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REVIEW

Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis

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Aim: Patients with type 2 diabetes mellitus (T2DM) have an increased risk of bone fractures. A variable increase in fracture risk has been reported depending on skeletal site, diabetes duration, study design, insulin use, and so on. The present meta-analysis aimed to investigate the association between T2DM with fracture risk and possible risk factors.

Methods: Different databases including PubMed, Institute for Scientific Information, and Scopus were searched up to May 2016. All epidemiologic studies on the association between T2DM and fracture risk were included. The relevant data obtained from these papers were analyzed by a random effects model and publication bias was assessed by funnel plot. All analyses were done by R software (version 3.2.1) and STATA (version 11.1).

Results: Thirty eligible studies were selected for the meta-analysis. We found a statistically significant positive association between T2DM and hip, vertebral, or foot fractures and no association between T2DM and wrist, proximal humerus, or ankle fractures. Overall, T2DM was associated with an increased risk of any fracture (summary relative risk =1.05, 95% confidence interval: 1.04, 1.06) and increased with age, duration of diabetes, and insulin therapy.

Conclusion: Our findings strongly support an association between T2DM and increased risk of overall fracture. These findings emphasize the need for fracture prevention strategies in patients with diabetes.

Keywords: diabetes mellitus, fractures, bone, osteoporosis, risk factors, meta-analysis

Introduction

Diabetes is an increasingly prevalent disease, with significant associated morbidity and mortality.[1] Type 2 diabetes mellitus (T2DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1,2] Long-term hyperglycemia and inadequate glycemic control both contribute to the development of diabetic complications, including nephropathy, retinopathy, neuropathy, and macrovascular diseases such as acute coronary syndrome, claudicatio intermittens, and stroke.[1–3]

Besides micro- or macrovascular long-term complications, T2DM patients also have various skeletal disorders, including osteoporosis and fractures.[4] Diabetes could impact the bone through several mechanisms, some of which may have contradictory effects.[5] The bone turnover and, thus, the skeletal integrity may also be affected by diabetes, and diabetic bone disease can represent an overlooked complication of diabetes.[6] Diabetic osteopathy is characterized by microarchitectural changes that decrease the bone quality and strength, leading to an increased risk of bone fracture

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in both types of diabetes.[2] Patients with T2DM display a unique skeletal phenotype and impaired structural and geometric properties.[7]

The prevalence of osteoporosis increases dramatically with age.[8] T2DM also increases with increasing age, and therefore, diabetes and osteoporosis often coexist in older adults.[8–10] Authors present the overview of factors involved in the risk of osteoporosis and fractures in both types of diabetes.[1]

In T2DM patients, bone mineral density (BMD) seems to be normal to elevated.[11] For many years, diabetic patients were not considered to be at risk of osteoporosis, based on reports of their higher BMD compared with healthy individuals. However, later studies revealed that persons with T2DM might be at increased risk for bone fractures, despite having higher BMD.[12,13] The risk of bone fractures in patients with diabetes may be unrelated to BMD, and T2DM reduces bone quality rather than BMD.[11] These findings suggest that factors other than BMD may be underlying the higher fracture risk observed in diabetes patients. For example, the association of diabetes with fracture risk has differed depending on the location of fracture, sex, age, duration of diabetes, and the effect of diabetes medications.[11,14–16] Longer disease duration, the presence of diabetic complications, inadequate glycemic control, insulin use, and increased risk for falls are all reported to increase fracture risk.[7] A variable increase in fracture risk has been reported, ranging from onefold to threefold, depending on the risk factors.[7,11,14–16]

The relationship between T2DM and fracture risk has been the subject of considerable interest over the past years, and several studies have examined the risk of fracture in persons with T2DM.[4–17] These studies have demonstrated inconsistent conclusions: reported associations have been positive,[18–21] null,[15,16,22] or even inverse.[23,24] Since a meta-analysis is warranted to clarify the association between T2DM and fracture risk, this study provides a systematic review and meta-analysis of association between T2DM and risk of fracture. We also evaluated possible sources of heterogeneity between studies and the risk factors for fracture among diabetic patients, including age, body mass index (BMI), sex, fracture site, duration of diabetes, the effect of diabetes medications, and so on.

Methods

Search strategy

We performed a literature search in reputable databases including PubMed/Medline, Scopus, and Institute for Scientific Information Web of Knowledge from 1980 to May 2016 using special keywords such as "diabetes mellitus", "type 2 diabetes mellitus", "glucose", "insulin", "fracture", "bone", "osteoporosis", "bone mineral density", and "risk factors". In the initial search, all articles that had these keywords in their titles or abstracts were chosen, and other unrelated articles were eliminated. The obtained articles were rechecked by the other expert authors. We also searched bibliographies of retrieved articles for additional references. The human researches only were highlighted. To decrease bias, two authors performed the search, selection of papers, and extracting data of articles independently.

Inclusion and exclusion criteria

All epidemiologic studies presenting cohort and case–control studies on the association between T2DM and fracture risk (low-trauma hip, distal forearm, proximal humerus, ankle, foot, nonvertebral, or vertebral fracture) were considered. Studies were excluded: if they were performed on individuals with type 1 diabetes mellitus or impaired glucose tolerance, if they did not provide data that allowed calculation of standard errors for effect estimates, if they were meta-analyses and systematic reviews. We also excluded studies with duplicate citation. When there were multiple publications from the same population or cohort, only data from the most recent report were included. When necessary, authors were contacted for additional information.

Data extraction

For all studies, the following data were extracted: first author's name, year of publication, country, study design, sample size, age, sex, BMI, follow-up period (for cohort studies), duration of diabetes, diabetes medications, fracture site and number of cases, risk estimates and corresponding confidence intervals (CIs), factors controlled for by matching or multivariable analysis and adjustment for potential confounders. Two of the authors independently reviewed the abstracts and full articles and collected data according to a standard protocol. Discrepancies were resolved in a joint meeting through discussion. The data were entered into data collection forms and then entered in Microsoft Excel.

