OPG after oral glucose - No effect on baseline CTX or OPG
[22]	Dennison et al.	909 (65 T2DM; 844 non-DM)	Age: Mean 84.6–66.4 UK Citizens 48.8% women	Unadjusted	T2DM not associated with: - OC or sclerostin

[34]	Ardawi et al.	964 (482 T2DM; 482 non-DM)	Age: Mean 59.60 ±7.90 Saudi Arabians Postmenopausal women	Age, BMI, HbA1c, vitamin D, BMD	T2DM associated with: - Increased sclerostin - Reduced OC, P1NP, CTX, and urinary NTX - Lower PTH and IGF-1
[33]	García-Martín et al.	124 (74 T2DM; 50 non-DM)	Age: 57.7 ±6.5 Spanish 52% women	Unadjusted	T2DM associated with: - Higher sclerostin - Lower CTX - Lower TRAP5b - Unaffected OC and vitamin D Sclerostin (pmol/L) linearly correlated with: - Duration of T2DM (years): r = 0.238, p = 0.044 - Not significantly with HbA1c (%): r = 0.200, p = 0.09

25(OH)D: 25-hydroxy-vitamin D, ALP: alkaline phosphatase, AZGP1: zinc-binding alpha-2-glycoprotein 1, BMD: bone mineral density, BMI: body mass index, crea: creatinine, CTX: carboxy-terminal collagen crosslinks, DM: diabetes mellitus, T2DM: type 2 DM, DPD: deoxypyridinoline, FGF21: fibroblast growth factor 21, FPG: fasting plasma glucose, FPI: fasting plasma insulin, HbA1c: hemoglobin A1c, HOMA: homeostatic model assessment, HOMA-IR: HOMA for insulin resistance, HOMA-β: HOMA–beta-cell, HTN: hypertension, IFG: impaired fasting glucose, IGF-1: insulin-like growth factor 1, OC: osteocalcin, iOC: intact OC, TOC: total OC, ucOC: undercarboxylated OC, NAFLD: non-alcoholic fatty liver disease, NTX: amino-terminal collagen crosslinks, OPG: osteoprotegerin, P1NP: procollagen type 1 n-terminal propeptide, PTH: parathyroid hormone, SD: standard deviation, TRACP5b: tartrate-resistant acid phosphatase 5b, U-DPD/crea: urine-DPD/creatinine-ratio, WHR: waist-hip ratio.

Table 2 Overview of findings related to structural markers in type 2 diabetes mellitus.

Ref.	Author	n =	Population	Measurement	Adjusted for	Findings
Randomized Controlled Trials						
[52]	Schwartz et al.	107 (3,655 intensive glycemia; 3,632 standard glycemia) All w/T2DM.	Age: 62.5 ±6.7. US and Canadian 34.6% women All: T2DM and history of, subclinical evidence of, or significant risk factors for CVD	DXA aBMD: spine, hip, whole body.	Baseline BMD, age, sex, race, DXA site, comorbidity[a], medication[a], trial intervention[a].	Intensive glycemic control (vs. standard glycemic control): - No difference in aBMD change at any site
Prospective Cohort Studies						
[90]	Iki et al.	1,951 (200 T2DM; 1,751 non-DM)	Age: ≥65. Japanese Men All: T2DM	DXA aBMD: hip + lumbar spine	Unadjusted	Higher HbA1c or fasting glucose: - Higher hip aBMD - Higher lumbar spine aBMD
[75]	Napoli et al.	5,554 (875 T2DM; 4,679 non-DM)	Age: ≥65 (73.6 ±5.6). US Men	DXA aBMD: Lumbar spine, total hip, femoral neck, trochanter. QCT vBMD: Lumbar spine.	Logistic regression: BMI, eGFR, history of falls, and prior fracture history.	T2DM: - Higher spine aBMD. - Higher integral spine vBMD.
[65]	Mitama et al.	6,556 (792 T2DM; 649 IGM; 5,115 non-DM)	Age: Means 67.7 (men), 68.3 (women) Japanese 57.5% women	DXA aBMD: Lumbar spine	Age, BMD, CRP, eGFR, albumin, exercise, smoking, alcohol, family history of fracture, IHD, CVD and previous fracture	T2DM: - Higher aBMD.
[105]	Majumdar et al.	57,938 (8,840 T2DM; 49,098 non-DM)	Age: Means 67.1/63.8 Canadian Women	DXA aBMD: femoral neck	Unadjusted	T2DM: - Higher aBMD at baseline. T2DM duration: - No difference in aBMD
[84]	Pritchard et al.	Baseline: n = 60 (30 T2DM) Complete follow-up: n = 37 (15	Age: ≥60. Canadian Postmenopausal women	DXA aBMD: Lumbar spine, total hip, femoral neck. MRi radius	Unadjusted	T2DM: - Higher aBMD at all sites. No change in trabecular microarchitecture over 2 year follow-up.

		T2DM)				
[113]	Schwartz et al.	16,885 (1,969 T2DM; 14,916 non-DM)	Age: Mean >73. American 56% women	DXA aBMD: T-score, femoral neck	Unadjusted	T2DM: - Higher femoral neck BMD T-score
[31]	Dobnig et al.	1,664 (583 T2DM; 1,081 non-DM)	Age: >70 Austrian Women	QUS: Calcaneus, radius, proximal third phalanx.	Age-, weight-, and mobility score.	T2DM: - Higher QUS aBMD.
[80]	Strotmeyer et al.	2,979 (566 T2DM; 177 IFG; 2,236 NGM)	Age: 70–79 US (white and black) 51.1% women	DXA aBMD: Total hip. CT vBMD: L3.	Sex, race, clinic site, diabetes variables.	T2DM (and w/impaired glucose metabolism): - Higher hip aBMD - No difference in vBMD
[32]	Gerdhem et al.	1,132 (74 T2DM; 1,058 non-DM)	Age: >75 Swedish Women	DXA aBMD: lumbar spine, femoral neck. QUS calcaneus.	Body weight	T2DM: - Higher BMD at all sites. - No difference in bone mass by QUS.
[123]	de Liefde et al.	6,655 (792 T2DM; 5,863 non-DM)	Age: ≥55 (mean 74) Dutch 59.6% women	DXA aBMD: lumbar spine, femoral neck.	Age, sex, BMI, lower-limb disability, smoking, use of either loop or thiazide diuretics at baseline	Prevalent or incident T2DM: - Higher aBMD at lumbar spine and femoral neck Impaired glucose tolerance: - No difference in aBMD
[129]	Napoli et al.	5,995 (881 T2DM; 5,114 non-DM)	Age: ≥65, median 73.5 US (90% white) Men	DXA aBMD: total femur.	Unadjusted	T2DM: - Higher aBMD Impaired glucose tolerance: same but less pronounced effect
[14]	Schwartz et al.	9,548 (551 T2DM; 8,997 non-DM)	Age: Mean >70 US (white) Women.	DXA aBMD: proximal femur. Single photon absorptiometry BMD: distal radius, calcaneus.	Unadjusted	T2DM: - Higher aBMD at all sites.
Retrospective Cohort Studies						
[97]	Baltrusaitis et al.	36,744 (19,430 T2DM; 17,314 non-DM)	Age: ≥65 U.S. Veterans 1.7% women	DXA: Osteoporosis diagnosis	Unadjusted	T2DM: - Lower prevalence of osteoporosis
[87]	Leslie et al.	4,960 (346 DM [>97% T2DM];	Age: 62.1 ±9.8 Canadian Women	DXA aBMD: lumbar spine, total hip, femoral neck	Age, BMI	T2DM: - Higher aBMD at all sites (unadjusted). T2DM duration > 4 years:

		4,614 non-DM)				- Greater aBMD loss at femoral neck BMD loss at the lumbar spine attenuated in the obese
[102]	Lee et al.	2,798,309 (900,402 T2DM; 1,897;905 non-DM)	Age: ≥65. U.S. Veterans Men >98% of DM was T2DM	DXA aBMD: femoral neck	Unadjusted	T2DM: - Higher femoral neck aBMD.
[91]	Oei et al.	4,135 (420 T2DM; 3,715 non-DM)	Age: ≥55. Dutch 59.4% women	DXA aBMD: lumbar spine, femoral neck. DXA Hip geometry; cortical thickness.	Sex, age, height, and weight (and femoral neck BMD)	HbA1c ≥ 7.5% (vs. HbA1c < 7.5%) **and** T2DM: - Higher aBMD at lumbar spine and femoral neck - Thicker cortices and smaller bone diameter at femoral neck
[71]	Leslie et al.	29,407 (2,356 T2DM; 27,051 non-DM)	Age: 65.4 ±9.4. Canadian Postmenopausal women	DXA aBMD: lumbar spine, total hip, femoral neck. DXA lumbar spine TBS	Unadjusted	T2DM: - Lower prevalence of osteoporosis. - Higher BMD - Lower lumbar spine TBS
Case-control Studies						
[56]	Amer et al.	61 (31 T2DM; 30 non-DM)	Age: ≥60. Egyptian 48.4% women (in T2DM group)	DXA aBMD: lumbar spine, femoral neck.	Age-matched	T2DM: - No difference in aBMD.
[23]	Sahin et al.	99 (47 T2DM; 52 non-DM)	Age: Mean >60 Turkish Postmenopausal women.	DXA aBMD: lumbar spine, total hip, femoral neck.	Unadjusted	T2DM: - Higher BMD at all sites.
Cross-sectional Studies						
[88]	Xu et al.	1,222 All w/T2DM	Age ≥50. Tianjin, China 53% women	DXA aBMD: whole body.	Age, sex, BMI, smoking, alcohol, comorbidities[a], medications[a], glycemic control, diabetes duration	Poor glycemic control (HbA1c ≥ 7.5%): - Higher OR of osteoporosis in men HbA1c higher in women with normal aBMD (not in men) DM duration: No difference in aBMD
[69]	Sakane et al.	62 (11 T2DM; 25 prediabetes; 26 NGM)	Age: Median 59 (19–81) São Paolo. All: postsurgical hypoparathyroidism	DXA, TBS.	BMI, glycemic profile, and densitometric diagnosis.	T2DM: - Lower TBS

