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Epidemiology of Skeletal Health in Type 1 Diabetes

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Abstract

The skeleton is adversely affected by type 1 diabetes (T1D). Patients with T1D of both sexes have an increased risk of fracture that begins in childhood and extends across the entire lifespan. T1D is characterized by mild to modest deficits in bone density, structure, and microarchitecture. Current evidence suggests that the observed bone deficits in T1D are the result of impaired bone formation rather than increased bone resorption. There is emerging data that bone quality is impaired in T1D, which may explain the findings that fracture risk is elevated out of proportion to the degree of bone mineral deficit. In this review, we summarize the current knowledge regarding the epidemiology of skeletal health in T1D. Given the high individual and societal burden of osteoporotic fracture, there is an urgent need to better understand the etiology of T1D-related bone disease so that clinical strategies to prevent fracture can be developed.

Keywords

Type 1 diabetes; Fracture; Bone mineral density; Osteoporosis; Epidemiology

Introduction

Type 1 diabetes (T1D) is a condition characterized by chronic insulin deficiency and hyperglycemia that develops as the result of autoimmune or other destruction of the pancreatic beta cells [1]. The majority of patients living with T1D develop the disease during childhood [2] and are therefore exposed to the deleterious effects of insulin deficiency and hyperglycemia for decades. The negative effects of chronic hyperglycemia on body systems are profound, and patients with T1D are at risk for the development of a number of well-known complications including retinopathy, nephropathy, neuropathy, and cardiovascular

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Compliance with Ethical Standards

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disease. It is now apparent that the skeleton is also adversely affected by T1D, resulting in a lifelong increased risk of fracture for patients afflicted with this disease. Unlike other T1D-related complications, however, there are no standard guidelines for the screening and treatment of T1D-related skeletal disease. In part, this is due to an incomplete understanding of the etiology of skeletal fragility in T1D.

The number of patients at risk for T1D-related osteoporotic fracture is expected to rise as a result of both increased incidence of T1D and improvements in medical care that are allowing patients to live longer [1]. Given the high morbidity and mortality associated with osteoporotic fracture [3], there is an urgent need to better understand the determinants of T1D-related bone disease so that effective clinical strategies to prevent fractures can be developed and implemented. In recent years, there has been a surge of publications related to the skeletal effects of T1D. This has included a large number of clinical studies which have helped to define the magnitude of the fracture risk and also to characterize the nature of the skeletal deficits seen in T1D. The intent of this article is to summarize what is known about the clinical epidemiology of T1D-related bone disease, to identify potential limitations in the existing literature, and highlight areas for future research.

Methods

We searched PubMed through July 2016 to identify published manuscripts related to the clinical epidemiology of skeletal health in T1D. Key studies were identified as those that defined how the exposure of T1D was differentiated from other forms of diabetes, investigated clinically relevant outcomes, and provided sufficient methodological detail to interpret results. The search was limited to studies conducted in humans and published in English.

Fracture Risk in Type 1 Diabetes

Population-based studies have consistently found that individuals with TID are at greater risk for fracture compared to the general population. A summary of the participant characteristics, fracture outcomes, and method of risk determination for the 10 major published epidemiologic studies of fracture risk in T1D is provided in Table 1 [4–9, 10•, 11, 12•, 13••]. Taken together, these studies utilized data from seven different countries and included participants from both sexes and across the entire age range. The majority of studies (8/10) specifically reported hip fracture as an outcome, while half (5/10) also reported risk for all skeletal or other non-hip fracture sites. The magnitude of the increased fracture risk associated with T1D varied considerably between studies, a finding that is likely attributable to differences in study population, method of exposure and outcome ascertainment, and the statistical approach taken to estimate risk.

At the hip, the increase in fracture risk associated with T1D ranged from 70 % higher in a study utilizing clinical data from the National Hospital Discharge Register in Denmark [7] to greater than 12-fold higher for self-reported fracture in the Iowa Women's Health Study in the USA [5]. Studies that included data for all skeletal sites found that T1D populations demonstrated increased fracture risk ranging from 1.2- to 2.5-fold higher compared to unexposed participants [11, 12•]. While the markedly increased risk of hip fracture for adults

with T1D has garnered the most attention, it is notable that the increased fracture risk associated with T1D is already apparent early in the disease and that T1D patients of all ages are at increased risk of fracture. This was illustrated in a study using The Health Improvement Network database from the United Kingdom, which analyzed medical record data in a cohort of over 30,000 T1D patients ranging in age from 1 month to 90 years [13••] (Fig. 1). An additional study in young adults with T1D identified a higher prevalence of vertebral compression abnormalities identified by means of vertebral fracture assessment (VFA), compared to healthy controls [14].