Data synthesis and analysis

We used the logarithm of the relative risk (RR) with its standard error for the meta-analysis. The method of DerSimonian and Laird was used for extracting summary RR estimates and the corresponding 95% CIs. The Cochran's Q, meta-regression, and I^2 were used as measures of heterogeneity of the studies. Considering the significant

heterogeneity of the studies, the random effects model was applied. We conducted a meta-regression analysis with age, BMI, region, sex, fracture site, duration of follow-up (in cohort studies), and duration of diabetes as independent variables and log RR as the dependent variable to assess sources of heterogeneity. Funnel plots and Egger's test were used to examine the publication bias. Sensitivity analyses were prespecified. Statistical analyses were carried out with using R software (version 3.2.1) and STATA (version 11.1). *P*-values <0.05 were considered as significant in heterogeneity tests. All statistical tests were two sided.

Results

In the primary search, about 1,200 titles were retrieved and about 203 were considered relevant and screened. In a secondary screening, 91 papers were excluded based on abstract evaluation. Therefore, 112 articles were retained for detailed full-text evaluation. After full-text evaluation, we excluded another 81 articles of these: six were excluded because of overlapping publication, 17 were duplicated articles, 15 were retrospective and review studies, five were meta-analyses, 12 studies were performed on persons with type 1 diabetes mellitus or impaired glucose tolerance, 21 did not provide data that allowed calculation of standard errors for effect estimates, and five reported only crude data that were not adjusted for age. Finally, 30 epidemiologic studies including two case–control and 28 cohort studies on the association between T2DM and fracture risk and possible risk factors, which were published between 1980 and 2016, were selected for the meta-analysis (Figure 1).[15,16,24–51] The characteristics and extracted data from these studies are shown in Table 1.

We included both the case–control studies and the 28 cohort studies in the primary meta-analysis. Due to severe heterogeneity of the reported prevalence ($P<0.001$), meta-analysis was performed by using a random effects method.

Considering all the included studies, the total number of participants and incident cases of fracture were 5,815,277 and 113,203, respectively.

Table 2 shows a summary of the RR estimates from the included studies of the association between T2DM and fracture incidence. Fifteen of 30 studies had reported the association between T2DM and hip fracture incidence. We found a statistically significant positive association between T2DM and hip fracture incidence (summary RR =1.20, 95% CI: 1.17–1.23; Figure 2). Also, the association between T2DM and fracture of the vertebral (summary RR =1.16, 95% CI: 1.05–1.28) or foot (summary RR =1.37, 95% CI: 1.21–1.54) was statistically significant (Table 2).

As seen in Figure 3, there was no significant association between T2DM and wrist fracture incidence. Ten of 30 studies had reported the association between T2DM and wrist fracture incidence, and the summary RR for all 10 studies combined was 0.98 (95% CI: 0.88–1.07; Figure 3). Also, we found no association between T2DM and fracture of the proximal humerus (summary RR =1.09, 95% CI: 0.86–1.31) or ankle (summary RR =1.13, 95% CI: 0.95–1.32; Table 2).

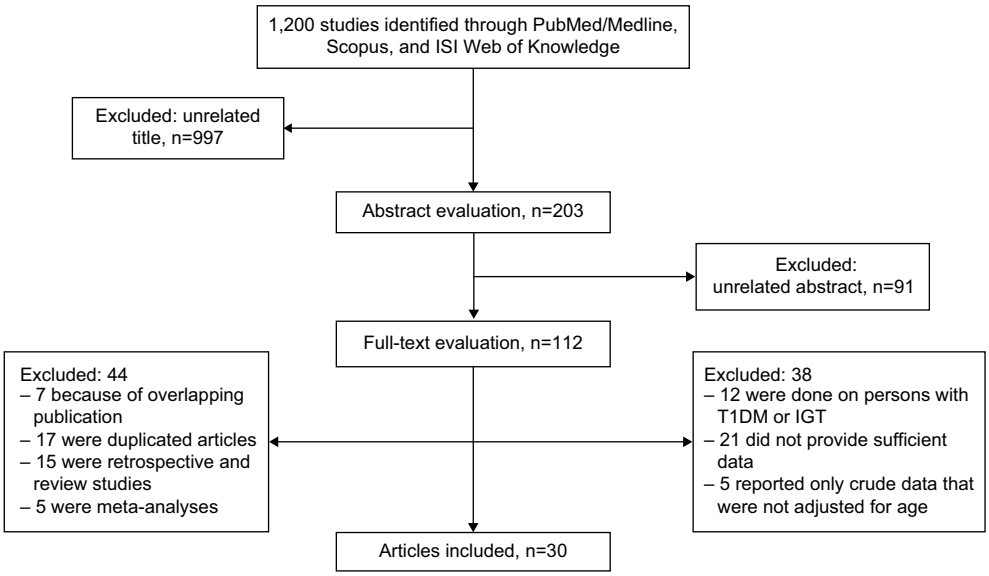

Figure 1 Flowchart of the literature search.
Abbreviations: IGT, impaired glucose tolerance; ISI, Institute for Scientific Information; T1DM, type 1 diabetes mellitus.

