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Fracture risk in young and middle-aged adults with Type 1 diabetes mellitus: a systematic review and meta-analysis

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ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) is associated with skeletal fragility. While previous meta-analyses have demonstrated an increased risk of fracture in individuals with

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T1DM, little is known about fracture risk in T1DM, in the absence of age-related confounders.

Aims: To determine the risk of fracture in young and middle-aged adults with T1DM aged 18 to 50 years old.

Design: Systematic review and meta-analysis.

Data sources: Ovid MEDLINE, PubMed, EMBASE, EBM reviews, and relevant conference abstracts.

Study inclusion criteria: Studies of adults aged between 18 to 50 years with Type 1 diabetes mellitus, with reported fracture outcomes.

Primary outcomes: Incident or prevalent fracture.

Results: Six studies were included in the meta-analysis. 1724 fractures occurred in 35,925 patients with T1DM and 48,253 fractures occurred in 2,455,016 controls. RR for all fractures was 1.88 (95% CI 1.52 – 2.32, $p < 0.001$). 56 hip fractures occurred among 34,707 patients with T1DM and 594 hip fractures occurred in 2,295,177 controls. The RR of hip fractures was 4.40 (95% CI 2.58 – 7.50, $p < 0.001$). Females and males with T1DM had a RR of 5.79 (95% CI 3.55 – 9.44, $p < 0.001$) and 3.67 (95% CI 2.10 – 6.41, $p < 0.001$), respectively.

Conclusions: In the absence of age-related comorbidities, fracture risk remains significantly elevated in young and middle-aged adults with T1DM. Younger age does not mitigate against hip fracture risk in T1DM, and health professionals need to be aware of this risk. Further studies are needed to evaluate the mechanisms of fracture in T1DM.

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Conflicts of Interest: None.

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INTRODUCTION

Both diabetes mellitus and osteoporosis represent important public health concerns associated with rising mortality, morbidity and healthcare costs. Current projections estimate that by

2030, the number of individuals with diabetes will grow to 366 million worldwide. The burgeoning global prevalence of diabetes appears to occur in parallel with the increase in osteoporotic fractures, with a projected 2.6 million hip fractures occurring by 2025¹. Emerging evidence from large observational studies, particularly in the last decade, supports a direct detrimental impact of diabetes on skeletal health, particularly in Type 1 diabetes mellitus (T1DM).

T1DM is an autoimmune condition characterised by destruction of pancreatic islet cells, leading to absolute insulin deficiency. Several mechanisms have been identified to account for skeletal fragility in T1DM² and deficits in bone mineral density (BMD)^{3,4}, bone geometry⁵, bone microarchitecture⁶ and biomechanical properties^{7,8} have been identified in humans and animal models of T1DM⁹. Previous meta-analyses^{3,10-12} have demonstrated a four- to seven-fold increased risk of hip fracture in T1DM compared to controls; however, significant heterogeneity exists across study cohorts, with one meta-analysis including studies of children¹⁰ and others incorporating predominantly older study cohorts^{3,12}. Fractures in children are frequent, compared to young and middle-aged adults; this can largely be attributed to a combination of reduced bone mass and size, physical activity and trauma¹³, rather than true skeletal fragility. Furthermore, peak bone mass is accrued in adolescence¹⁴ and completed by the third decade of life. Hence, fracture risk in children who have yet to achieve maximal growth and bone mass, cannot be extrapolated to adults. Conversely, in studies of older adults, potential age-related confounders for bone fragility and falls, such as menopause and sarcopenia, can overestimate the true fracture risk in T1DM.