			85% women			
[26]	Liu et al.	775 (388 T2DM; 245 IGM; 142 NGM)	Age: ≥50. Beijing, Han Chinese Men	DXA aBMD: Lumbar spine, total hip, femoral neck.	BMI, age	T2DM: No difference in aBMD. Glycemic status: No difference in aBMD
[137]	Holloway-Kew et al.	1,828 (138 T2DM; 418 IGM; 1,272 NGM)	Age: Mean 67 (T2DM) Australian. 46.9% women	DXA aBMD: femoral neck, lumbar spine	Age, weight, height, mobility, smoking, alcohol, medication.	T2DM or IGM (compared to normoglycemia): - Higher aBMD in obese T2DM women - No difference in men
[158]	Dawson-Hughes et al.	184 (40 T2DM; 88 prediabetes; 56 NGM)	Age ≥55. US (white, black, Asian, Hispanic, one other) 48.9% women	DXA aBMD: lumbar spine, femoral neck, mid-tibia. TBS. Osteoprobe BMSi.	Age, sex, BMI.	T2DM: - Higher femoral neck aBMD (in white individuals) - Lower BMSi (in black individuals) - Unaffected TBS HbA1c levels: - No difference in BMSi or TBS
[142]	Chi et al.	7,835 (1,313 T2DM; 6,522 non-DM)	Age: Means 60–63 (T2DM) Korean 60% women	DXA aBMD: total femur, trochanter, intertrochanter, femoral neck, ward, lumbar spine, whole body.	Age, BMI	T2DM: - Women: Higher aBMD at Ward's triangle and lumbar spine - Men: Higher aBMD in lumbar and thoracic spine - aBMD as a predictor of T2DM: associated with increased odds for T2DM
[54]	Cherif et al.	81 All w/T2DM	Age: Mean 58.4 Tunisian Postmenopausal women All: Obese	DXA aBMD: lumbar spine, femoral neck, total hip. BMC (content)	Multiple linear regression: Age, years since menopause, weight, height, waist circumference, BMI, alkaline phosphatase, body composition[a]	Glycemic status: - Not correlated to aBMD
[70]	Baleanu et al.	260 (65 T2DM; 195 non-DM)	Age: 60–85 Belgian Postmenopausal women	DXA aBMD: lumbar spine, total hip, femoral neck. DXA TBS.	BMI FRAX-matched 1:3	T2DM: - Increased total hip aBMD. - Reduced TBS (with similar FRAX).
[136]	Zhong et al.	2,170 All w/T2DM	Age: ≥50 (means 61–72) Chinese 54.7% (postmenopausal)	DXA aBMD: lumbar spine, total hip and femoral neck	Age, BMI, diabetic status, comorbidities[a], sex hormones, 25(OH) vitamin	Presence of microangiopathy: - Lower aBMD at all sites in women - No difference in men

			women		D.	
[159]	Valentini et al.	242 (119 T2DM; 123 non-DM)	Age: ≥50 (mean 74) Italian Unspecified sex fractions	DXA aBMD, femoral neck	Unadjusted	T2DM: - Higher femoral neck aBMD and T-score Lower FRAX-score: may underestimate the risk of fracture
[82]	Nakamura et al.	826 (122 T2DM; 704 non-DM)	Age: Mean 62.3 (T2DM) Japanese Women	UL distal radius: Cortical Thickness, Trabecular BMD.	Age, BMI, HGS, eGFR, serum albumin, HbA1c	T2DM: - Higher trabecular BMD after age 60 - Lower cortical thickness after age 40
[42]	Mitchell et al.	5,165 (393 T2DM; 947 IFG; 3,825 NGM)	Age: Mean 82 (men), 68 (women) Swedish 91.2% women	DXA aBMD: total hip and femoral shaft. BMA (cm2) Femoral neck diameter	Multiple regression: age, height, weight, categorical variables (questionnaires) smoking, physical activity, education.	T2DM: - Higher aBMD. - Lower BMA at hip and femoral shaft Similar but less pronounced findings for individuals with IFG.
[86]	Jang et al.	3,383 (644 T2DM; 1,037 prediabetes; 1,702 NGM)	Age: ≥50. Korean men	aBMD: lumbar spine, total hip, femoral neck	Age, BMI, alcohol, smoking, serum vitamin D, lipid levels[a], hypertension, physical activity, HOMA-IR	T2DM: - Higher aBMD at all sites. aBMD in men with pre-DM were similar to men with DM in all cases. T2DM duration >5 years: - Lower femoral neck aBMD
[76]	Ho-Pham et al.	1,729 (137 T2DM; 1,592 non-DM)	Age: Mean 58.5 (T2DM) Vietnamese 64.5% women	DXA aBMD: Lumbar spine, total hip, whole body. pQCT vBMD: Tibia, radius. SSI: Bone strength	Matched: sex, age, BMI	T2DM: - Higher aBMD at all sites. - Higher radial and tibial trabecular vBMD - Lower bone strength (SSI) - Near-significant reduced radial cortical vBMD
[79]	de Waard et al.	608 (98 T2DM; 91 prediabetes; 419 NGM)	Age: Mean 58 Dutch 51.2% women	HRpQCT vBMD (Trabecular and Cortical). Microarchitecture. Bone strength.	age, sex, BMI, level of education, smoking, alcohol, CVD, physical activity, fracture at or above the age of 50, antihyperglycemic medication.	T2DM w/HbA1c > 7% (53 mmol/mol): - Lower cortical density at distal radius - Lower trabecular thickness at distal tibia T2DM duration > 5 years: - Higher trabecular number (Tb.N) of the radius Pre-DM: - Only associated with lower Tb.N of the tibia. - No difference in bone strength.
[160]	Zhou et al.	99 All w/T2DM.	Age: 62 ±8. Tibetan	DXA aBMD: T-score lumbar spine, total	Multiple regression: age, BMI, menopausal period,	HbA1c: - Positively correlated with spine T-score

			Postmenopausal women, dwelling in high altitudes (2500~4500 m)	hip, femoral neck	DM duration, hypertension, smoking, pregnancies, systolic blood pressure, Hbg, creatinine, uric acid, HbA1c.	Age inversely correlated with aBMD/T-score in femoral neck and hip
[63]	Sun et al.	4,080 (906 T2DM; 3,174 non-DM)	Age: Means 57/59 Chinese Postmenopausal women	Quantitative ultrasound (QUS): SOS, BUA, stiffness, T-score	Age, physical activity, smoking, alcohol menopause age, BMI	Lower odds for osteopenia with: - T2DM - HbA1c > 6.5 - FPG > 7.0 - PPG ≥ 15
[78]	Sheu et al.	156 (38 T2DM; 118 non-DM)	Age: ≥65, Mean 80.5 American (+3 African) Men	MRI: Bone marrow fat (BMF) DXA aBMD: lumbar spine, total hip, femoral neck. pQCT vBMD: tibia and radius.	Age, race, BMI, Leptin, adiponectin, insulin	T2DM: - Higher BMF content. - Higher baseline aBMD at total hip and total spine - No difference in vBMD at any site.
[38]	Raška et al.	283 (112 T2DM; 171 non-DM)	Age: Means 64.0/65.6 Czech Postmenopausal women	DXA aBMD: Lumbar spine, total hip, femoral neck	Unadjusted	T2DM: - Higher osteoporosis prevalence. - Higher aBMD at lumbar spine, total femur and femoral neck T2DM+VF (compared to T2DM+osteoporosis w/o fracture): - Higher aBMD at lumbar spine, total femur and distal radius - No effect at femoral neck
[36]	Osima et al.	443 (22 T2DM; 421 non-DM)	Age: Means 70.9/68.2 Norwegian Postmenopausal women	CT scan vBMD: Hip.	Age, fracture status.	T2DM: - Lower cortical porosity - Higher total vBMD and cortical vBMD. Higher glucose levels: - Lower cortical porosity Higher total vBMD with higher glucose, insulin and HOMA-IR
[39]	Iki et al.	1,683 (313 T2DM; 1,370 non-DM)	Age: ≥65, 72.9 ±5.2. Japanese Men	DXA TBS and aBMD: Lumbar spine	Age, BMI and aBMD/TBS. Bone turnover, pentosidine	Higher FPG, HOMA-IR and HbA1c associated with: - Higher aBMD - Lower TBS

[161]	Hyassat et al.	1,079 (530 T2DM; 404 prediabetes; 145 non-DM)	Age: 61.1 ±7.2. Jordanian Postmenopausal women	DXA aBMD: lumbar spine, femoral neck	Multiple regression: BMI, diabetes status, family history of osteoporosis, physical activity, sun exposure, diet[a], age at menarche, menopausal duration, parity	T2DM: - Lower osteoporosis risk.
[55]	Razi et al.	110 (55 T2DM; 55 non-DM)	Age: Median 58 (39–79). Iranian Postmenopausal women	aBMD: Lumbar spine, hip, and subregions.	Age at menopause. BMI, BMD values at different sites, s-Bone ALP, vitamin D, systolic blood pressure	T2DM: - No difference in bone mass values.
[28]	Furst et al.	35 (16 T2DM; 19 non-DM)	Age: Mean ≈ 65.5 US (white) Postmenopausal women	OsteoProbe BMSi (bone strength). DXA aBMD: lumbar spine, total hip, femoral neck. HRpQCT vBMD: radius, tibia.	Age, nephropathy, retinopathy, neuropathy, cardiac disease.	T2DM: - Reduced BMSi. - Higher aBMD at femoral neck and total hip. - Higher trabecular vBMD and stiffness at radius - Greater trabecular thickness at radius and tibia - No other differences in vBMD or cortical porosity
[59]	Cui et al.	4,988 (T2DM prevalence not specified)	Age: Means 65 (men), 59 (women) Chinese 79.3% women	DXA aBMD: lumbar spine.	Unadjusted	Osteoporosis associated with: - Higher fasting glucose and postprandial glucose (PPG) - No effect on HbA1c T2DM w/PPG > 7.0 (compared to PPG < 7.0): - Lower aBMD
[162]	Siddapur et al.	60 (30 T2DM; 30 non-DM)	Age: Mean 59.5 Indian Postmenopausal women All: Osteoporosis	DXA aBMD: lumbar spine.	Age-matching.	T2DM + osteoporosis (vs. Non-DM + osteoporosis): - Higher T-score.
[163]	Schacter et al.	34,338 (2,929 T2DM; 28,719 non-DM)	Age: Means 68.0 (men), 65.4 (women) Canadian 92.2% women	DXA aBMD: anteroposterior spine-hip tissue thickness.	Age, BMI.	T2DM: - Higher spine-hip tissue thickness difference (SHTD) Greater SHTD associated with higher likelihood of T2DM.