Table 1 The characteristics of the studies entered into the meta-analysis

References	Country	Follow-up period (years)[a]	Age at enrollment (years)[a]	BMI (kg/m^2)[a]	T2DM subjects (n)	NDM subjects (n)	T2DM vs NDM (95% CI) results
Cohort design							
Heath et al[24] (1980)	USA	Unknown	<103	NR	T: 986	T: 986	Adjusted RR[b] Vertebral T: 0.6 (0.3–0.7) Proximal humerus T: 0.6 (0.3–0.9) Distal forearm T: 0.7 (0.5–0.9) Proximal forearm T: 0.8 (0.5–0.9)
Meyer et al[25] (1993)	Norway	10.9	35–49	NR	M: 180 F: 118	M: 24,333 F: 23,850	Adjusted RR[c] Hip M: 9.4 (2.9–30.5), F: 9.2 (3.4–24.9)
Forsen et al[26] (1999)	Norway	9	≥50	28.5	M: 220 F: 274	M: 13,210 F: 13,685	Adjusted RR[d] Hip M: 1.2 (0.4–3.2), F: 1.8 (1.1–2.9)
Ivers et al[16] (2001)	Australia	5	≥49	NR	T: 216	T: 3,438	Adjusted RR[e] All fractures T: 0.9 (0.7–1.2) Hip T: 0.6 (0.2–2.2) Distal forearm T: 0.7 (0.2–2.3) Proximal humerus T: 0.7 (0.2–2.3) Ankle T: 1.1 (0.6–1.9)
Nicodemus and Folsom[15] (2001)	USA	11	55–69	30.5	F: 1,682	F: 30,377	Adjusted RR[f] Hip F: 1.7 (1.2–2.4)
Ottenbacher et al[27] (2002)	USA	7	≥65	NR	T: 690	T: 2,194	Adjusted HR[g] Hip T: 1.5 (1.0–2.3)
de Liefde et al[28] (2005)	the Netherlands	6.3±2.3	≥55	26.8±4.1	T: 792 M: 309 F: 438	T: 5,863 M: 2,382 F: 3,481	Adjusted HR[h] Any nonvertebral T: 1.3 (1.0–1.8), M: 1.6 (0.9–2.9), F: 1.3 (0.9–1.8) Hip T: 1.3 (0.8–2.3), M: 1.3 (0.4–4.2), F: 1.4 (0.8–2.5) Wrist T: 1.4 (0.8–2.4), M: 1.3 (0.4–10.4), F: 1.5 (0.8–2.6)
Gerdhem et al[29] (2005)	Sweden	4.6	75	NR	F: 74	F: 1,058	RR Any fracture F: 0.8 (0.5–1.3)
Strotmeyer et al[30] (2005)	USA	4.5	70–79		T: 566	T: 2,236	Adjusted RR[i] Any fracture T: 1.64 (1.1–2.5)
Bonds et al[31] (2006)	USA	7	64.9±7	NR	F: 5,285	F: 88,120	Adjusted RR[j] All fracture F: 1.2 (1.1–1.3) Hip F: 1.5 (1.2–1.8) Wrist F: 1.02 (0.85–1.2) Ankle F: 1.1 (0.95–1.9) Foot F: 1.3 (1.07–1.6) Vertebral F: 1.3 (1.0–1.6)

Holmberg et al[32] (2006)	Sweden	17	27–68	NR	M: 276 F: 166	M: 22,444 F: 10,902	Adjusted RR[k] Any fracture M: 2.4 (1.7–3.4), F: 1.9 (1.3–2.8) Forearm M: 2.2 (0.95–4.8), F: 1.5 (0.7–3.0) Proximal humerus M: 1.1 (0.2–7.9), F: 2.1 (0.8–6.0) Hip M: 6.4 (3.4–11.8), F: 4.0 (1.7–9.4) Ankle M: 1.4 (0.5–4.5), F: 2.4 (1.1–5.4) Vertebral M: 1.1 (0.4–3.5), F: 2.9 (1.3–6.3)
Dobnig et al[33] (2006)	Australia	2	≥70	26.4±4.8	F: 583	F: 1,081	Adjusted HR[l] Hip F: 1.5 (1.3–1.8)
Ahmed et al[34] (2006)	Norway	6	25–98	28.7	M: 175 F: 198	M: 12,639 F: 14,065	Adjusted RR[m] Any nonvertebral M: 1.2 (0.6–2.5), F: 1.1 (0.7–1.7) Hip M: 1.6 (0.6–4.5), F: 1.9 (1.0–3.5)
Janghorbani et al[35] (2006)	USA	20.4±3.4	34–59	31±6.4	F: 8,345	F: 101,343	Adjusted RR[n] Hip F: 2.2 (1.8–2.7)
Leslie et al[36] (2007)	Canada	10	≥20	NR	T: 82,094; newly diagnosed: 42,874; short duration: 16,081; long duration: 23,139	T: 236,682	Adjusted RR[o] All fractures Newly diagnosed: 0.91 (0.86–0.95) Short term: 1.00 (0.93–1.07) Long term: 1.15 (1.09–1.22) Hip Newly diagnosed: 0.83 (0.75–0.92) Short term: 1.13 (1.00–1.28) Long term: 1.40 (1.28–1.53)
Lipscombe et al[37] (2007)	Canada	6.1	≥66		M: 100,322 F: 97,090	M: 202,875 F: 198,525	Adjusted HR[p] Hip M: 1.2 (1.1–1.3), F: 1.1 (1.1–1.2)
Melton et al[38] (2008)	USA	11.8	30–97		T: 1,964 M: 992 F: 972	NR	SIR All fractures T: 1.3 (1.2–1.4), M: 1.4 (1.3–1.6), F: 1.3 (1.2–1.6) Hip T: 1.1 (0.9–1.4) Wrist T: 1.2 (0.9–1.5) Vertebral T: 2.8 (2.4–3.2)
Chen et al[39] (2008)	Taiwan	6	≥35		M: 227,289 F: 257,498	M: 227,303 F: 257,303	Adjusted HR[q] Hip M: 1.3 (1.2–1.3), F: 1.7 (1.66–1.8)
Mancini et al[40] (2009)	Italy	13	44–82	31	M: 43	M: 22	Adjusted OR[r] Vertebral M: 6.5 (1.3–38.1)
Yamamoto et al[41] (2009)	Japan	NR	≥50	23.7±3.5	M: 161 F: 137	M: 76 F: 622	OR Vertebral M: 4.73 (2.19–10.2), F: 1.9 (1.1–3.1)
Schneider et al[42] (2013)	USA	20	45–64	31±6.1	T: 1,195 M: 501 F: 694	T: 13,340 M: 5,936 F: 7,404	Adjusted HR[s] All fractures T: 1.74 (1.4–2.2), M: 1.9 (1.5–2.5), F: 1.5 (1.1–2.2)
Chung et al[43] (2013)	Korea	NR	≥50	25.1±3.5	F: 2,239	NR	Adjusted OR[t] Hip F: 1.03 (1.02–1.04) Vertebral F: 1.03 (1.02–1.04)

(*Continued*)

Table 1 (*Continued*)