T1DM disproportionately affects children and young adults, with the peak incidence spanning from birth to 14 years of age¹⁵. Individuals with juvenile-onset T1DM are consequently exposed to disease for a longer duration throughout their lifetime, and may be at risk of developing diabetes-related complications earlier in life. In the largest UK-based prospective cohort study of over 30,000 individuals with T1DM and over 300,000 non-diabetic controls, Weber et al¹⁴ demonstrated that individuals with T1DM had an increased risk of incident fracture across all ages, from birth to age 89 years, as well as a predilection for lower extremity fractures. Similarly, in a population-based study from Scotland, Hothersall et al¹⁶ reported substantially higher hip fracture risks in men and women with T1DM across the ages of 20 to 49 years, compared to age-matched controls. Thus, the

findings from large cohort studies support the notion that young to middle-aged adults with T1DM are equally vulnerable to fracture as their older, postmenopausal counterparts.

While T1DM is recognised as an established risk factor for osteoporosis and fracture, the recommendations for bone health assessment in this cohort is still unclear. Bone health screening programs are commonly targeted at older populations, given the low absolute numbers of osteoporotic fracture in young adults. In light of mounting evidence for increased skeletal fragility in young adults with T1DM, we undertook a systematic review and meta-analysis dedicated to evaluating fracture risk in a younger adult cohort, with the aims of addressing the following questions:

1. What is the risk of overall fracture in young to middle-aged adults (aged 18 to 50 years) with T1DM, compared to controls?
2. What is the risk of hip fracture in young to middle-aged adults with T1DM?
3. Is fracture risk in T1DM different between sexes?

METHODS

This systematic review and meta-analysis was performed in accordance with the PRISMA statement¹⁷. The protocol has been registered with PROSPERO (CRD42017077850) and is available at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=77850.

Search strategy

We conducted a systematic search in several databases including Ovid MEDLINE, PubMed, EMBASE, all EBM reviews from 1980 to present (28 November 2017).

Abstracts from annual scientific meetings of the American Society for Bone and Mineral Research, American Diabetes Association, European Association for the Study of Diabetes, European Calcified Tissue Society and World Congress of Osteoporosis (from 2005 onwards) were also screened.

All aforementioned databases were searched for keywords including:

‘Type 1 diabet*’ OR ‘Type I diabet*’ OR ‘T1DM’ OR ‘TIDM’ OR ‘insulin dependent diabet*’
AND ‘fracture’ OR ‘bone’ OR ‘bone mineral*’
OR ‘osteoporo*’ OR ‘osteopaeni*’ OR ‘osteopeni*’

The literature search was limited to studies carried out in humans and published in English.

Study selection

Study selection was performed by two independent reviewers (EPT and MH). Only studies published in English were screened. Abstracts were assessed if the study fulfilled the inclusion criteria of: 1) cases as adults aged 18 years and above with established Type 1 diabetes mellitus and controls as non-diabetic subjects; 2) criteria for classifying individuals with T1DM was clearly defined; 3) fracture rates were reported. Studies were excluded if cases also included individuals with Type 2 diabetes mellitus, and outcomes were not differentiated by diabetes type, or if no control group was included. Studies comprising post-transplant individuals were also excluded. Fractures occurring at sites other than that considered to be typical of major osteoporotic fractures, such as those of the skull, facial, metacarpals, metatarsals, fingers or toes, were excluded. Full texts of all eligible studies were reviewed and consensus achieved between the two reviewers. Disagreements were resolved with face-to-face discussion or adjudication by the senior author.

Data extraction

Information from included studies comprised of: name of first author, publication year, country of origin, study design, study population and recruitment setting, number of participants (cases and controls, male vs. female distribution), mean ages and reported measures of fracture risk, and variables considered in the adjusted fracture risk. If the age range of participants fell outside the 18 to 50 years age group, we contacted individual authors of eligible studies to obtain secondary data analyses for individuals with Type 1 diabetes mellitus and age-matched controls for the pre-specified age range.

Risk of bias assessment

Methodological quality, as determined by bias analysis, was assessed by two independent reviewers (EPT and MH) using criteria established *a priori*, outlined in the Monash Centre for Health Research and Implementation (MCHRI) Evidence Synthesis Program critical appraisal template¹⁸.