[164]	Aypak et al.	275 (66 T2DM; 209 non-DM)	Age: 72.1+5.4. Turkish Women	DXA aBMD: lumbar spine, total hip, femoral neck, T-score.	Unadjusted	T2DM: - Higher femoral neck aBMD. - Higher osteoporosis rate.
[30]	Yamamoto et al.	495 (255 T2DM; 240 non-DM)	Age: Mean >60. Japanese 63% (postmenopausal) women	DXA aBMD: lumbar spine, femoral neck.	Unadjusted	T2DM: - Higher aBMD in women but not in men.
[48]	Xia et al.	110 (70 T2DM; 40 non-DM)	Age: ≥60. Chinese Men	DXA aBMD: lumbar spine, total hip, femoral neck.	Age-matched. Multivariate regression controlled for patient characteristics and comorbid conditions[a]	T2DM: - Lower aBMD at both lumbar spine and femoral neck. Osteoporosis associated with increased albuminuria in T2DM
[50]	Rasul et al.	120 All w/T2DM.	Age: Mean > 60. Austrian 40.1% (postmenopausal) women	DXA aBMD: lumbar spine, femoral neck.	Sex	Presence of polyneuropathy: - No difference in aBMD
[83]	Pritchard et al.	60 (30 T2DM; 30 non-DM)	Age: ≥65. Canadian Postmenopausal women	DXA aBMD: lumbar spine, femoral neck, total hip. MRi.	BMI, % body fat, ethnicity, age-adjusted Charlson Index, TUG test result, total calcium intake, and total vitamin D intake.	T2DM: - Higher lumbar spine aBMD (unadjusted) - Great hole size within trabecular network at distal radius
[165]	Karimifar et al.	600 (200 T2DM; 400 non-DM)	Age: ≥60. Iranian Postmenopausal women	DXA aBMD T-scores: lumbar spine, femoral neck	Age, height, weight, BMI, duration of menopause, BMD T-score	T2DM: - No difference in lumbar T-score. - Lower femoral neck T-score HbA1c > 7% vs. HbA1c ≤ 7%: - No difference in lumbar spine T-score - Higher femoral neck T-score
[64]	Shan et al.	2,447 (1,253 T2DM; 1,194 non-DM)	Age: 40–80 (mean 60) Chinese Women	DXA aBMD: lumbar spine, femoral neck, total hip, wards. Bone projective area (BPA).	Age, BMI, years since menopause (YSM), duration of diabetes	T2DM: - Higher aBMD at lumbar spine but not hip - Higher BPA of the vertebrae aBMD decreases with age: trend toward slower decrease in T2DM.
[51]	Bulló et al.	251 (110 T2DM; 141 non-DM)	Age: Mean >65. Spanish 50.6% women	QUS: BUA, BMD, QUI, SOS	Sex, age, physical activity	T2DM (or metabolic syndrome): - Higher BUA, more solid bone structure

[41]	Zhou et al.	1,579 (890 T2DM; 689 non-DM)	Age: Mean >56. Chinese Postmenopausal women	DXA aBMD: lumbar spine, total hip, femoral neck	Age and BMI-matched.	T2DM: - Lower aBMD at femoral neck (in those with BMI < 25)
[77]	Burghardt et al.	38 (19 T2DM; 19 non-DM)	Age: 62.9 ±7.7. US Postmenopausal women	HRpQCT vBMD Radius, tibia, bone strength.	Age, ethnicity, and height matched	T2DM: - No difference in radial vBMD. - Higher tibial vBMD with higher peripheral trabecular density and thickness. - Higher cortical porosity at radius.
[89]	Sosa et al.	202 (101 T2DM; 91 non-DM)	Age: >65. Spanish (Caucasian) Postmenopausal women	DXA aBMD: lumbar spine, total hip, femoral neck. QUS aBMD	Age and weight matched	T2DM: - Higher aBMD at the lumbar spine. - No difference in aBMD at proximal femur or QUS measurements of the heel.
[166]	Asano et al.	294 All w/T2DM	Age: 63.1 ±10.4. Japanese Men	QUS: Bone stiffness index	Age, diabetes duration, BMI, HbA1c, systolic blood pressure, serum total cholesterol, serum bioavailable testosterone, smoking status.	T2DM w/insulin (vs. w/o insulin): - Less bone stiffness. Nephropathy or retinopathy: - No difference in bone stiffness
[60]	Xu et al.	131 All w/T2DM	Age: ≥65, 73.12 ±5.54 Chinese (Han) Men	DXA aBMD: lumbar spine, femoral neck, femoral trochanter.	Weight	HbA1c: - Negatively associated with aBMD at femoral neck and lumbar spine
[167]	Korpelainen et al.	407 (38 T2DM; 369 non-DM)	Age: 70–73 Finnish Women All: BMI ≤ 25.1	QUS: Calcaneum bone mass (BUA). DXA aBMD: distal radius	Weight, height in all multivariate models. Grouped variables (physical activity, falls, physical mental capacity, other lifestyle variables, education, reproductive history, general health, medication) for forward stepwise regression procedures.	T2DM: - Higher calcaneal bone mass Body weight and T2DM associated with: - Higher aBMD at distal radius
[81]	Strotmeyer et al.	2,979 (566 T2DM; 2,413 non-DM)	Age: 70–79 US (white and black) 51.1% women	DXA aBMD: Total hip, femoral neck, and whole-body aBMD. CT vBMD: L3.	Age, race, sex, study site, smoking, alcohol, Health ABC performance battery categorical score (0–12), recent weight gain/loss,	T2DM: - Higher aBMD at all sites. - Lower spine vBMD.

					osteoporosis, calcium and vitamin D supplement, medications[a].	
[168]	Horiuchi et al.	85 All w/T2DM	Age: Mean > 69 Japanese Women.	DXA aBMD: lumbar spine, T-score	Unadjusted	T-score < –2.5 (vs. T-score ≥ –2.5): - No difference in HbA1c
[22]	Dennison et al.	909 (65 T2DM; 844 non-DM)	Age: 59–71, mean > 64 Hertfordshire (UK) 48.8% women None w/DM at inclusion	DXA aBMD: lumbar spine, total hip, femoral neck.	Body weight, age, smoking, alcohol, social class, activity level, replacement therapy and menopausal status (in women)	Newly diagnosed T2DM (vs. controls): - Only lumbar spine aBMD in men was higher Insulin resistance or glucose levels: - No aBMD difference
[61]	Sert et al.	539 (277 T2DM; 262 non-DM)	Age 30–60, subgroup 51–60 Turkish 65.3% women	DXA aBMD: lumbar spine, total hip, femoral neck.	Age- and sex-matched controls + age sub groups	T2DM: - Higher femoral neck aBMD (in men and women aged 51–60) - Higher total femoral aBMD (in men aged 51–60) - Lower spine aBMD (in men aged 51–60)
[140]	Lunt et al.	Nearly 4,000 (~8.4% T2DM; ~91.6% non-DM)	Age: Mean ≥ 64 European (Multi-country) Unspecified sex fractions	DXA aBMD: lumbar spine, trochanter, femoral neck.	Sex-stratified by 5 years. Age, weight, center, menopausal status, years since menopause, age at menarche, ever use of OCP and ever use of HRT, risk factor groups (physical activity, hormonal factors, diet, smoking, diabetes)	T2DM w/o insulin use: - Higher aBMD at all sites in women - Higher aBMD at spine only in men
[53]	Tuominen et al.	622 (68 T2DM; 56 T1DM; 498 non-DM)	Age: Mean >60 Finnish 51.3% women	DXA aBMD: femoral neck, trochanter.	Age, BMI, duration of diabetes, duration of insulin therapy, physical activity, calcium intake, use of estrogens.	T2DM: - No difference in femoral neck or trochanter aBMD T1DM: - Lower femoral neck aBMD than T2DM - Lower femoral neck and trochanter aBMD than controls
[138]	Barrett-Connor et al.	970 None w/DM at inclusion	Age: 67 ±8.9 US (Caucasian) 57.6% women	DXA aBMD: lumbar spine, hip, radius.	Age, BMI, waist-to-hip ratio, family history of diabetes, exercise, thiazide use, smoking, estrogen use	T2DM: - Higher aBMD at lumbar spine, femoral neck and radius (only in women)

					and age at menopause (women).	
[99]	van Daele et al.	5,931 (578 T2DM; 5,353 non-DM)	Age: Mean >67 Dutch 58.2% women	DXA aBMD: lumbar spine, proximal femur.	Sex, age, BMI, waist-to-hip ratio, current use of thiazides, loop diuretics, and estrogens, smoking, s-creatinine, impairment in activities of daily living.	T2DM: - Higher aBMD at proximal femur and lumbar spine High fasting insulin: - Higher aBMD at radius, spine and hip in women - Higher aBMD at hip in men
[141]	Rishaug et al.	72 (36 T2DM; 36 non-DM)	Age: Mean >60 Norwegian 41.7% (postmenopausal) women	DXA aBMD: lumbar spine, femoral neck, whole body. BMC QUS (BUA, SOS)	Sex- and age-matched control.	T2DM: - No difference in aBMD, BMC, SOS or BUA in women - Higher whole body aBMD in men Insulin levels: - Positive correlation to femoral neck aBMD in men
[169]	Bauer et al.	9,704 (6% ≈ 522 T2DM; 95% ≈ 9,122 non-DM)	Age: Mean 71.1 US (non-black) Women	Single photon absorptiometry BMD: distal radius, mid-radius, calcaneus.	Age, multivariate regression[a]	T2DM: - Higher aBMD at distal radius
[139]	Barrett-Connor et al.	627 (80 T2DM; 166 IGM; 381 non-DM)	Age: Mean 72 US 70% women	DXA aBMD: radius, femoral neck, lumbar spine.	Age, BMI, alcohol, smoking, exercise, diuretic use, estrogen	T2DM: - Higher aBMD at all sites in women - No difference in men. Hyperglycemia: - Higher aBMD at all sites in women - No difference in men aBMD increase with post-challenge glucose in female controls
[57]	Akeroyd et al.	1,137 (142 T2DM; 995 non-DM)	Age: Mean 56.6 (T2DM) US (Black, White, Hispanic) Men	DXA aBMD: lumbar spine, femoral neck. Single photon absorptiometry BMD: radius.	Age, race/ethnicity, BMI, physical activity	T2DM: - No difference in aBMD.
[58]	Kim et al.	2,733 (695 T2DM; 2,038 non-DM)	Age: Mean >60 Korean 55.4% (postmenopausal)	DXA aBMD: lumbar spine total hip, femoral neck.	Age, BMI, prior major fracture, arthritis, alcohol, smoking, exercise,	T2DM: - Lower lumbar spine TBS - No difference in aBMD.