References	Country	Follow-up period (years)[a]	Age at enrollment (years)[a]	BMI (kg/m^2)[a]	T2DM subjects (n)	NDM subjects (n)	T2DM vs NDM (95% CI) results
Oei et al[44] (2013)	the Netherlands	12.2	≥55	26.9±4	T: 217	T: 3,715	Adjusted HR[u] All fractures T: 1.5 (1.1–1.9) Hip T: 1.2 (0.6–2.1) Wrist T: 1.7 (1.03–2.9)
Reyes et al[45] (2014)	Spain	2.55	≥65		M: 36,865	M: 149,306	Adjusted RR[v] Hip M: 1.9 (1.2–3.1)
Napoli et al[46] (2014)	USA	9.1	≥65	29.5±4.4	M: 801	M: 3,086	Adjusted HR[w] Any nonvertebral M: 1.3 (1.1–1.5)
Leslie et al[47] (2014)	Canada	6	≥40	30.2±6.2	T: 6,455	T: 55,958	Adjusted HR[x] All fractures T: 1.3 (1.2–1.5)
Hothersall et al[48] (2014)	Scotland	2	20–84		T: 180,841	T: 3,066,000	Adjusted IRR[y] Hip M: 0.97 (0.92–1.02), F: 1.05 (1.01–1.10)
Looker et al[49] (2016)	USA	6.7	≥65	29.5±0.41			Adjusted HR[z]
					NHW: 398 NHB: 178 MA: 226	NHW: 2,554 NHB: 631 MA: 601	Non-skull fracture NHW: 1.2 (0.93–1.6) NHB: 1.9 (1.02–3.40) MA: 2.4 (1.5–3.8)
Case–control							
Kegan et al[50] (2002)	USA	NR	≥45	NR	T: 1,913	T: 1,913	Adjusted OR[aa] Forearm T: 0.9 (0.7–1.2) Foot T: 1.4 (1.1–1.8) Proximal humerus T: 1.7 (1.2–2.3)
Vestergaard et al[51] (2005)	Denmark	NR	43±27	NR	T: 3,241	T: 6,375	Adjusted OR[bb] Any fracture T: 1.2 (1.1–1.3) Hip T: 1.4 (1.2–1.6) Forearm T: 1.2 (1.01–1.5) Spine T: 1.3 (0.97–1.86)

Notes: [a]Data shown as mean, range, or mean ± SD. [b]Adjusted for age, sex, race, residence, year, and institution. [c]Adjusted for age, height, BMI, physical activity, stroke, receipt of a disability pension, marriage, and smoking. [d]Adjusted for age, BMI, and daily smoking. [e]Adjusted for age, sex, and BMI. [f]Adjusted for age, BMI, smoking, estrogen use, and waist:hip ratio. [g]Adjusted for age, BMI, smoking, and previous stroke. [h]Adjusted for age, sex, BMI, smoking, serum creatinine, visual acuity, falling frequency, lower limb disability. [i]Adjusted for age, sex, race, site, hip BMD, lean mass, fat mass, and abdominal visceral fat. [j]Adjusted for age; ethnicity; weight; height; time-dependent history of falls; previous fracture; history of osteoporosis; trouble seeing at baseline; alcohol or tobacco use; calcium and vitamin D intake; exercise; bisphosphonate, estrogen, steroid, insulin, SERM, or thyroid hormone use. [k]Adjusted for age, BMI, and smoking. [l]Adjusted for age, weight, and calcaneal bone mass. [m]Adjusted for age, BMI, smoking, and metabolic features (mean blood pressure, HDL, and triglycerides). [n]Adjusted for age, BMI, physical activity, menopausal status, estrogen use, smoking, daily intake of calcium, vitamin D, and protein. [o]Adjusted for age, sex, income quintile, area of residence, and ethnicity. [p]Adjusted for age-group; chronic unstable disease; prior stroke; visual impairment; neuropathy; amputation; treatment with nitrates, statins, anticonvulsants, inhaled corticosteroids, and medications that increase the risk of fall; history of BMD test; and income quintile. [q]Adjusted for age as a continuous variable, geographic area, and urbanization status. [r]Adjusted for age and BMI, rosiglitazone plus metformin treatment. [s]Adjusted for age, sex, race/study center, BMI, sports activity tertile, alcohol consumption, cigarette smoking, glucocorticoid or antidepressant use, and thiazide diuretic use. [t]Adjusted for age, BMI, duration of diabetes, DM complications, HbA1c, serum creatinine, DM medications, risk factors for osteoporosis (alcohol and smoking), and history of fragility fracture. [u]Adjusted for age, sex, height, weight, and femoral neck BMD. [v]Adjusted for age, BMI, smoking, alcohol consumption, use of oral corticosteroids, and comorbid conditions. [w]Adjusted for age, race, clinic site, total hip BMD. [x]Adjusted for WHO Fracture Risk Assessment (FRAX™) tool including femoral neck BMD. [y]Adjusted for age, sex, survey, BMI, self-rated physical activity compared to others, hospital visits in past year, and smoking. [aa]Adjusted for age, sex, and race/ethnicity. [bb]Adjusted for the variables in the table plus prior fracture, corticosteroid use, use of antiepileptic drugs, use of diuretics (loop, thiazide, potassium-sparing, other types), use of anxiolytics and sedatives, use of neuroleptics, use of antidepressants, alcoholism, use of statins and non-statin cholesterol-lowering drugs, use of antihypertensives, myocardial infarction, stroke, number of bed days in 1999, number of contacts to GP or specialists in 1999, working or not, income, living with another person vs living alone.

Abbreviations: BMD, bone mineral density; BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; F, female; GP, general practitioner; HbA1c, glycated hemoglobin; HR, hazard ratio; IRR, incidence risk ratio; M, male; MA, Mexican American; NDM, nondiabetic subjects; NHB, non-Hispanic Black; NHW, non-Hispanic white; NR, not reported; OR, odds ratio; RR, relative risk; SERM, selective estrogen-receptor modulator; SIR, standardized incidence ratio; T2DM, type 2 diabetes mellitus; T, total; WHO, World Health Organization.

Table 2 Summary relative risk estimates from case–control and cohort studies of the association between type 2 diabetes mellitus and fractures incidence using meta-analysis methods

Type of fractures	Number of studies	Summary relative risk	95% confidence interval	Between studies	
				I^2 (%)	*P* for heterogeneity
Hip fractures	15	1.20	1.17–1.23	85.5	0.000
Wrist fractures	10	0.98	0.88–1.07	61.3	0.006
Vertebral fractures	9	1.16	1.05–1.28	95.9	0.000
Proximal humerus	5	1.09	0.86–1.31	84.0	0.000
Ankle fractures	3	1.13	0.95–1.32	0.0	0.762
Foot fractures	3	1.37	1.21–1.54	0.0	0.90
All fractures, total	27	1.17	1.15–1.20	85.5	0.000

Figure 4 shows the individual study results and the overall summary results for the included studies of T2DM and overall fracture incidence. As observed in the figure, there was a statistically significant positive association between T2DM and overall fracture (summary RR =1.05, 95% CI: 1.04–1.06).