Studies were assessed on individual criteria relating to external validity (methodology, inclusion/exclusion criteria, and appropriateness of measured outcomes) and internal validity (selection, attrition, detection and reporting bias and confounders). Studies that fulfilled all, most or few criteria were deemed to have low, moderate and high levels of bias, respectively. Only studies of low-to-moderate bias were included.

Statistical methods

Data were analysed using RevMan version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Fracture outcomes were presented as relative risks (RR) with 95% confidence intervals. RRs were calculated from raw data obtained by authors for the specified age ranges, using Stata statistical software: Release 15 (College Station, TX, Statacorp LLC). Heterogeneity was assessed using the I^2 test, where I^2 values greater than 50% and 75% are indicative of moderate and high heterogeneity, respectively. A random-effects model was employed in the analysis if moderate or high heterogeneity between studies were observed. Funnel plots, Begg's adjusted rank correlation test and Egger's regression test of asymmetry were used to assess publication bias. All statistical tests were two-tailed, with a p-value of <0.05 considered to be statistically significant. Subgroup analyses were performed by fracture type (hip) and sex.

RESULTS

Study selection

After excluding duplicate records, a total of 2901 publications and conference abstracts were identified in the screening search. 2178 articles were excluded based on title, and a further 110 articles excluded based on abstracts. Twelve studies met eligibility criteria to be included in the qualitative analysis, after full-text review of 21 studies. Corresponding authors of individual studies were contacted by electronic-mail to obtain secondary data analyses of fracture outcomes for the pre-specified age range. All authors were contacted a second time if a response had not been received after 4 weeks. Of the 12 studies that met criteria, 6 studies were included in the quantitative analysis. (Figure 1).

Study characteristics

Characteristics of the selected studies are described in Table 1. Of the six studies included, two were cohort studies^{14,16}, one was a case-control study¹⁹ and three were cross-sectional studies²⁰⁻²². The two largest studies were cohort studies by Weber et al¹⁴ and Hothersall et

al¹⁶, both set in the United Kingdom. The remainder of the studies were conducted in America, Denmark and Belarus. Four studies had fracture events as the primary outcome. Two studies compared bone mineral density as the primary aim, with fracture events being the secondary aim. One study reported solely on vertebral fractures, one reported hip fracture outcomes only, and the rest reported all types of fractures. Fracture ascertainment was determined by vertebral fracture assessment and spinal radiographs in one study²⁰, by International Statistical Classification of Diseases and Related Health Problems (ICD) codings or discharge codes in two cohort studies^{14,19}, and from hospital admission data in one study¹⁶. Fractures were self-reported in the two small studies^{21,22}, with further confirmation of fracture in Danielson et al²¹. Classification of individuals with T1DM was clearly defined in all studies. Two studies^{20,22} were conducted in women only, and were included in the analysis despite having participants of a slightly higher age range of participants, up to 55 years, with the justification that only premenopausal or eugonadal women, with no other secondary cause of osteoporosis, were recruited. All studies were population- or registry-based with the exception of one study, which recruited from a hospital outpatient setting. Overall, the six included studies were heterogenous in terms of study population, classification of T1DM, and methodology.

Risk of bias across studies

The studies by Vestergaard et al¹⁹, Hothersall et al¹⁶ and Weber et al¹⁴ involved a large population- or registry-based cohort with objective definitions for T1DM and fracture ascertainment, and were therefore of higher quality. While Hothersall et al¹⁶ captured hip fractures solely from hospital admission records, the potential for under-reporting of fractures from this study was thought to be low, as almost all hip fractures are managed in hospital. The use of self-reported fracture without further validation in the study by Strotmeyer et al²² is subject to recall bias, although the majority of clinically important fractures are likely to be memorable. Unlike the other studies, which were population-based, Zhukouskaya et al²⁰ recruited participants from hospital outpatient clinics, where the selection of patients with potentially more complex or poorly controlled diabetes was thought to account for the four-fold increased odds of vertebral fracture amongst young adults with T1DM, compared to controls from the community. In addition, the unique methodology of fracture ascertainment in this study, via active screening, led to the detection of asymptomatic vertebral fractures, which would otherwise have been missed clinically. This raises an important consideration of

potential under-detection of asymptomatic fractures in the larger registry-linked studies, which relied on clinically detected fractures as outcomes. In light of significant study heterogeneity, we performed sensitivity analyses, excluding outliers and including only higher quality studies (Table 2).