			women	TBS	osteoporosis treatment.	
[62]	Yamamoto et al.	996 (298 T2DM; 698 non-DM)	Age: 46–89 (means 65/67) Japanese 76.2% (postmenopausal) women	DXA aBMD: lumbar spine, femoral neck. Single photon absorptiometry BMD: radius.	Unadjusted	T2DM: - Higher aBMD at all sites
[143]	Patsch et al.	85 (43 T2DM; 42 non-DM)	Age: 57 ±11.4/58 ±4.29 Austrian 30.7% women	HRpQCT radius/tibia	Sex	T2DM: - Higher trabecular number and cortical thickness - Trend toward higher cortical BMD Men had higher radial trabecular BMD and number and cortical thickness
[34]	Ardawi et al.	964 (482 T2DM; 482 non-DM)	Age: Mean 59.60 ±7.90 Saudi Arabians Postmenopausal women	DXA aBMD: Lumbar spine, femoral neck	Unadjusted	T2DM: - Higher lumbar spine and femoral neck BMD
[33]	García-Martín et al.	124 (74 T2DM; 50 non-DM)	Age: 57.7 ±6.5 Spanish 52% women	DXA BMD and T-scores: lumbar spine, femoral neck, total hip	Unadjusted	T2DM: - No differences in BMD at any site

ALP: alkaline phosphatase, BMA: bone mineral area, BMC: bone mineral content, BMD: bone mineral density, aBMD: areal BMD, vBMD: volumetric BMD, BMF: bone marrow fat, BMI: body mass index, BMSi: bone material strength index, BPA: bone projective area, BUA: broadband ultrasound attenuation, CRP: c-reactive protein, CT: computed tomography, QCT: quantitative CT, pQCT: peripheral QCT, HRpQCT: High resolution pQCT, CVD: cardiovascular disease, DM: diabetes mellitus, T1DM: type 1 DM, T2DM: type 2 DM, DXA: dual-energy x-ray absorptiometry, eGFR: estimated glomerular filtration rate, FPG: fasting plasma glucose, FRAX: fracture risk assessment tool, HbA1c: hemoglobin A1c, HGS: handgrip strength, HOMA: homeostatic model assessment, HOMA-IR: HOMA of insulin resistance, HRT: hormone replacement therapy, IFG: impaired fasting glucose, IGM: impaired glucose metabolism, IHD: ischemic heart disease, OCP: oral contraceptive pills, OR: odds ratio, PPG: postprandial glucose, QUI: quantitative ultrasound index, QUS: quantitative ultrasound, SHTD: spine-hip tissue thickness difference, SOS: speed of sound, SSI: stress strain index, Tb.N: trabecular number, TBS: trabecular bone score, TUG: timed up-and-go test, VF: vertebral fracture, w/: with, w/o: without

Table 3 Overview of findings related to fracture risk in type 2 diabetes mellitus.

Ref.	Author	1) n = ; 2) Follow-up	Population	Adjusted for	Primary (positive) findings: Effect size [95% CI]	Full conclusion
Meta-analyses						
[104]	Dytfeld et al.	765,121 (263,006 T2DM; 502,115 non-DM)	Age: ≥50 Various nationalities Women	Unadjusted	Vertebral fracture: OR 1.134 [0.936–1.374] Hip fracture (all articles): **OR 1.296 [1.069–1.571]** Hip fracture (homogenous sample): **OR 1.314 [1.193–1.448]**	T2DM associated with: - Increased risk of hip fracture (both in full study sample and smaller, homogenous study sample). - No increased risk of vertebral fracture.
Randomized Controlled Trials						
[52]	Schwartz et al.	7,287 (3,655 intensive glycemia; 3,632 standard glycemia) Mean 3.8 (±1.3) yrs FU	Age: mean 62 US and Canada 34.6% women All: T2DM and history of, subclinical evidence of, or significant risk factors for CVD	Assignment to blood pressure or lipid trial, randomization to blood pressure or lipid intervention, baseline history of CVD		Intensive glycemic control vs. Standard glycemic control: - No effect on fracture risk (nonspine, hip, ankle, foot, proximal humerus, distal forearm)
Prospective Cohort Studies						
[100]	Tebé et al.	126,035 (44,802 T2DM; 81,233 non-DM) 8 yr FU	Age: 65–80, mean 72 Spanish 53% women	Age, corticoid use, calcium + Vit-D, antiosteoporotic use. Previous: IHD, CVD, major fracture, nephropathy	Hip fracture in T2DM vs. Non-DM: **HR 1.24** (men) **HR 1.48** (women)	T2DM associated with: - Increased risk of hip fracture. - Increased post-hip fracture mortality.
[90]	Iki et al.	1,951 (200 T2DM; 1,751 non-DM)	Age: ≥65, mean 73 Japanese Men	Spine- and hip aBMD, triglycerides, insulin use (ever), current antidiabetic	Every 1 SD increase in HbA1c: **HR for OPF of 1.38 [1.10–1.73]** and a **HR for MOPF of**	HbA1c and FPG linearly correlated with: - Risk of osteoporotic fractures

		Median FU 54.3 mo 8480 person-yrs		medications, comorbidities[a]	**1.48 [1.16–1.88]** Every 1 SD increase in FPG: **HR for OPF of 1.39 [1.15–1.69]** and a **HR for MOPF of 1.45 [1.18–1.79]**	(OPF) - Risk of major osteoporotic fracture (MOPF) No effect of diabetes status, HOMA-IR or HOMA-ß.
[101]	Tebé et al.	158,984 (55,891 T2DM, 103,093 non-DM) Median 6.4/8.0 yrs FU (T2DM/non-DM) 1,053,768 person-yrs	Age: mean 75 Catalonia, Spain 56.3% women	Comorbidities[a], medications[a]. Age- and sex-matched	**HR 1.31 [1.23–1.40]** for hip fracture **Subhazard ratio (SHR) 1.15 [1.09–1.21]** (corrected for death)	T2DM increases risk of hip fracture even after correcting for death as a competing event.
[75]	Napoli et al.	5,554 (875 T2DM; 4,679 non-DM) Mean 4.6 yr FU	Age: ≥65, mean 73 US Citizens Men	Age, race, clinical site, BMI, aBMD/vBMD		T2DM not associated with: - Prevalent vertebral fracture - Incident vertebral fracture
[124]	Wallander et al.	428,305 (79,159 T2DM; 5,543 T1DM; 343,603 non-DM) Median 1.3 yrs FU 670,000 person yrs	Age: mean 79–81 Swedish 57.6% women	Age, sex, height, weight, (insulin use)	Compared to Non-DM: T2DM total: **HR for hip fracture 1.10 [1.05–1.15]**. No correlation after adjusting for insulin use. T2DM w/oral medication or insulin (women vs. men): **HR 1.26 [1.04–1.53]** and **HR 1.42 [1.19–1.68]**, respectively. T2DM w/o medication: **HR for hip fracture in men 0.78 [0.64–0.94]**. Not reduced in women.	T2DM w/o medication (vs. non-DM): - Unaffected overall fracture risk (men/total), increased in women - Hip fracture risk reduced in men but increased in women T2DM w/oral medication or insulin (women vs. men): - Larger increase in risk of hip, any, MOPF, ankle, upper arm fracture T2DM w/insulin (vs. non-DM):

					Any diabetic complication (DM type I or II): **HR for hip fracture 1.16 [1.06–1.26]**. Not significant after adjusting for insulin use. Retinopathy: **HR for hip fracture 1.17 [1.06–1.29]**. Not significant after adjusting for insulin use.	- Increased risk of any fracture, MOPF, upper arm, hip and ankle fracture T2DM total (vs. non-DM): - Increased hip fracture risk (fully attenuated by correction for insulin) T1DM vs. T2DM: Risk of any, hip MOPF and ankle fractures higher in T1DM than in all T2DM medication subgroups.
[65]	Mitama et al.	6,556 (792 T2DM; 649 IGM; 5,115 non-DM) Mean FU 7.4 yrs	Age: mean 67–68 Japanese 57.5% women	age, BMD, eGFR, albumin, exercise, smoking, alcohol, family history of fracture, IHD, CVD	Compared to HbA1c ≤ 5.6%: HbA1c 5.7%–6.4%: No increased risk HbA1c ≥ 6.5% (DM): **HR for incident fracture 1.31 [1.02–1.51] in men**, not significant in women.	T2DM associated with: - Increased risk of hip fracture in men - No increased risk in women
[103]	Kim et al.	51,330 (17,110 T2DM, 34,220 non-DM) 7 yrs FU (or until death)	Age: ≥50 Korean 54% women	Age, household income, comorbidities[a], steroid use, osteoporosis[a]	Fracture in diabetics vs. controls: Hip: **HR 1.73 [1.38–2.16] in women, HR 1.84 [1.29–2.63] in men**	T2DM associated with: - Increased hip fracture risk (irrespective of sex) - No increased risks of non-vertebral, vertebral or any fracture
[105]	Majumdar et al.	57,938 (8,840 T2DM; 49,098 non-DM) 0–17 yrs FU (mean 7 yrs]) >420,000	Age: mean 73 Canadian Women All: Undergoing DXA, ≥10 years of health coverage	FRAX-scores: computed with BMD, BMI, prior fracture. Comorbidity[a], falls, antiosteoporotic drugs, insulin.	T2DM vs. Non-DM: Prior fracture: **16.5% vs. 14.3% (p < .0001)** MOPF: **9.2% vs. 8.6% (p = 0.05)** Hip: **3.2% vs. 2.3% (p < 0.0001)** Vertebral: **2.3% vs. 1.9% (p = 0.04)** Humerus: **2.3% vs. 1.7% (p < 0.0001)** Foot: **2.8% vs. 3.7% (p < 0.0001)**	T2DM in women is associated with: - Increased risk of hip fracture – regardless of duration. - Increased risk of MOPF – only if long disease duration. - Increased risk of vertebral, humerus and forearm fracture