We also conducted subgroup meta-analyses for the most important known confounders and for risk factors that have an influence on the association between T2DM and fracture risk. Table 3 gives the summary RR and *P*-value estimates from the included studies for incident fracture according to the risk factors.

The association of T2DM with fracture risk differed by age, although diabetes was associated with a significantly higher risk of fractures for all age subgroups; the risk of fracture was increased with age (continuous; summary RR =1.10, 95% CI: 1.07–1.13). Also, effect modification was much greater in the oldest subgroup, with progressively less effect modification in younger age subgroups (summary RR age 50–59 years 1.17 [95% CI: 1.15–1.21], age 60–69 years 1.20 [95% CI: 1.10–1.30], age ≥70 years 1.30 [95% CI: 1.21–1.40]); there was heterogeneity among studies by age (*P* for heterogeneity [P_{het}] <0.001; Table 3).

The result of our meta-analysis showed increased risk of overall fractures in diabetic men compared with diabetic women (P_{het} =0.043; Table 3).

For BMI, the estimation of summary was stronger for BMI <30 kg/m^2 (summary RR =1.44, 95% CI: 1.24–1.64)

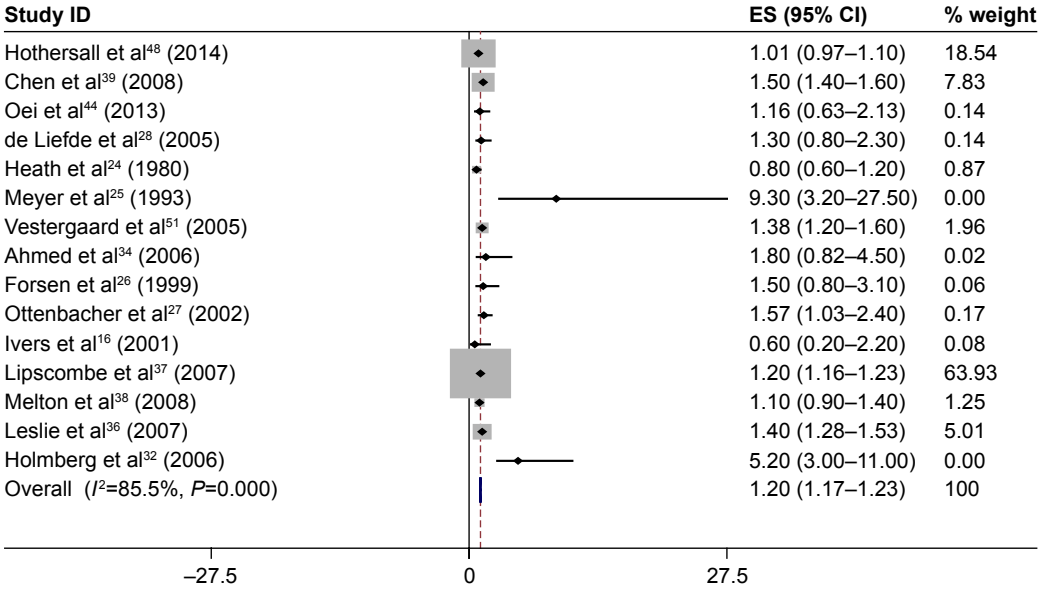

Figure 2 The results of meta-analysis of the association between type 2 diabetes mellitus and risk of hip fracture.
Notes: Each square shows the study specific relative risk estimate. Square sizes are proportional to the weight assigned to the study in the meta-analysis and the horizontal line shows the related 95% CI. The diamond shows the summary relative risk estimate and its width represents the corresponding 95% CI. All statistical tests were two sided. Statistical heterogeneity between studies was assessed with Cochran's Q test. Meta-analysis was performed by using a random effects method.
Abbreviations: CI, confidence interval; ES, effect size.

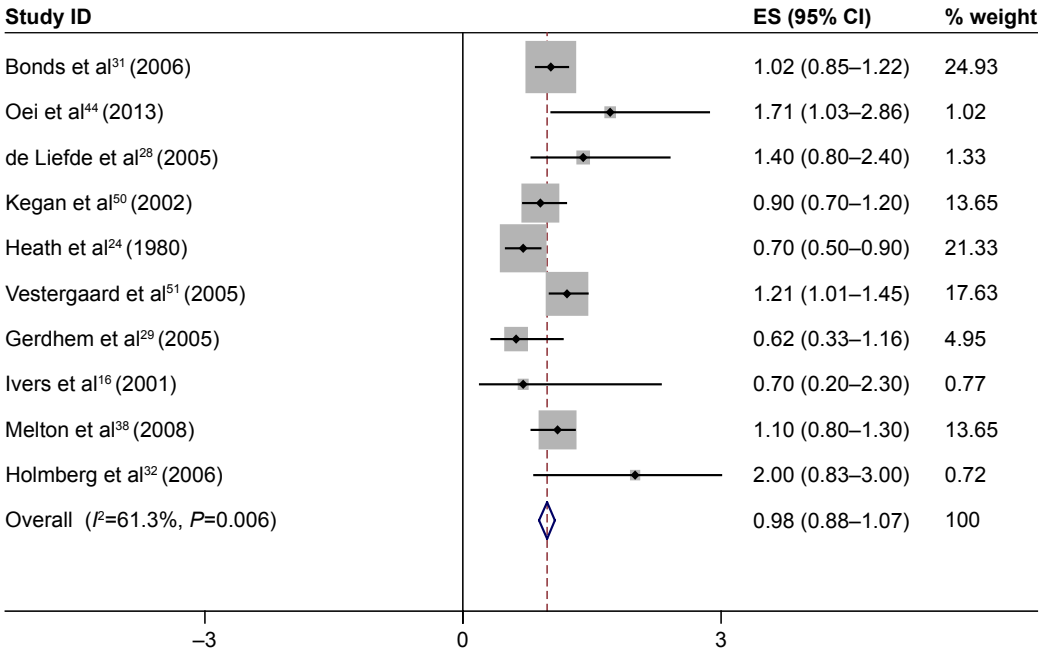

Figure 3 The results of meta-analysis of the association between type 2 diabetes mellitus and risk of wrist fracture.
Notes: Each square shows the study specific relative risk estimate. Square sizes are proportional to the weight assigned to the study in the meta-analysis and the horizontal line shows the related 95% CI. The diamond shows the summary relative risk estimate and its width represents the corresponding 95% CI. All statistical tests were two sided. Statistical heterogeneity between studies was assessed with Cochran's Q test. Meta-analysis was performed by using a random effects method.
Abbreviations: CI, confidence interval; ES, effect size.

than for BMI ≥30 kg/m^2 (summary RR =1.30, 95% CI: 1.22–1.37; P_{het}<0.001; Table 3).