Synthesis of results

A total of 1724 fractures occurred amongst 35,925 patients with T1DM (4.8%) and 48,253 fractures occurred amongst 2,455,016 age-matched controls (2.0%). The pooled relative risk (RR) for all fractures in individuals with T1DM was 1.88 (95% CI 1.52 – 2.32, $p < 0.001$), compared to controls (Figure 2). The degree of heterogeneity across studies was high ($I^2 = 88\%$, $p < 0.001$). Fracture outcomes were further stratified by type (hip fracture) and sex, in the pre-specified subgroup analyses. 56 hip fractures occurred amongst 34,707 patients with T1DM (0.16%) and 594 hip fractures occurred amongst 2,295,177 controls (0.03%). The pooled RR for hip fracture in individuals with hip fracture was 4.40 (95% CI 2.58 – 7.50, $p < 0.001$), compared to controls (Figure 3).

Females and males with T1DM had an increased risk of any fracture, compared to their non-diabetic counterparts, with a RR of 1.85 for women with T1DM (95% CI 1.50 – 2.30, $p < 0.001$) and a RR of 1.73 for men with T1DM (95% CI 1.37 – 2.20, $p < 0.001$). Women and men with T1DM had a near 6-fold (RR 5.79, 95% CI 3.55 – 9.44, $p < 0.001$) and 4-fold (RR 3.67, 95% CI 2.10 – 6.41, $p < 0.001$) increased risk of hip fracture, respectively, compared to controls. Statistical analyses were also performed to compare RRs for overall and hip fracture, respectively, between sexes, and no significant differences were found (Table 2).

Sensitivity analyses were performed as previously described and presented in Table 2. The RR for any fracture was 1.53 (95% CI 1.47 – 1.61, $p < 0.001$, $I^2 = 0\%$) and 2.25 (95% CI 1.61 – 3.14, $p < 0.001$, $I^2 = 94\%$), after the exclusion of outliers and lower quality studies, respectively. There was no funnel plot asymmetry for T1DM and fracture risk. P-values of 0.37 and 0.85 were obtained for Egger's regression asymmetry test and Begg's adjusted rank correlation test, respectively, indicating a low probability of publication bias.

DISCUSSION

The findings from this meta-analysis demonstrate that young and middle-aged adults are twice as likely to fracture, compared to non-diabetic controls. This is somewhat lower than the previously reported RR of 3.16 in the meta-analysis by Shah et al¹⁰, but can be reasonably expected in a younger cohort of adults. We report a 4-fold increased hip fracture risk, which is slightly lower than the RRs of 5.76 and 6.3 reported in previous meta-analyses of predominantly older cohorts by Fan et al¹¹ and Janghorbani et al¹², respectively. Despite the deliberate exclusion of older and post-menopausal females in our analysis, hip fracture risk in younger adult females with T1DM was almost 6-fold higher than controls of similar age. Similarly, younger men with T1DM exhibited a similarly elevated hip fracture risk, nearly four times that of controls. Overall, there was no difference observed in hip fracture risk between sexes.

Increased hip fracture risk in T1DM has been established in previous meta-analyses^{3,10,11} and cohort studies²³⁻²⁵. However, the majority of such studies have comprised of adults older than 40 years, which could lead to overestimation of fracture risk attributable to T1DM due to confounders such as post-menopausal osteoporosis, increased frailty and susceptibility to falls. Nevertheless, a few cohort studies have demonstrated that hip fracture risk remains elevated in younger adults. A large Swedish prospective registry-based cohort study by Miao et al showed increased standard hospitalisation ratios of 7.6 and 3.4 for hip fracture in women and men with T1DM under the age of 40, respectively²⁶. In a more recent cohort study, Weber et al¹⁴ reported an adjusted hazard ratio of 4.16 for hip fracture in women with T1DM aged 30 – 39 years, which was comparably higher than that of their counterparts over the age of 60. While hip fractures are generally uncommon events in young adults, the four-fold risk of hip fracture reported in our meta-analysis, raises important clinical concerns about fracture mechanisms in young people with T1DM. With only a modest reduction of 0.055g/cm² in femoral neck BMD in individuals with T1DM reported in a recent meta-analysis by Shah et al⁴, low bone mass alone does not adequately explain the discrepant risk of hip fracture.