		person-years			Ankle: 1.7% vs. 1.5% (p = 0.2) Diabetes duration groups vs. non-DM: New onset: HR 0.99 [0.86–1.14] for MOPF, **HR 1.30 [1.01–1.65] for HF** < 5y: HR 1.07 [0.92–1.25] for MOPF, **HR 1.54 [1.19–1.99] for HF** 5–10 y: HR 1.10 [0.93–1.29] for MOPF, **HR 1.55 [1.17–2.06] for HF** '> 10 y': **HR 1.47 [1.30–1.66] for MOPF, HR 1.94 [1.54–2.44] for HF**	- Increased prevalence of prior fracture
[107]	Hamilton et al.	6,450 (1291 T2DM; 5159 non-DM) Mean 14.1 (±5.9) yrs FU 90,808 patient-years	Age: ≥55 Australian 51.3% women	Age, sex, comorbidities (Charlson Comorbidity Index excluding diabetes-specific chronic complications)	First hip fracture (T2DM vs. non-DM): Age 75–84: **Crude IRR 1.80 [1.26–2.55]** All ages: **Crude IRR 1.33 [1.05–1.68] (0 = 0.013)** All ages: **csHR 1.50 [1.19–1.89] (p = 0.001)** All ages: sdHR 1.21 [0.96–1.52] (p = 0.11) First hip fracture (predictors): Diabetes duration (increase of 1 y): **csHR 1.02 [1.01–1.03], p < 0.001** HbA1c (increase of 1%): **csHR 1.07 [1.02–1.13], p = 0.005** 1 unit increase in ln(urine-A:C-ratio): **csHR 1.1 [1.13–1.26], p = 0.001** Peripheral sensory neuropathy: **csHR 1.38 [1.16–1.64], p < 0.001** All incident hip fractures (T2DM vs. non-DM): All ages: **Crude IRR 1.28 [1.02–1.59] (p = 0.029)** Age groups (10 yr intervals): **IRR between**	T2DM associated with: - Increased risk of first and all incident hip fractures (HF) – this effect only found in subgroup with age 75–84. Effect on first incident HF attenuated after allowing for competing risk of death Peripheral sensory neuropathy (PSN) associated with: - Increased risk of multiple incident hip fracture (HF) First incident HF risk increased by: - Diabetes duration, HbA1c, proteinuria, PSN

					1.60–1.87 Multiple incident HF: Peripheral sensory neuropathy vs. no neuropathy: **RR 1.65 [1.07–2.54]**	
[122]	Conway et al.	10,572 All w/T2DM Mean 3.3 yrs FU	Age: mean 71 US Citizens 50.8% women	Model 1: age, sex, race Model 2: age, sex, race, number of BMI-measurements	Compared to HbA1c 7.0%–7.9% (HRs of model 1, model 2): HbA1c < 6.5%: HR 0.96 [0.81–1.13], HR 0.97 [0.82–1.14] HbA1c 6.5%–6.9%: **HR 0.77 [0.64–0.93], HR 0.80 [0.66–0.97]** HbA1c 8.0%–8.9%: HR 1.22 [0.99–1.50], HR 1.13 [0.92–1.40] HbA1c ≥ 9%: **HR 1.55 [1.21–2.00],** HR 1.19 [0.93–1.54]	Risk of any fracture: - Lower in HbA1c 6.5–6.9%. - Highest in HbA1c ≥ 9%. Risk attenuated in adjustment model 2
[127]	Martinez-Laguna et al.	171,931 (58,483 T2DM; 113,448 non-DM) Median 2.63 yrs FU	Age: mean 62 Spanish 43.5% women	All age- and sex-matched. *BMI, previous fracture, oral corticoids. **Prevalent CVD, IHD, CKD and falls history.	Subhazard ratio (SHR) in T2DM vs. Non-DM: *Partially adjusted risk of HF: **SHR 1.20 [1.06–1.35]** **Fully adjusted risk of HF: SHR 1.10 [0.98–1.24] ≥1 osteoporotic fracture: SHR 0.97 [0.92–1.02] Major osteoporotic fracture: SHR 0.95 [0.89–1.01]	T2DM associated with: - 20% increased risk of fracture; non-significant after adjustment for comorbidities and falls. Significant interaction between T2DM and BMI, CKD and IHD on hip fracture risk.
[108]	Lee et al.	70,829 (4,805 T2DM; 66,024 non-DM) "EPESE study: Mean 6.5/8.1	Age: means 73–74, 61–63 USA Postmenopausal women	*Age, race, BMI **Age, race, BMI, functional impairments, comorbidity[a], alcohol use, tobacco use, vision impairment, medications[a].	Hazard ratio in EPESE and WHI study: *Any fracture (AF): **HR 1.36 [1.08–1.72]** and **HR 1.29 [1.19–1.39]** **AF fully adjusted: HR 1.22 [0.96–1.56] and **HR 1.20 [1.11–1.30]** *Hip fracture (HF): HR 1.27 [0.80–	T2DM associated with: - 29–36% increased risk of any clinical fracture; attenuated in full model adjustment in one study (EPESE). - Hip fracture risk only in WHI

		yrs FU (EPESE/WHI studies)			2.20] and **HR 1.45 [1.08–1.94]** **HF fully adjusted: HR 1.08 [0.66–1.76] and HR 1.28 [0.95–1.73] *NHNVF: HR 1.23 [0.97–1.56] and **HR 1.28 [1.18–1.39]** **NHNVF fully adjusted: HR 1.13 [0.87–1.46] and **HR 1.20 [1.10–1.31]**	study (by 45%); attenuated in full model adjustment - Risk of non-hip, non-vertebral fracture in one study by 28% (WHI), still significant after full model adjustment
[109]	Reyes et al.	186,171 (36,865 T2DM; 149,306 non-DM) Median 2.99 yrs FU	Age: mean 76/84 Catalonia, Spain Men	Age, BMI, smoking, alcohol consumption, oral corticosteroids, comorbidities[a]	Relative risk for hip fracture: T2DM (vs. Non-DM): **RR 1.45 [1.25–1.69], p < 0.001** T2DM w/complications: **RR 1.89 [1.15–3.21], p < 0.012**	Hip fracture associated with: - T2DM. - Diabetic complications.
[110]	Hothersall et al.	3,840,841 (180,841 T2DM; 3,660,000 non-DM) 461,120 person-yrs (T2DM) 10,980,599 person-yrs (non-DM)	Age: 50–84 Scottish Unspecified sex fractions	Age, calendar year, SIMD (Scottish Index of Multiple Deprivation),	Incident Rate Ratio (IRR) of T2DM vs. Non-DM (by age and sex): Men 60–69: **IRR 0.87 [0.76–1.00], p = 0.046** Men Total: IRR 0.97 [0.92–1.02], p = 0.234 Women 50–59: **IRR 1.21 [1.04–1.41], p = 0.013** Women 60–69: **IRR 1.14 [1.08–1.21], p < 0.001** Women 70–79: **IRR 1.06 [1.01–1.12], p = 0.032** Women Total: **IRR 1.05 [1.01–1.10], p = 0.013** IRR for diabetes duration > seven years vs. non-DM: Men: **IRR 1.25 [1.08–1.45]** Women: **IRR 1.55 [1.38–1.75]**	T2DM associated with increased risk of hip fracture: - In females (total) and in all age-subgroups except 80–84. - In all diabetics with long disease duration (> seven years) T2DM associated with reduced risk of hip fracture: - In 60–69 year old males (not in full male cohort)

[128]	Schneider et al.	15,140 (1,195 T2DM; 605 undiagnosed DM; 13,340 non-DM) Median 20 yrs FU	Age: mean 55 USA 55.4% women	Age, sex, race/study center, BMI, sports activity tertile, alcohol/smoking, medications[a]	Hazard ratio (HR) for fracture according to diabetes status at baseline (compared to non-DM): Undiagnosed diabetics (n = 547): HR 1.12 [0.82–1.53] Diagnosed diabetics: **HR 1.74 [1.42–2.14]** HR for fracture by HbA1c: HbA1c ≥ 8.0% vs. < 8.0% (T2DM): **HR 1.63 [1.09–2.44]** Undiagnosed diabetics vs. HbA1c <5.7% (non-DM): HR 1.05 [0.72–1.54]	Higher risk of any fracture associated with: - T2DM (only if present at baseline) - Higher HbA1c
[112]	Hippisley-Cox et al.	3,142,673 (88,540 T2DM; 3,054,133 non-DM) 23,608,337 person-yrs	Age: 50+ UKGB 50.6% women	Age, BMI, ethnic origin, alcohol intake, smoking status, medical or social factors (comorbidities, medications)	HR for fracture in women (T2DM vs. Non-DM): Osteoporotic fracture: **HR 1.27 [1.21–1.34]** Hip fracture: **HR 1.57 [1.45–1.69]** HR for fracture in men (T2DM vs. Non-DM): Osteoporotic fracture: **HR 1.25 [1.15–1.36]** Hip fracture: **HR 1.33 [1.19–1.49]**	T2DM associated with (in both sexes individually): Higher risk of hip fracture Higher risk of any osteoporotic fracture
[113]	Schwartz et al.	16,885 (1,969 T2DM; 14,916 non-DM) [3 prospective studies] - SOF study: 2 yrs FU	Age: means 73 US 56% women	Unadjusted	Rate of fracture per 1000 person-years (T2DM vs. Non-DM): Hip, Study 1 (Women): **13.4 ±1.7 vs. 11.1 ±0.3, p < 0.0001** Hip, Study 2 (Men): **3.0 ±0.7 vs. 3.3 ±0.3, p < 0.0001** Hip, Study 3 (Women): **6.7 ±2.1 vs. 5.3 ±0.7, p < 0.0001** Hip, Study 3 (Men): **4.9 ±1.5 vs. 3.3 ±0.6, p**	T2DM associated with rate of fracture (hip and any nonvertebral): - Increased in women in study "SOF" (n = 7,926) - Increased in women in study "Health ABC" (n = 1,523) - Increased in men in study "Health ABC" (n = 1,442)