We conducted subgroup meta-analyses by region. Twelve studies were conducted in the USA,[15,24,27,28,31,32,36,39,43,47,50,51] three in Canada,[37,38,48] 11 in Europe,[25,26,29,30,33,35,41,45,46,49,52] three in Asia,[40,42,44] and two in Australia.[16,34] Results were consistent by geographic area (P_{het} =0.29; Table 3).

The estimation of summary for incident fracture according to duration of diabetes was stronger with 10 or more years of diabetes (summary RR =1.0, 95% CI: 0.93–1.6) than diabetes duration of <10 years (RR =1.19, 95% CI: 1.13–1.26); there was heterogeneity by duration of diabetes (<10 years vs ≥10 years; P_{het} <0.001; Table 3).

Finally, the estimation of summary was stronger with follow-up durations of <10 years (RR =1.19, 95% CI: 1.16–1.22) than 10 or more years of follow-up (summary RR =1.13, 95% CI: 1.08–1.18; P_{het} =0.004; Table 3).

The results of meta-analysis of association of T2DM with fracture risk by physical activity showed a significant inverse association between T2DM and fracture (summary RR =0.75, 95% CI: 0.65–0.86) and that physical activity was associated with a decrease risk for fracture incidence in diabetic patients and might be more protective in this regard. We found no significant association between T2DM and fracture incidence by smoking status (summary RR =1.29, 95% CI: 0.92–1.88). Insulin therapy and use of systemic corticosteroids were associated with an increased fracture risk; the summary of estimation was 1.52 (95% CI: 1.42–1.61) for insulin therapy and 1.51 (95% CI: 1.29–1.72) for use of systemic corticosteroids. Also, treatment with thiazolidinediones (TZDs) was not associated with an increase fracture risk (summary RR =0.75, 95% CI: 0.60–0.91; Table 3).

According to the publication bias tests, the effect of bias in these studies was not significant. *P*-values for Egger's regression asymmetry test were 0.32. Figure 5 presents the Begg's funnel plot of the included trials related to the risk of factors in diabetic patients. Regression analysis of this plot indicated no significant asymmetry (P≥0.05) and thus no evidence of bias (Figure 5).

Interpretation of meta-regression showed that there was no significant relationship between the risk factors in diabetic patients and the year of study (P≥0.05; Figure 6).

Discussion

Osteoporotic fractures and diabetes mellitus (DM) continue to be important medical, social, and economic concerns to the society. Our study gives an overall picture of the risk of any fracture in people with T2DM. The risks reported from previous studies of people with T2DM vary substantially. In some studies, diabetes was significantly associated