Bone geometry and bone microarchitecture are important determinants of bone strength and may provide further insights into the structural mechanisms of hip fracture. Failure to accrue peak bone mass as a result of childhood-onset T1DM may result in smaller and shorter bones in adulthood, which could portend less favourable bone geometry to resist fracture²⁷. Only a few studies have evaluated hip structure in adults with T1DM thus far. In a small cross-sectional study of middle-aged males, Miazgowski et al found no difference in hip strength

indices between those with T1DM and controls, although there was a non-significant trend toward decreased cross-sectional area and moment of inertia in males with T1DM on hip structural analysis (HSA)²⁸. However, in a more recent study utilising quantitative computed tomography, Ishikawa et al were able to demonstrate significantly reduced cortical volumetric bone mineral density (vBMD) and a higher buckling ratio, a marker of cortical instability, in the intertrochanteric region of young to middle-aged males with T1DM compared to controls²⁹. Cortical bone is a key component of bone tissue in the skeleton, and perturbations of cortical bone integrity may predispose individuals to fracture at sites composed of cortical bone predominantly, such as the femoral neck. In a larger cross-sectional study of middle-aged adult patients with T1DM, Verroken et al found that those with T1DM exhibited cortical bone size deficits at the radial shaft on peripheral quantitative computed tomography (pQCT). These findings were more pronounced at the endosteal envelope, and in association with the finding of lower bone marrow density, are suggestive of a potential role of increased marrow adiposity in the pathogenesis of cortical bone deficits in T1DM³⁰.

Microangiopathy may also serve as a mechanism by which T1DM exerts its effects on bone microstructure³¹. Shanbhogue et al⁶ described reduced trabecular and cortical vBMD, in addition to thinning of the trabeculae and cortex on high-resolution peripheral quantitative computed tomography (HR-pQCT) in patients with T1DM and microvascular disease, while no differences were observed between individuals with T1DM without complications and non-diabetic controls. As bone is highly vascular, disruption of the microvascular circulation in bone may impair osteoblast function and reduce bone remodelling capacity, thereby leading to decreased bone quality. In addition, it is conceivable that the vascular supply to the femoral head may be compromised in diabetic microangiopathy, which could explain the predilection for hip fracture in T1DM³². Vestergaard et al¹⁹ reported a two-fold increased risk of fracture in those with T1DM and nephropathy, while Weber et al¹⁴ observed a positive association of retinopathy and neuropathy in individuals with T1DM who had sustained a lower extremity fracture. In light of these findings, it is possible that microangiopathy not only has direct effects on bone quality, and may also indirectly potentiate the risk of falls and consequent fracture in susceptible individuals, via visual or physical impediments. Microvascular disease is often regarded as a surrogate of longstanding poor glycaemic control, and the impact of hyperglycaemia on bone health may therefore play an important role in fracture pathophysiology. Previous studies evaluating the effect of hyperglycaemia

have yielded inconsistent results, owing to differing methods used in the assessment of glycaemic control. Neumann et al³³ were able to demonstrate a positive association between poor long-term glycaemic control and prevalent fractures in adults with T1DM, independent of BMD. Chronic hyperglycaemia drives the non-enzymatic glycosylation of proteins, leading to the formation of advanced glycation end-products (AGEs), which can disrupt bone collagen matrix and weaken its biomechanical properties². The detrimental effects of AGEs on bone tissue *in vivo* has been demonstrated by the presence of increased pentosidine, a surrogate marker of AGEs, on bone histomorphometry in individuals with T1DM with prevalent fractures, compared to those without fracture³⁴.