		- MrOS: 9 yrs FU - Health ABC: 10 yrs FU			**< 0.0001** Nonvertebral, Study 1 (Women): **51.0 ±3.8 vs. 42.5 ±0.8, p < 0.0001** Nonvertebral, Study 2 (Men): **15.7 ±1.7 vs. 16.5 ±0.7, p < 0.0001** Nonvertebral, Study 3 (Women): **23.3 ±4.1 vs. 19.9 ±1.4, p < 0.0001** Nonvertebral, Study 3 (Men): **12.1 ±2.5 vs. 9.8 ±1.1, p < 0.0001** For any given fracture risk (T2DM vs. Non-DM): - Women, higher aBMD T-score: **Mean difference 0.59 [0.31–0.87]** - Men, higher aBMD T-score: **Mean difference 0.38 [0.09–0.66]**	- Reduced in men in study "MrOS" (n = 5,994) T2DM vs. Non-DM, both sexes: - For a given fracture risk, there was a higher femoral aBMD T-score - Conversely, increased fracture risk for similar T-scores (see article *Figure 1*)
[115]	Janghorbani et al.	109,691 (8,348 T2DM; 101,343 non-DM) Mean 20.4/20.0 (T2DM/non-DM) yrs FU	Age: mean 62 US Women	Age, BMI, physical activity, menopausal status, estrogen use, smoking, daily intake of calcium, vitamin D and protein	Relative risk (RR) of hip fracture (compared to non-DM): T2DM: **RR 2.2 [1.8–2.7], p < 0.001** Diabetes duration < five years: **RR 1.7 [1.2–2.4], p < 0.001** Diabetes duration 5–11 years: **RR 1.8 [1.3–2.6], p < 0.001** Diabetes duration ≥12 years: **RR 3.1 [2.3–4.0], p < 0.001** T2DM in the obese (BMI ≥ 30 kg/m^2): **RR 2.2 [1.4–3.3], p < 0.001** T2DM in non-obese: **RR 2.5 [1.9–3.1], p < 0.001**	T2DM associated with: - Increased risk of hip fracture Effect of T2DM is lower in obese individuals Diabetes duration (<5 yr, 5–11 yr, ≥12 yr) associated with: - Increasing risk of hip fracture with increasing duration
[31]	Dobnig et al.	1,664 (583 T2DM;	Age: ≥70 Austrian	Age, weight, calcaneal bone mass	Hazard ratio (HR) for incident hip fracture: Model 1: T2DM vs. Non-DM: HR 0.90	T2DM associated with: - Increased risk of hip fracture, only

		1,081 non-DM) 2 yrs FU	Women		[0.60–1.34] Model 2: T2DM vs. Non-DM: **HR 1.46 [1.25–1.81], p = 0.01**	when adjusted for calcaneal bone mass.
[80]	Strotmeyer et al.	2,979 (566 T2DM; 177 IFG; 2,236 NGM) 5.4 ±1.1 yrs FU	Age: mean 73–74 US (white and black) 51.1% women	Sex, race, age, site, hip BMD, lean mass, fat mass, visceral fat	Relative risk (RR) for any fracture (compared to NGM): T2DM: **RR 1.64 [1.07–2.51]** Impaired fasting glucose: RR 1.34 [0.67–2.67]	Overall fracture risk associated with: - T2DM. No association with: - Diabetes duration - HbA1c
[32]	Gerdhem et al.	1,132 (74 T2DM; 1,058 non-DM) Mean 4.6 yrs FU	Age: All 75 Swedish Women	Unadjusted		T2DM not associated with fracture (any, hip, forearm, vertebral): - Lifetime risk, risk after the age of 75, age at first fracture Prevalent fracture not associated with: - Diabetes duration
[123]	de Liefde et al.	6,655 (792 T2DM; 5,863 non-DM) Mean 6.8 yrs FU	Age: ≥55 (mean 74) Dutch 59.6% women	Age, sex, BMI, smoking, s-creatinine, visual acuity, falling frequency, lower limb disability, femoral neck BMD	Fracture in the previous five years (T2DM vs. Non-DM): Nonvertebral fracture: 13,5% vs. 14,5%, p ≥ 0.05 Hazard ratio (HR) of fracture (T2DM vs. Non-DM): Nonvertebral: **HR 1.33 [1.00–1.76]** HR for treated diabetics vs. Controls: Nonvertebral: **HR 1.69 [1.16–2.46]** Hip: **HR 1.26 [0.57–2.78]** Wrist: **HR 2.14 [1.10–4.18]**	T2DM associated with: - Increased risk of nonvertebral fracture - No increased risk of hip fracture - No increased risk of wrist fracture Newly diagnosed T2DM not associated with increased risk. Treatment with antidiabetics associated with increased risk of all fracture types
[116]	Taylor et al.	6,787 (5.6% T2DM; 94.4% non-DM)	Age: mean 74 US Women	*Adjusted for BMD, age, weight, vision, height, education level, digit symbol	Hazard ratio (HR) of hip fracture (T2DM vs. Non-DM): In full population: **HR 1.83 [1.34–2.50]***	T2DM associated with: - Increased risk of hip fracture Effect of T2DM on fracture risk not

		Mean 10.1 yrs FU		test score, walking speed, parity, follow-up time	In osteoporotic subpopulation: HR 1.06 [0.52–2.16] In non-osteoporotic subpopulation: **HR 1.97 [1.39–2.80]**	present in osteoporotic subgroup
[117]	Ottenbacher et al.	3,050 (690 T2DM; 2,360 non-DM) 7 yrs FU	Age: ≥65 Mexican Americans (USA) 57.9% women	Model 1: age, sex, smoking status, BMI, history of stroke Model 2: Model 1 + measure of lower body function, test for distant vision	Hazard ratio (HR) for hip fracture (T2DM vs. Non-DM): Model 1: **HR 1.57 [1.03–2.39], p = 0.04** Model 2: HR 1.50 [0.97–2.32], p = 0.07 Bivariate analysis of those with/without diabetes vs. Those with/without hip fracture: **Chi^2 = 4.20, p < 0.03, df = 1**	T2DM associated with: - Increased risk of hip fracture in two analyses. Adjustment for previous tests for lower body function and distant vision fully attenuated association.
[118]	Nicodemus et al.	32,059 (1,682 T2DM; 30,377 non-DM) 306,900 person-yrs FU	Age: mean 61 US Postmenopausal women	Age, smoking, estrogen use, BMI, waist-to-hip ratio	Relative risk (RR) for hip fracture (compared to non-DM): T2DM: **RR 1.70 [1.21–2.38]** Diabetes duration 0–4 years: RR 1.44 [0.79–2.63] Diabetes duration 5–12 years: RR 1.40 [0.77–2.57] Diabetes duration 13–40 years: **RR 2.30 [1.39–3.81]** Nonobese (T2DM vs. non-DM): **RR 1.74 [1.14–2.67]** Never used estrogen (T2DM vs. non-DM): **RR 1.66 [1.10–2.51]** Ever estrogen users or obese (T2DM vs. non-DM): p > 0.05	T2DM associated with: - Increased risk of hip fracture. Increased risk only found in subgroups: - Diabetes duration ≥ 13 years - Non-obese - Never users of estrogen.
[92]	Ivers et al.	3,654 (216 T2DM; 3,438 non-DM)	Age: mean 66 Australian 56.7% women	Age, sex	Relative risk of fracture (T2DM vs. Non-DM): Diabetes duration 5–9 years, proximal	T2DM not associated with fracture risk: - Hip, distal forearm, ankle,

		Mean 5 yrs FU			humerus: **RR 11.4 [1.4–91.9]** Diabetes duration ≥10 years, all fractures: **RR 2.9 [1.2–7.0]** Diabetes duration ≥10 years, proximal humerus: **RR 11.0 [2.3–51.8]** Diabetic retinopathy vs. no retinopathy: Any fracture: **RR 4.6 [2.3–9.1]** Proximal humerus: **RR 9.4 [2.0–43.5]**	proximal humerus or 'any' fracture Diabetes duration associated with higher risks of: - Any fracture and proximal humerus fracture. Diabetic retinopathy associated with higher risks of: - Any fracture and proximal humerus fracture.
[129]	Napoli et al.	5,995 (881 T2DM; 5,114 non-DM) Mean 9.1 yrs FU	Age: mean 73 US Men	Age, race, clinic, hip BMD, previous falls/fractures, BMI, comorbidities[a], TCA use, smoking, grip strength, lower body function	Hazard ratio (HR) of incident fracture (compared to NGM): T2DM, all: HR 1.08 [0.91–1.29] (not adjusted for hip BMD) T2DM, all: **HR 1.30 [1.09–1.54]** (adjusted for hip BMD) T2DM, no insulin: HR 1.00 [0.80–1.25] T2DM, insulin: **HR 1.74 [1.13–2.69]**	T2DM associated with: - Increased risk of fracture only when adjusting for hip BMD. Increased risk not found in subgroup of non-insulin users. - No association with fracture prevalence
[14]	Schwartz et al.	9,548 (551 T2DM; 8997 non-DM) Mean 9.4 yrs FU	Age: ≥65 US Women	Age, BMI, calcaneal BMD, height, height loss since age 25, contrast sensitivity, mother fractured hip, medications[a], recent falls, clinic, vision, comorbidities[a], more[a]	Relative risk (RR) of fracture (T2DM vs. non-DM): Hip: **RR 1.82 [1.24–2.69]** Proximal humerus: **RR 1.94 [1.24–3.02]** All nonvertebral: **RR 1.30 [1.10–1.53]** Distal forearm, ankle, foot, vertebral: $p > 0.05$ Diabetes duration (≥14 years vs. <14 years): Hip: **RR 2.40 [1.55–3.71]** Any other site: $p > 0.05$	T2DM associated with: - Increased risk of hip, proximal humerus and all nonvertebral fracture - No increased risk of distal forearm, ankle, foot or vertebral fracture. Diabetes duration associated with: - Increased hip fracture risk
Retrospective Cohort Studies						