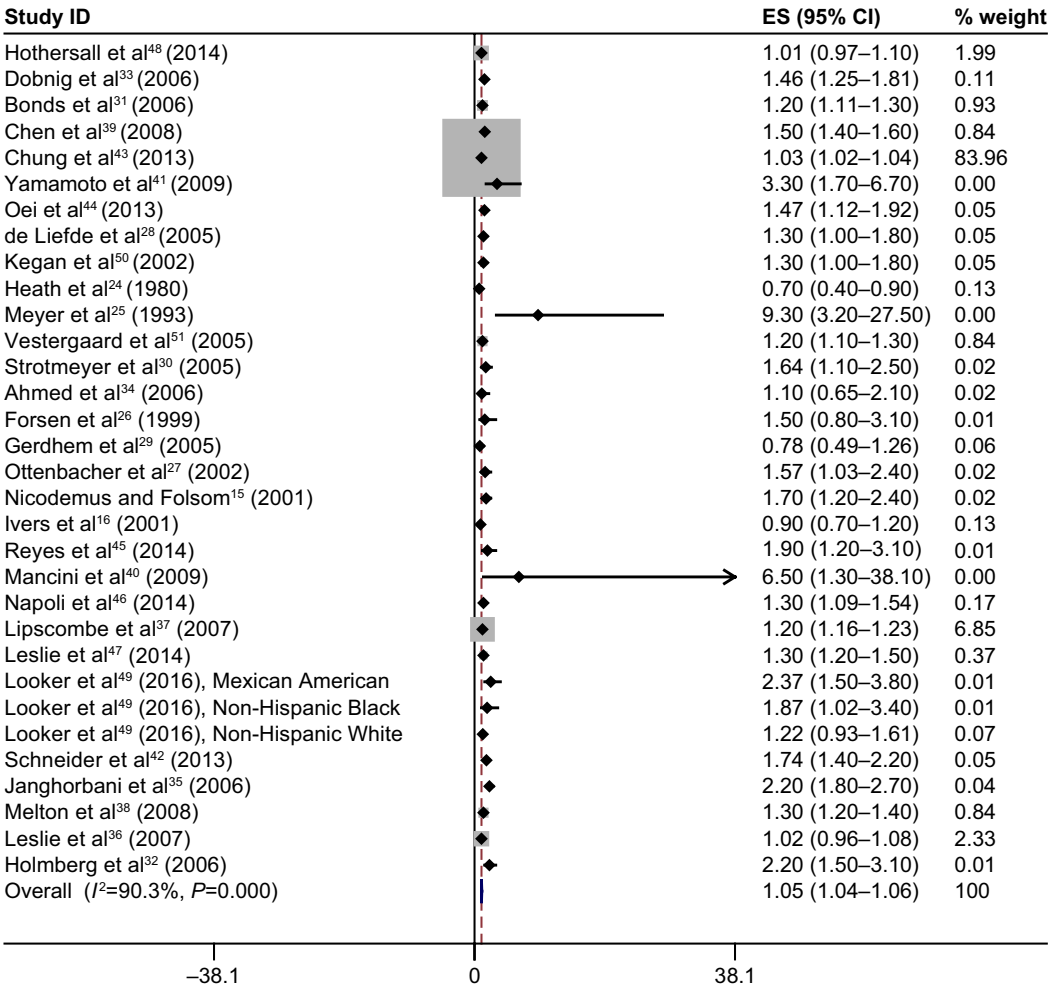

Figure 4 The results of meta-analysis of association between type 2 diabetes mellitus and risk of overall fractures.
Notes: Each square shows the study specific relative risk estimate. Square sizes are proportional to the weight assigned to the study in the meta-analysis and the horizontal line shows the related 95% CI. The diamond shows the summary relative risk estimate and its width represents the corresponding 95% CI. All statistical tests were two sided. Statistical heterogeneity between studies was assessed with Cochran's Q test. Meta-analysis was performed by using a random effects method.
Abbreviations: CI, confidence interval; ES, effect size.

with an increased risk for hip fractures,[25,27,32,36,37,39,51] wrist fractures,[44,51] proximal humerus fractures,[38,50] vertebral fractures,[31,38,40,41,43] and overall fractures.[30–32,38,42,44,47,51] In contrast, other studies have found no association between diabetes with hip fractures,[16,24,26,28,34,38,44,48] wrist fractures,[1,6,24,28,29,31,32,38,50] proximal humerus fractures,[16,24,32] vertebral fractures,[24,29,32,51] or overall fractures.[16,29] We found an association between T2DM and overall fracture (summary RR =1.05, 95% CI: 1.04–1.06). These results strongly agreed with previous meta-analysis studies that showed an increase risk of fractures in T2DM patients.[11,14] Janghorbani et al, in a meta-analysis of case–control and cohort studies, confirmed a 1.2 (95% CI: 1.01–1.5) RR for any fracture and 1.7 (95% CI: 1.3–2.2) RR for hip fracture in both men and women suffering from T2DM.[14] Vestergaard[11] combined studies up to 2007 in a meta-analysis and concluded that the risk ratio for hip fracture in T2DM was 1.38 (95% CI: 1.25–1.53). The observed differences in RR between the oldest and most recent meta-analyses discussed were small. Thus, the estimation from meta-analyses of fracture RR in T2DM showed a statistically significant positive association between T2DM and fracture incidence.

T2DM and fracture share similar and opposing risk factors. In our effort to identify the variables contributing to the higher risk of fracture among diabetic patients, we found a range of risk factors for fracture that are also associated with diabetes. In accordance with previous studies, some of the risk factors identified were increasing age, sex, BMI, physical activity, smoking status, duration of diabetes, and glycemic control.

The results of our meta-analysis showed that the incidence of fractures increased with age and duration of diabetes.

Table 3 Risk factors for the association between type 2 diabetes and fracture risk

Subgroup	Studies (n)	Summary relative risk	95% confidence interval	Between studies		Between subgroups	
				I^2 (%)	*P* for heterogeneity	I^2 (%)	*P* for heterogeneity
Age (years)							
50–59	5	1.17	1.15–1.21	94.7	0.000	85.5	<0.001
60–69	12	1.20	1.10–1.30	81.2	0.000		
≥70	12	1.30	1.21–1.40	45.7	0.005		
Sex							
Female	7	1.44	1.18–1.70	91.3	0.000	91.3	0.043
Male	3	1.90	1.3–2.58	0.00	0.000		
BMI (kg/m^2)							
<30	11	1.44	1.24–1.65	29.5	0.193	92.6	<0.001
≥30	11	1.30	1.22–1.37	72.5	0.000		
Geographic area							
Europe	11	1.10	1.03–1.13	69.8	0.000	90.6	0.29
North America	17	1.18	1.15–1.20	85.5	0.000		
Asia	3	1.24	1.14–1.40	90.6	0.000		
Australia	2	1.18	1.0–1.36	91.7	0.000		
Follow-up period, years							
<10	21	1.19	1.16–122	83.2	0.000	89.9	0.004
≥10	8	1.13	1.08–1.18	89.9	0.000		
Duration of diabetes, years							
<10	6	1.00	0.93–1.06	78.2	0.003	93.2	<0.001
≥10	6	1.19	1.13–1.25	93.2	0.000		
Physical activity	3	0.75	0.65–0.85	92.4	0.000	NR	NR
Smoking status	3	1.29	0.92–1.88	92.0	0.000	NR	NR
Users of systemic corticosteroids	3	1.51	1.29–1.72	38.6	0.196	NR	NR
Insulin therapy	11	1.52	1.42–1.61	4.8	0.393	NR	NR
Treated with thiazolidinediones	3	0.75	0.60–0.91	0.0	0.513	NR	NR

Abbreviations: BMI, body mass index; NR, not reported.

Studies showed that patients' age and duration of diabetes were negatively correlated with insulin-like growth factor-1 (IGF-1), and serum IGF-1 levels were negatively associated with increased risk of fractures in diabetic patients.[52] Thus, the incidence of fractures may increase with age and duration of diabetes in diabetic patients.

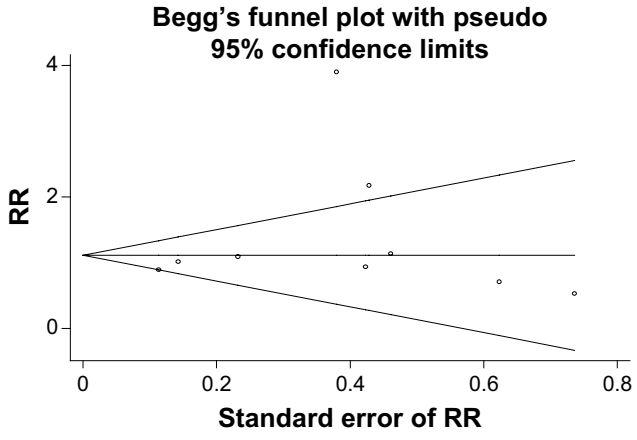

Figure 5 Begg's funnel plot for publication bias in the risk difference analysis.
Abbreviation: RR, relative risk.