Last but not least, hypoglycaemia is a common adverse effect of insulin therapy, and its contribution to fracture risk should not be overlooked. The sympatho-adrenal response to hypoglycaemia is reduced in the face of recurrent hypoglycaemic episodes, and the threshold at which symptoms develop, is subsequently lowered³⁵. Individuals with hypoglycaemic unawareness are prone to developing severe hypoglycaemia, which can culminate in an altered conscious state predisposing to falls and injury, particularly in the setting of a hypoglycaemic seizure. Several case reports³⁶⁻³⁸ have described the traumatic component of such seizures, leading to vertebral fractures. In individuals with underlying bone fragility, avoidance of hypoglycaemia is therefore an important component of fracture prevention.

Overall, there is clear evidence for increased skeletal fragility in T1DM, and our findings support a consistent, but unexplained risk of hip fracture in this younger cohort, designed to exclude age-related confounders. We acknowledge that there are several limitations to this meta-analysis. Firstly, only a small number of studies were included, as procurement of data for participants in our pre-specified age range of 18 to 50 years was limited to authors who had responded. The majority of studies that were excluded in the quantitative analysis were at least a decade old and had small numbers of individuals with T1DM, with the exception of Miao et al²⁶ which included 25,000 individuals with T1DM. As reported previously, the standardised hospitalisation ratios for hip fracture in a subgroup of adults under the age of 40 were 3.4 and 7.6, for men and women, respectively, which are in keeping with our results. While the potential for reporting bias exists, the inclusion of larger and newer studies may be more representative of contemporary fracture risk in T1DM, in light of current diabetes therapies. Although there were only two studies included for hip fracture, these were the two largest observational studies, with well-characterised cohorts with objective diabetes and

fracture classification. We note that the subgroup analysis of hip fracture risk gave rise to point estimates of relative risks which were much higher than that of the pooled overall fracture risk and its confidence interval. A major limitation of this meta-analysis, was the heterogeneity in fracture ascertainment and endpoints of the included studies. Virtually all hip fractures are clinical events, and the detection rate of such fractures is likely to be higher than other types of fracture, which may be clinically silent. It is notable that the pooled relative risk and confidence interval for hip fracture in our analysis, is quite similar to the relative risk of 4.0 in the study by Zhukouskaya et al²⁰, where vertebral fractures were actively screened for in asymptomatic individuals. The study populations included in these analyses originated from America or Europe with predominantly Caucasian participants, thus the findings from this study may not be generalizable to other ethnic groups. The methodologies of the included studies did not allow for the classification of fracture aetiology, and confounders such as trauma-related or sporting injuries in younger adults may over-estimate the risk of fragility fractures in this cohort. Data on body mass index, glycaemic control, duration of diabetes, presence of microvascular complications and concomitant autoimmune disease was not available for all included studies.

To our knowledge, this is the first meta-analysis of fracture risk specifically targeted at young to middle-aged adults with T1DM, with application of strict selection criteria to reduce heterogeneity and confounding due to age-related factors. We included the two largest cohort studies to date^{14,16}, comprising over 34,000 individuals with T1DM, and our findings for hip fracture risk are consistent with previous meta-analyses and cohort studies.

Conclusions

In a young to middle-aged cohort of T1DM, we show that hip fracture risk is comparable to previously reported RRs of between 4 to 6, albeit in predominantly older adult study populations^{3,11,12}. Young adults with T1DM may be at risk of fracture at a younger age compared to their non-diabetic counterparts. The impact of a hip fracture in a young adult is potentially devastating, with ramifications of physical and psychological morbidity, in addition to increased mortality. Although T1DM is widely acknowledged as a risk factor for secondary osteoporosis and fracture, there is no consensus on the timing and modality of bone health assessment in this cohort. However, we show that young adults with T1DM have an increased risk of fracture, and awareness is needed early in diagnosis. While the absolute numbers for hip fracture are low in this younger cohort, we urge clinicians to be cognizant of