[119]	Lee et al.	662,628 All w/T2DM Avg. FU 3.43 yrs Total 2,272,930 person-yrs	Age: ≥65, mean 74–76 US Citizens Male veterans	Comorbidities[a], race, BMI and age.	Compared with HbA1c between 7.5% and 8.5%: HbA1c < 6.5%: **HR 1.08** (Any fracture) HbA1c < 6.5%: **HR 1.13** (hip fracture) HbA1c > 9.5%: **HR 1.1** (hip fracture)	Elevated HbA1c (>9.5%) associated with: - Increased risk of hip fracture. Low HbA1c (< 6.5%) associated with: - Increased risk of hip- and any fracture
[94]	Kabue et al.	120,256 All w/T2DM Unspecified FU/OT	≥65, mean 73 US Citizens 49.5% women	Adjusted, unspecified	No effect of HbA1c on fracture risk **Retinopathy: OR = 1.70 [1.40–2.07] (p < 0.001)** for hip fracture	Hip fracture risk: - Associated with diabetic retinopathy - Not associated with HbA1c
[97]	Baltrusaitis et al.	36,744 (19,430 T2DM; 17,314 non-DM) 7 yr OT	Age: ≥65 US Citizens Veterans 1.7% women	Age, sex, race, BMI, s-creatinine, hypoglycemia, prior fracture, medications[a], comorbidities[a]	Compared to T2DM participants with HbA1c ≤ 7%: Non-DM: **HR of fracture 1.233 [1.130–1.345]** HbA1c 7.1–8%: **HR 0.718 [0.626–0.825]** HbA1c 8.1–9%: **HR 0.682 [0.545–0.854]** HbA1c > 9%: No significant effect (HR 0.887 [0.633–1.242], p = 0.4915)	Risk of any fracture: - Highest in non-diabetics - Lowest in diabetics with HbA1c between 7.1–9%
[98]	Martinez-Huedo et al.	43,872 (8,049 T2DM; 35,823 non-DM)	Age: ≥65, mean 76 Spanish 83% women All: From database of proximal humerus fractures *with* hospitalization ≥ 24 h	Age	Incidence rate ratio (IRR) in T2DM vs. Non-DM: Proximal humerus fracture, men: **IRR 0.87 [0.82–0.93, p < 0.01]** Proximal humerus fracture, women: **IRR 0.97 [0.95–1.00, p < 0.01]**	T2DM associated with: - Lower incidence rate of PHF in men. - No difference in women.
[102]	Lee et al.	2,798,309 (900,402 T2DM;	Age: mean 72 U.S. Veterans Men	Age, race, ethnicity, BMI, alcohol and tobacco use, rheumatoid arthritis,	T2DM vs. Non-DM: Hip fracture: **OR 1.21 [1.19–1.23]** Any fracture: **OR 1.22 [1.21–1.23]**	T2DM associated with increased risk of hip fracture and of any clinical fracture.

		1,897,905 non-DM) 10 yrs OT		corticosteroids		A significant proportion of increased risk due to peripheral neuropathy, CVD and CHF.
[133]	Zhao et al.	8,430 All w/T2DM 2 yrs OT (1 yr baseline + 1 yr FU)	Age: mean 76 US Veterans Unspecified sex fractions	Unadjusted	Hypoglycemia (HG) vs. Non-hypoglycemia: **20 hospital visits in HG vs. 4 visits in non-HG (p = 0.0015)**	Hypoglycemia associated with: - Higher risk of fall related events (fractures and head injury)
[126]	Sato et al.	15,559 (7,580 T2DM; 7979 non-DM) 30-month OT	Age: mean 60/65 Japanese Women All: osteoporosis	Matched: Age, osteoporosis drug at index, sex, medications[a], comorbidities[a].	Fractures during follow-up in T2DM vs. non-DM, respectively: Clinical fractures: **12.7% vs. 9.9% (p < 0.001)** Non-vertebral fractures: **10.1% vs. 7.2% (p < 0.001)** Days to first fracture: **455.5 ±259.2 vs. 453.3 ±265.5 (p = 0.0003)**	T2DM associated with: - Increased risk of fractures (all and non-vertebral) - Shorter time to first fracture (slight effect). Same effects not found in subgroup treated with Raloxifene
[120]	Chiang et al.	26,501 All w/T2DM Mean 8.12 yrs FU	Age: mean 64/70 Taiwanese 55% women	Age, sex, smoking, alcohol consumption, diabetes duration, medications[a], BMI, baseline FPG, HbA1c, comorbidity[a], complications[a], (FPG-variability, HbA1c-variability)	Hip Fracture (HF)-group vs. non-HF group: HbA1c: **8.36 (2.03) vs. 8.14 (1.92). ; p < 0.001** Diabetes duration: **9.16 (7.43) vs. 7.29 (6.79); p < 0.001** FPG: **178.60 (75.00) vs. 170.30 (63.74); p < 0.001** HHNC prevalence: **1.23% vs. 0.59%; p = 0.009** Hazard ratio (HR) of hip fracture (compared to FPG-CV ≤ 14.3%): FPG-CV 14.3–25.4%: HR 1.09 [0.92–1.03] FPG-CV 25.4–42.3%: **HR 1.35 [1.14–1.60], p < 0.001**	Hip fracture associated with: - Higher HbA1c, higher FPG, longer diabetes duration, higher prevalence of hyperglycemic hyperosmolar nonketotic coma - High FPG-variability Hip fracture not associated with: - Neuropathy, retinopathy, hypoglycemia, DKA and HbA1c-variability.

					FPG-CV >42.3%: **HR 1.27 [1.07–1.52], p <0.01**	
[121]	Li et al.	20,025 All w/T2DM Mean 7.41 yrs FU	Age: mean 72–73 Taiwanese 54.1% women	HRs adjusted for: age, sex, smoking, alcohol consumption, diabetes duration, glycemia, comorbidities[a], medications[a], complications[a].	HF group vs. Non-HF group: Diabetes duration – Mean (SD): **9.21 (7.90) vs. 8.16 (7.55), p < 0.001** Diabetic retinopathy: **29.26% vs. 24.49%, p < 0.001** Hypoglycemia: 0.86% vs. 0.68%, p = 0.52 Peripheral neuropathy: **16.25% vs. 12.33%, p < 0.001** Hazard ratio (HR) for hip fracture by HbA1c: HbA1c 9–10%: **HR 1.24 [1.02–1.49], p < 0.05** HbA1c ≥10%: **HR 1.32 [1.09–1.58], p < 0.01**	Hip fracture associated with: - Longer diabetes duration, diabetic retinopathy and peripheral neuropathy. Hip fracture not associated with hypoglycemia. Higher risk of hip fracture in high HbA1c (9–10% and ≥10%).
[134]	Kachroo et al.	1,147,937 All w/T2DM 12 months FU	Age: ≥65 US Citizens 51.5% women	Age- and sex-matched. Falls, antidiabetic drug, region, healthcare plan, comorbidities[a]	Fractures in hypoglycemia vs. non-hypoglycemia group: All ages: **OR 2.16 [1.74–2.67]** Age < 75 years: **OR 2.30 [1.63–3.24]** Age ≥ 75 years: **OR 2.07 [1.58–2.72]**	Any fracture risk associated with: - Hypoglycemia.
[91]	Oei et al.	4,135 (420 T2DM; 3,715 non-DM) Mean 12.2 yrs FU	Age: mean 68–71 Dutch 59.4% women	Age, sex, height, weight, femoral neck BMD	Hazard ratio (HR) for all fractures: HbA1c ≥ 7.5% vs. < 7.5%: **HR 1.62 [1.09–2.40], p = 0.02** HbA1c ≥ 7.5% vs. Non-DM: **HR 1.47 [1.12–1.92], p = 0.005** HbA1c < 7.5% vs. Non-DM: HR 0.91 [0.67–1.23], p = 0.54	Inadequately controlled T2DM (HbA1c ≥7 (compared to adequately controlled T2DM and non-DM controls) associated with: - Any fracture - Wrist fracture risk T2DM not associated with:

					HR for wrist fracture: HbA1c ≥ 7.5% vs. Non-DM: **HR 1.71 [1.03–2.86], p = 0.04**	- Hip fracture risk (regardless of HbA1c)
[71]	Leslie et al.	29,407 (2,356 T2DM; 27,051 non-DM) Mean 4.7 yrs FU	Age: mean 65 Canadian Women	aHR adjusted for: Comorbidities[a], medications[a], BMI *Added lumbar spine TBS **Added lumbar spine BMD	T2DM vs. Non-DM: Prior major fracture: **16.3% vs. 13.3%, p < 0.001** Incident MOPF: **7.4% vs. 5.5%, p < 0.001** Incident MOPF: **HR 1.49 [1.27–1.74]** *Incident MOPF: **HR 1.35 [1.15–1.59]** **Incident MOPF: **HR 1.59 [1.35–1.86]**	T2DM associated with: - Higher prevalence of prior major osteoporotic fracture (MOPF) and risk of incident MOPF*/** Correction for BMD accentuates risk of incident MOPF, whereas correction for TBS attenuates the effect.
[114]	Lipscombe et al.	598,812 197,412 T2DM; 401,400 non-DM) Mean 6.12 yrs FU	Age: ≥66 Canadian 49.4% women	*Age-group, comorbidities[a], complications[a], medications[a], history of BMD test **Added insulin ***Added income quintile (IncQ) ****Added prevalent diabetes and IncQ.	Hazard ratio (HR) for hip fracture: Women, T2DM vs. Non-DM: **HR 1.11 [1.08–1.15]*** Women, Prevalent vs. Incident DM: **HR 1.24 [1.13–1.37]**** Men, T2DM vs. Non-DM: **HR 1.18 [1.12–1.24]***** Men, Prevalent vs. Incident DM: **HR 1.37 [1.18–1.59]******	T2DM associated with: - Increased risk of hip fracture in men and women.*/** Higher risk with prevalent compared to incident diabetes – hinting at a deleterious effect of diabetes duration.***/****
Case-control Studies						
[106]	Lopez-de-Andres et al.	432,760 (92,182 T2DM, 340,578 non-DM)	Age: mean 81–82 Spanish 77.4% women All: discharged after hip fracture	Year of discharge, age, comorbidity[a], complications, type of repair, diabetes status Age- and sex-matched	Incidence rate ratio (IRR) of diabetic vs. nondiabetic individuals: Men: **IRR 1.08 [1.06–1.09]** Women: **IRR 1.20 [1.19–1.21]**	T2DM associated with: - Increased risk of hip fracture (in both sexes)
[135]	Puar et al.	1,116 (558 hip fractures; 558 non-	Age: mean 77 Singaporean 73.3% women All: T2DM	Age, sex, race, diabetes duration, Charlson Comorbidity Index, complications[a]/comorbidities[a],	Odds ratio (OR) for hip fracture (compared to HbA1c ≤ 8%): HbA1c ≤ 6%: **OR 3.03 [2.03–4.52], p < 0.01** HbA1c 6.1–7.0%: **OR 2.38 [1.74–3.25], p <**	Higher risk of hip fracture in: - HbA1c ≤ 6% and - HbA1c 6.1–7.0% compared to HbA1c > 8%.