Three meta-analyses and one systemic review of fracture risk in T1D have been published. The first, published in 2007, incorporated data from five studies and determined the pooled relative risk for hip fracture in T1D participants compared to those without diabetes to be 6.9 [15]. More recent reports incorporated subsequently published data and found similar pooled relative risk estimates of 5.8 and 6.3, respectively, for hip fracture in T1D [16, 17]. An analysis of 14 studies incorporated data from fracture sites other than hip and determined that the pooled relative risk for fracture at any skeletal site for T1D participants was 3.2 [18].

Several studies have sought to identify risk factors for fracture within T1D participants. Poor glycemic control has emerged as a predictor of fracture in some [13••, 19], but not all [14] studies where hemoglobin A1c (HbA1c) data were available. Presence of a diabetes-related complication (retinopathy, neuropathy, nephropathy, cardiovascular disease) is another factor that has been shown to increase fracture risk [6, 13••, 20]. Deficits in BMD alone did not account for the degree of the increased fracture risk associated with T1D on meta-analysis [15]. Interestingly, sclerostin, an inhibitor of Wnt-mediated bone formation, was shown to be protective against fracture in an adult T1D cohort [21•]. Hypoglycemia-related falls have been commonly raised as a possible contributing factor to fracture risk in T1D; however, to date, no compelling data have been published to support this hypothesis.

The possibility of a cohort effect must also be considered, especially when evaluating studies including data from older adults. Intensive therapy to maintain glycemic levels as close to normal as possible is now the standard of care for the medical management of T1D. Prior to 1993 and the publication of the Diabetes Control and Complications Trial [22], however, this was not the case. Participants diagnosed with T1D prior to 1993 may have therefore been exposed to much higher glycemic levels in the past compared to what would be reflected by HbA1c at time of study inclusion. In theory, if hyperglycemia is detrimental to bone, exposure to higher glucose levels in the past could contribute to skeletal fragility later in life.

DXA-Based Assessment of Bone Mineral Content and Density

Dual energy X-ray absorptiometry (DXA) has been widely used to assess bone mineral content (BMC) and bone mineral density (BMD) in observational studies of bone health in T1D participants. The majority of published reports consist of cross-sectional studies where DXA-based BMC or BMD outcomes in T1D participants were compared to age- and sex-matched healthy controls. These studies have been conducted in diverse populations, with considerable variability in sample size and other potentially relevant characteristics including age, T1D duration, glycemic control, and presence of T1D-related comorbidities. Most studies identified significantly lower BMC or BMD at one or more skeletal sites in

T1D participants compared to matched controls or an established reference population [14, 23–41]. A few studies failed to detect differences between T1D and healthy participants [42–48].

Studies that reported age- and sex-specific Z-scores (standard deviation scores) for BMC and/or BMD relative to healthy reference populations are highlighted in Table 2. These results suggest that, on average, the magnitude of the deficits observed in association with T1D are mild to modest, as Z-scores ranged from near 0 (average compared to a reference population) to −1 (one standard deviation below average). The prevalence of BMC or BMD Z-scores of <−1 in T1D participants ranged from 22 to 45 % in six studies reporting this outcome [14, 28, 39, 46, 49, 50]. In comparison, approximately 16 % of individuals would be expected to fall below a Z-score of −1 in a normal population. It should be noted that there was variability in the methodology used to determine individual Z-scores across these studies. In some cases, Z-scores were reported as determined by the standard software provided by the DXA manufacturer, and in others, they were derived in comparison to a locally specific reference population. The later method is generally preferable as it may take into account racial/ethnic group or other locally specific contributors to bone mass that might confound comparisons to an unrelated population. While this limitation should be considered in the interpretation of these results, it is reassuring that the magnitude of the reported bone deficits were relatively consistent across studies.

Two meta-analyses evaluating the association between T1D and BMD have been published and support the conclusion that T1D is associated with mild to modest deficits in BMD. The first, published in 2005, calculated a lower weighted mean difference in BMD Z-score at the lumbar spine of −0.22 ± 0.01 and hip of −0.37 ± 0.16 in T1D participants compared to controls [15]. The second, published in 2014, attempted to quantify absolute differences in BMD between T1D and matched controls. The analysis included 25 studies and incorporated data from 2716 females (965 T1D) and 1230 males (537 T1D) [51]. The results identified lower total body BMD in T1D participants of both sexes compared to controls, with a pooled mean difference (MD) of −0.06 g/cm^2 (95 % CI −0.11, −0.01). Deficits were also seen at other skeletal sites, although these varied in significance and magnitude by sex.