the diverse risk factors for skeletal fragility, and treat reversible causes where possible. Individuals with poorly controlled T1DM and microvascular complications appear to be most at risk of fracture, based on observational studies. Concomitant comorbidities that may contribute to fracture risk, such as hypogonadism, autoimmune conditions and hypoglycaemia, should be identified and managed. Imaging modalities that allow indirect assessment of bone microarchitecture and structural properties, such as trabecular bone score, HR-pQCT and hip structural analysis, may be a useful adjunct to DXA in this cohort, where BMD is but one of many contributors to fracture risk. Further research evaluating hip fracture mechanisms in T1DM, screening and assessment, is needed to guide practice.

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Figure 1. Flowchart of study selection

Diagram adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

First author and year	Type of study	Setting	Country	Study period	Number of participants	Definition of T1DM	Fracture ascertainment	Age (years)	Total fracture events (fractured/total)	Fracture type	Fracture events by gender in those aged between 18-50 years (fractured/total)		OR/RR/HR	Variables adjusted
Zhukouskaya et al, 2013 ²⁰	Cross-sectional	Hospital outpatient	Belarus	2007-2011	82 T1DM (26M:56F); 82 controls (22M:60F)	American Diabetes Association criteria	Vertebral fracture assessment and spinal radiographs	20-55	20/82 of T1DM vs. 5/82 of controls	Vertebral	Males: 6/26 T1DM; 1/22 controls	Females: 14/56 T1DM; 4/60 controls	OR 4.20, 95% CI 1.40-12.70, p<0.01	Age, sex, BMI, lumbar spine BMD
Weber et al, 2015 ¹⁴	Prospective cohort	Population	UK	1994-2002	Total 30394 T1DM (17074M:13347F); 303872 controls (170421M:133451F)	Medical diagnoses (read codes) specific to T1DM or diabetes and < 35 years old	Diagnosis codes from outpatient electronic medical records consistent with incident fracture, classified by site; surgically-induced fractures or those associated with birth trauma or metastases were excluded	0-89	2615/30394 of T1DM vs. 18624/303872 of controls	Any fracture	Males: 779/10874 T1DM; 5367/109016 controls ^a	Females: 431/8193 T1DM; 2440/82156 controls ^a	Males: HR 1.55, 95% CI 1.44-1.67, p<0.001 ^a ; Females: 1.76 95% CI 1.58-1.96, p<0.001 ^a	Steroid use, prior fracture, CKD
										Hip	Males: 21/10983 T1DM; 75/109927 controls ^a	Females: 14/8321 T1DM; 28/82390 controls ^a	Males: HR 2.55, 95% CI 1.52-4.26, p<0.001 ^a ; Females: HR 3.36, 95% CI 1.61-7.10, p=0.001 ^a	
Hothersall et al, 2014 ¹⁶	Retro-spective cohort study	Population /registry-based	Scotland	2005-2007	21033 T1DM/59585 person-years; 3.66million/10,980,599 person-years	Clinical and prescription history (no evidence of lengthy diabetes duration prior to insulin prescription, no co-prescription of oral anti-diabetic drugs except for	Incident hip fracture admissions in 2005 to 2007 by linkage of diabetes register to national hospital admissions data (ICD codes)	20-84	105/21033 of T1DM vs. 11733/3660000 of controls	Hip	Males: 14/8844 of T1DM; 331/1026350 of controls ^b	Females: 7/6649 of T1DM; 160/1076510 of controls ^b	Males: RR 5.4, 95% CI 3.5-8.3, p<0.001 ^b ; Females: RR 7.9, 95% CI 3.4-18.5, p<0.001 ^b	Age, sex and calendar year