		fractures)		high-risk medications.	**0.01** HbA1c ratio (of fracture and non-fracture group): **0.78 [0.72–0.85], p < 0.01**	Lower mean HbA1c in hip fracture group.
[130]	Partanen et al.	114 (74 T2DM; 40 non-DM)	Age: mean 73.7 Finnish Postmenopausal women	Unadjusted	Use of oral antidiabetics in fracture group vs. Non-fracture group: **p = 0.029**	Use of oral antidiabetics: - Significantly more common in fracture group
Cross-sectional Studies						
[69]	Sakane et al.	82 (17 T2DM; 65 non-DM)	Age: median 59 São Paolo. 85% women All: Postsurgical hypoparathyroidism	Unadjusted	Patients w/fracture vs. non-fractured group: Mean glucose 118 mg/dL vs. 95 mg/dL **(p = 0.013)** More diabetic/prediabetic patients **(p = 0.017)**	Fracture correlated with: - Diabetic status - Glycemic control
[93]	Hatano et al.	384 All w/T2DM	Age: ≥65, mean 87 Japanese 76.6% women	None		HbA1c not associated with fracture risk
[38]	Raška et al.	112 All w/T2DM	Age: mean 65 Czech Postmenopausal women			Previous vertebral fracture not associated with FPG or HbA1c
[95]	Waard et al.	2,005 (400 T2DM; 359 IGM; 1246 healthy)	Age: mean 60–63 Netherlands 49.6% women	Age, sex, level of education, BMI, MVPA, comorbidities[a], smoking status, alcohol consumption, medications[a], cognitive function	T2DM vs. normal glucose metabolism (NGM): Fracture prevalence: **Lower in T2DM (5.4%) vs. NGM (10.3%), p = 0.006**	T2DM associated with: - Lower prevalence of fractures. T2DM, high (≥7%) HbA1c and long (≥5 yrs) diabetes duration: - No effect on Odds ratio (OR) for fracture
[131]	Starup-Linde et al.	96 All w/T2DM	Age: mean 60/65 Danish	Unknown	**Previous fracture associated with diabetes duration (p = 0.012)**	Disease duration associated with previous fracture.

			35.4% women			
[96]	Kilpadi et al.	296 (122 T2DM; 174 non-DM)	Age: mean 56 Southern Texas Latinos 56% women	Model for vertebral fracture (ethnicity, diabetes, sex, and propensity score[a])	T2DM vs. Non-DM group: Vertebral fracture: **27.9% vs. 13.8%, OR 2.86 [1.56–5.34], p < 0.001**	Vertebral fracture: - Associated with T2DM. - Not associated with HbA1c.
[111]	Carnevale et al.	1,751 (974 T2DM; 777 non-DM)	Age: mean 64–65 Italian 58.9% women	Unadjusted	T2DM vs. Non-DM: Men, All fractures: **30.99% vs. 21.70%, p = 0.009** Women, All fractures: **28.78% vs. 19.926%, p < 0.001** Both, All fractures: **29.88% vs. 20.46%, p < 0.001** Women Femoral: **0.41% vs. 1.845%, p = 0.032** Both, Humeral: **3.80% vs. 2.06%, p = 0.035** Both, Wrist: **4.21% vs. 1.80%, p = 0.004** Both; Radial, clinical vertebral, other: p > 0.05	T2DM associated with: - Higher prevalence of any previous fracture in both men and women - Higher prevalence of humeral and wrist fractures in total population - Higher prevalence of femoral fractures in females T2DM not associated with: - Fractures in any specific locations in males
[30]	Yamamoto et al.	495 (255 T2DM; 240 non-DM)	Age: mean 63 Japanese 63% (postmenopausal) women		**No statistical testing!** **Women (T2DM vs. Non-DM): 28.4% vs. 21.7%** Men (T2DM vs. Non-DM): 41.7% vs. 61%	T2DM associated with: - Higher prevalence of VF in women. - Lower prevalence of VF in men.
[125]	Viegas et al.	148 All w/T2DM	Age: mean 62 Brazilian Postmenopausal women	Age, T2DM duration, daily calcium intake, diabetic retinopathy, WHO BMD classification, renal function[a], PPG, HbA1c, s-triglycerides.	Values according to prevalence of VF (VF vs. No-VF): PPG: **141.79 ±74.78 vs. 178.15 ±86.64, p = 0.029** HbA1c: **7.13 ±1.80 vs. 7.80 ±1.70, p = 0.049** Odss ratio (OR) for VF:	Higher risk of vertebral fracture associated with: - Normal postprandial glucose (vs. high PPG), longer diabetes duration, presence of retinopathy - Not nephropathy or peripheral diabetic neuropathy

					Normal PPG (vs. abnormal): **OR 4.20 [1.45–12.33], p = 0.008** Other associations: Fracture increases with diabetes duration (≥10 years): **p = 0.037** Diabetic retinopathy increases fracture risk: **p = 0.030**	Women with prevalent vertebral fracture have: - Lower postprandial glucose and HbA1c
[51]	Bulló et al.	251 (110 T2DM; 141 non-DM)	Age: Mean 67.70–67.82 Spanish 50.6% women	Sex, age, BMI	Odds ratio (OR) in T2DM (vs. non-DM): Any fracture: **OR = 0.393 [0.167–0.965]**	T2DM associated with: Reduced risk of any fracture
[89]	Sosa et al.	202 (101 T2DM; 91 non-DM)	Age: ≥65 Spanish Postmenopausal women	Unadjusted		T2DM not associated with: - Risk of vertebral fracture - Risk of any fracture
[81]	Strotmeyer et al.	2,979 (566 T2DM; 2,413 non-DM)	Age: Mean 73.3–74.0 US 51.1% women	Unadjusted	Fracture (T2DM vs. Non-DM): White women: **21.4% vs. 34.1%, p < 0.05** Men and black women: p > 0.05	T2DM associated with: - Reduced risk of fracture in white women - No effect on fracture risk in black women or men
[99]	van Daele et al.	5,931 (578 T2DM; 5,353 non-DM)	Age: ≥55 Netherlands 58.2% women	Age, BMI	Odds ratio (OR) of nonvertebral fracture (compared to non-DM): Women with T2DM: **OR 0.63 [0.44–0.90]** Men with T2DM: OR 0.96 [0.60–1.52] Newly diagnosed T2DM: 0.62 [0.35–1.10]	T2DM associated with: - Reduced risk of nonvertebral fracture in women. - No altered risk in men. - No altered risk in newly diagnosed diabetics.
[62]	Yamamoto et al.	996 (298 T2DM; 698 non-DM)	Age: mean 65–67 Japanese 76.2% women	ORs adjusted for age, BMI and L-BMD.	Odds ratio of VF (T2DM vs. Non-DM): Women: **OR 1.86 [1.11–3.12], p = 0.019** Men: **OR 4.73 [2.19–10.20], p < 0.001**	Prevalent vertebral fracture associated with: - T2DM (in both sexes) - Not diabetes duration or

						complications (neuropathy/retinopathy) - Not fasting plasma glucose or HbA1c
[34]	Ardawi et al.	964 (482 T2DM; 482 non-DM)	Age: Mean 59.60 ±7.90 Saudi Arabians Postmenopausal women	Unadjusted and age-adjusted	Fracture prevalence (T2DM vs. non-DM): **24.5% vs. 0.0%, p < 0.0001** (unadjusted) Prevalent VF vs. no previous VF in those with T2DM: DM duration: **11.58 ±3.53 vs. 9.51 ±3.92, p<0.001** (adjusted p = 0.631) HbA1c: **10.52 ±2.28 vs. 9.64 ±1.85, p < 0.001** (adjusted p = 0.290)	Prevalent vertebral fracture (assessed by x-ray) associated with: - T2DM - Longer T2DM duration (fully attenuated after adjustment for age) - Higher HbA1c (fully attenuated after adjustment for age)

[a]: Parameters are summarized here (full list can be found in-article), s-: serum, p-: plasma, BMD: bone mineral density, BMI: body mass index, CHF: congestive heart failure, CKD: chronic kidney disease, CVD: cardiovascular disease, DM: diabetes mellitus, T1DM: type 1 DM, T2DM: type 2 DM, DXA: dual-energy X-ray absorptiometry, eGFR: estimated glomerular filtration rate, FPG: fasting plasma glucose, FPG-CV: FPG-coefficient of variation, FRAX: fracture risk assessment tool, FU: follow-up, HbA1c: hemoglobin A1c, HF: hip fracture, HHNC: hyperosmolar hyperglycemic nonketotic coma, HOMA: homeostatic model assessment, HOMA-β: HOMA–β-cell, HOMA-IR: HOMA of insulin resistance, HR: hazard ratio, csHR: cause-specific H, sdHR: sub-distribution H, SHR: sub-hazard ratio, IGM: impaired glucose metabolism, IHD: ischemic heart disease, IRR: incidence rate ratio, mo: months, MOPF: major osteoporotic fracture, MVPA: moderate-to-vigorous physical activity, NGM: normal glucose metabolism, OPF: osteoporotic fracture, OR: odds ratio, PPG: postprandial glucose, PSN: peripheral sensory neuropathy, RR: relative risk, VF: vertebral fracture, vit-D: vitamin D, yr/yrs: year/years.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Schematization of search terms used for PubMed.
2. Table S2: Search strings used for the respective databases.

Author Contributions

Authors ZAM and RV performed literature search, the article appraisal process and all data extraction. ZAM and RV devised the first draft of the manuscript. All additional authors reviewed all subsequent versions of the manuscript and provided detailed feedback for, and identified additional articles for inclusion.

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Competing Interests

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