We found that diabetic men had an increased risk of overall fractures compared with diabetic women (P_{het} =0.043). Meta-analysis conducted by Janghorbani et al[14] indicated that fracture risk was relatively higher in T2DM men than in T2DM women. The results of these meta-analysis studies could have easily been due to chance, because in these studies, the number of cases in men was relatively small.

Some studies have found that 21%–64% of T2DM men have hypogonadism, with higher prevalence rates in the elderly.[53,54] Thus, we can say that the presence of DM may cause hypogonadism and may be one of the risk factors of secondary osteoporosis, especially in elderly men. Furthermore, several studies have shown that the RR of fractures in men is significantly increased with smoking, alcohol consumption, anticonvulsant treatment, physical inactivity, and low free androgen index.[55,56]

Evidence regarding a direct relation of better glycemic control with reduced risk of fracture is very weak.[16] We were not able to evaluate the possible impact of all blood glucose-lowering drugs because of the limitations of the available data. Our findings showed an increased risk of

Meta-regression
REML estimate of between-study variance: number observed =9
% residual variation due to heterogeneity: τ^2=1.86
Proportion of between-study variance explained: I^2 squares =99.69%
With Knapp–Hartung modification: adjusted R^2 =4.46%

logRR	Coef	Standard error	Amount	*P*>|*t*|	95% CI	
Year	–0.1839506	0.1572668	–1.17	0.280	–0.5558274	0.1879263
Constant	371.1127	315.3554	1.18	0.278	–374.5843	1116.81

Figure 6 The meta-regression analysis of the relationship between the risk of factors in diabetic patients and the year of study.
Abbreviations: CI, confidence interval; Coef, coefficient of variation; REML, restricted (or residual) maximum likelihood estimation; RR, relative risk.

fracture in those using insulin or systemic corticosteroids. There was also no increased risk with TZD use. The use of TZDs has been associated with an increased fracture risk in both T2DM men and women. TZDs could have a negative effect on bone quality, since they suppress the differentiation of mesenchymal stem cells into osteoblasts in favor of differentiation to adipocytes.[57–59] Some previous studies have reported an increased risk of fracture in those using insulin.[34,38,60,61] This increased fracture risk was most probably due to an increased risk of falls because of hypoglycemic events which may impair the bone quality in the diabetic skeleton and also because insulin is often used in patients with diabetes of longer duration, thus diabetic patients are likely to have long-term negative hyperglycemic effects on bone quality that lead to increased fracture risk.[62–64]

The mechanisms whereby diabetes increases the fracture risk are not entirely clear. A possible cause of the increased risk of fracture in T2DM is diabetes-related comorbidity, such as diabetic retinopathy, peripheral neuropathy, and cerebral stroke or hypoglycemia, which may increase the risk of falling.[14,43,65,66] It has been hypothesized that physiologic changes resulting from chronic hyperglycemia could degrade the bone quality through inhibition of osteocalcin, increased reactive oxygen species, accumulation of advanced glycation end products in bone, or inhibition of IGF-1.[67] In addition, other factors related to T2DM, such as the microvascular and macrovascular complications, oxidative stress, renal dysfunction, elevated renal calcium loss, and persistent inflammation present in T2DM, may further impair bone health and increase fracture risk.[46] It is documented that poor nerve function is a cause of falls[68] and that an increased risk of fractures is associated with DM retinopathy, longer DM duration, and insulin treatment.[16] Thus, these DM-related complications increase fracture risk.

The combination of poor bone quality and frequent falls would be expected to increase the risk of fracture independently of BMD.[16] In some studies with T2DM women, lower total hip BMD was significantly associated with higher risk of fractures, even after adjustment for multiple covariates.[43] In contrast, some studies reported lack of statistical association between BMD and fractures in subjects with T2DM.[41] From these observations, the authors concluded that BMD was not sensitive enough to assess the risk of fracture in subjects with T2DM.[43] A meta-analysis also showed that T2DM patients had higher hip BMD than non-DM controls, despite an increased risk of hip fracture, suggesting that BMD values may not reflect bone fragility in T2DM.[11]

It has been hypothesized that the complications of diabetes (peripheral neuropathy, peripheral vascular disease), diabetes treatment (insulin), or both could increase the risk of falls and fractures.[69,70]

Limitations

Our results have important clinical and public health implications; it will further contribute to the public health burden of any fractures. Also, our meta-analysis had several limitations. In this meta-analysis, we were unable to conduct separate analyses by ethnicity; insufficient available data about association between T2DM and fracture by ethnicity prevented us from the evaluation of such cases. Other limitation is the lack of information on BMD, which could explain part of the observed associations. Thus, it was not possible for us to evaluate the impact of controlling for BMD on the relation between diabetes and fracture risk. Furthermore, some included studies did not enjoy acceptable quality or presented defective quantitative data that could not be included in the meta-analysis. Finally, some studies associated with diabetes and fracture risk were not accessible.

Conclusion

This study gives an overall picture of the risk of all fractures in people with T2DM. Our findings showed a positive association between T2DM and hip fractures, vertebral fractures,

and foot fractures. We also found no association between T2DM and wrist fractures, proximal humerus fractures, or ankle fractures. Overall, the results of this meta-analysis strongly support an association between T2DM and increased risk of any fracture. With a worldwide increasing prevalence of diabetes, the contribution of diabetes to the incidence of low-trauma fracture may increase.

In our effort to identify the variables contributing to the higher risk of fracture among diabetic patients, we found a range of risk factors for fracture that are also associated with diabetes. The incidence of fractures increased with age and was higher in T2DM men than in T2DM women. According to the results, the expected rate of BMD loss in bones in diabetics seems to be higher than in nondiabetics. But in some studies, this trend was reversed. Due to limited data on BMI studies, our analysis showed that patients with T2DM have higher BMI and have lesser risk of fracture. Also, elevated RRs are seen in those with longer diabetes duration and in those using insulin and systemic corticosteroids. These findings emphasize the need for developing risk prediction models in order to avoid systematically underestimating the risk of osteoporosis-related fracture in patients with diabetes. Also, our findings emphasize the need for fracture prevention strategies in patients with T2DM.

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Disclosure

The authors report no conflicts of interest in this work.

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