						metformin)								
Vestergaard et al, 2009 ¹⁹	Case-control	Population	Denmark	2000	4369 T1DM, 484615 controls	WHO standards	National Hospital Discharge Register & ICD codes	43±27	1703/4369 of T1DM vs. 122952/371296 of controls	Any fracture	Males: 284/797 of T1DM; 26201/105458 of controls ^c	Females: 139/344 of T1DM; 13677/55132 of controls ^c	Males: OR 1.67, 95% CI 1.45-1.94, p<0.001 ^c ; Females: OR 2.06, 95% CI 1.66-2.55, p<0.001 ^c	Macro- and micro-vascular complications
Danielson et al, 2009 ²¹	Matched, nested cross-sectional	Population	USA	2005	T1DM females 75; controls 75	New cases of T1DM defined as diagnosis ≤ age 30, clinical symptoms of hyperglycaemia and insulin-requiring	Self-reported fractures confirmed by physician or radiograph	18-50	Fracture: 28 T1DM, 18 controls	Any	N/A	Females: 28/75 of T1DM; 18/75 of controls	Females: OR 2.3, 95% CI 1.0-5.2, p<0.05	Not reported
First author and year	Type of study	Setting	Country	Study period	Number of participants	Definition of T1DM	Fracture ascertainment	Age (years)	Total fracture events (fractured/ total)	Fracture type	Fracture events by gender in those aged between 18-50 years (fractured/total)		OR/RR/HR	Variables adjusted
Strotmeyer et al, 2006 ²²	Cross-sectional	Population (volunteer subgroup from prospective study)	USA	Unknown	T1DM females 67; controls 237	Premenopausal women on diabetes registry diagnosed at age <17 years in hospital	Self-reported	35-55	Fracture: T1DM 33.3% vs. controls 22.6%, age-adjusted OR 1.89 (95% CI 1.02-3.49)	Any fracture after age 20 (site not specified)	N/A	Females: 22/67 of T1DM; 54/237 of controls	Females: OR 1.89, 95% CI 1.02-3.49, p>0.05	Age

Table 1. Characteristics of studies included for quantitative analysis

^aPart of a secondary analysis of dataset initially assembled to describe fracture incidence from birth to 89 years, using data from The Health Improvement Network; data obtained from investigators through personal communication.

^bPart of a secondary analysis of original dataset; data obtained from investigators through personal communication.

^cPart of a secondary analysis of original dataset; data obtained from investigators through personal communication.

Abbreviations: UK, United Kingdom; USA, United States of America

Figure 2. All fractures

Figure 3. Hip fractures

Variable	Studies included (references)	RR, 95% CI, p-value	Heterogeneity (I^2), p-value
Sex and fracture type			
Men			
All fractures	N = 4 (14,16,19,20)	RR 1.73, 95% CI 1.50 – 2.30, p<0.001*	86%, p<0.001
Hip fracture	N = 2 (14,16)	RR 3.67, 95% CI 2.10 – 6.41, p<0.001*	58%, p=0.12
Women			
All fractures	N = 6 (all studies)	RR 1.85 95% CI 1.37 – 2.20, p<0.001*	71%, p=0.004
Hip fracture	N = 2 (14,16)	RR 5.79, 95% CI 3.55 – 9.44, p<0.001*	43%, p=0.15
Higher quality studies (all fractures)	N = 3 (14, 16, 19)	RR 2.25, 95% CI 1.61 – 3.14, p<0.001*	94%, p<0.001
Excluding outliers^a (all fractures)	N = 4 (14, 19, 21, 22)	RR 1.53, 95% CI 1.47 – 1.61, p<0.001*	0%, p=0.85
Ratio of relative risks (RRR) between sexes, by fracture type			
All fractures	N = 6 (all studies)	RRR 0.94, 95% CI 0.68 – 1.29, Z = -0.41 ^b	p=0.68
Hip fracture	N = 2 (14,16)	RRR 0.63, 95% CI 0.30 – 1.33, Z= -1.20 ^b	p=0.23

Table 2. Subgroup and sensitivity analyses

*Denotes significant p-value.

^aFixed effects model used due to low heterogeneity.

^bDenotes Z-score (test of interaction)

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