Large, long-term natural history studies evaluating changes in BMD or BMC in T1D over time are lacking, and only a few studies have reported longitudinal or follow-up DXA bone outcome data in T1D cohorts. Despite these limitations, the published literature may provide some insight into the natural history of the effects of T1D on the skeleton. It appears that deficits in BMD begin to manifest early in the disease course. This is supported by two studies performed shortly after T1D diagnosis. The first, conducted in 23 pre-pubertal children at mean duration of 5.8 months after T1D diagnosis, identified significantly lower lumbar spine BMD Z-scores (−0.89 ± 1.2) compared to matched controls [50]. The second, performed in 32 young adults (age 20–39 years) at the time of T1D diagnosis, also identified significant deficits in lumbar spine BMD Z-scores (−0.61 ± 1.2) compared to controls [27]. T1D may also be associated with impaired bone accrual during childhood and adolescence. A study conducted in 39 T1D children found a mean loss of lumbar spine BMD of 0.006 gm/cm^2/year over a mean follow-up period of 51 months, after adjustment for confounders [52]. Longitudinal data in a matched control population were not collected; however, this

sample consisted entirely of children; therefore, BMD would have been expected to increase over time in conjunction with known developmental patterns in bone accrual [53].

The BMD of T1D patients appears to remain relatively stable throughout early and middle adulthood. The longest longitudinal study in adults reported DXA BMD measures at baseline and 7-year follow-up in 57 participants [49]. Lumbar spine Z- and T-scores were below zero at baseline and follow-up; however, there was no significant change between baseline and follow-up measures for BMD (g/cm^2) or BMD T- or Z-scores over the study period. Mean HbA1c decreased over the study from 8.5 to 7.9 %; therefore, the possibility of a beneficial effect of improved glycemic control on BMD must be considered. A second study in 26 adults with T1D found a small, but statistically significant decline in femoral neck BMD over 5 years in males but not females [54]. There were no changes at other skeletal sites in either males or females. In a third study of 63 young T1D women, BMD was lower than matched controls at multiple skeletal sites at both baseline and 2-year follow-up, but the rate of change over the study period did not differ in T1D participants versus controls [29, 34]. Additionally, mean BMD Z-score deficits are relatively consistent across studies including participants of different ages (Table 2). If T1D resulted in clinically significant bone loss over time, BMD Z-scores would be expected to be relatively lower in older versus younger cohorts. There is an under representation of BMD data from older adults in the published literature, however, so the impact of T1D on bone loss in postmenopausal women and older men is unclear.

Taken together, the clinical DXA studies suggest that T1D is associated with mild to modest deficits in BMC and BMD that develop early in the disease course but remain relatively stable during adulthood. These results fit with animal data suggesting that the observed bone deficits in T1D are largely due to diminished bone formation as opposed to increased bone resorption [55]. A preferential effect on bone formation would be expected to result in poor bone accrual during childhood and adolescence and thereby negatively affect peak bone mass in young adulthood. Future longitudinal studies are needed to test this hypothesis.

Peripheral Quantitative CT and MRI Assessment of Bone Size and Structure

DXA has a number of limitations that may contribute to the discrepancy between the high degree of fracture risk and relatively modest BMD deficits observed in T1D [15]. These limitations include a failure to differentiate between cortical and trabecular bone compartments, inability to assess bone microarchitecture, structure, or material properties, and a tendency to underestimate BMD in individuals who are small or skeletally immature for age. In recent years, advanced imaging techniques including peripheral quantitative computed tomography (pQCT) and magnetic resonance imaging (MRI) have emerged as alternative bone imaging modalities that may address some of the limitations of DXA.

A few studies have utilized pQCT or MRI to assess bone parameters in T1D. Three pQCT studies conducted in T1D children identified deficits in bone size, as assessed by total and cortical cross-sectional area, compared to healthy reference data [30, 56, 57]. These deficits persisted over 12 months in one study [30] but had normalized at 5-year follow-up in the other study with longitudinal data [58]. The effects of T1D on other bone parameters including trabecular and cortical volumetric BMD varied between the studies. The skeleton

was analyzed at the radius in two studies [56, 57] and the tibia in the other [30], which may affect comparison of results as one site is weight-bearing and the other is not. A study in adults utilizing high-resolution pQCT found that T1D participants had smaller bone area, and lower total and cortical volumetric BMD at the radius, but not tibia, compared to controls [47•]. MRI-based measures of tibial trabecular architecture including apparent bone volume to total volume ratio, apparent trabecular number, and apparent trabecular thickness were found to be lower in 30 young adult women with T1D compared to healthy controls [59•]. Both adult studies identified a negative effect of microvascular disease on bone microarchitecture in T1D participants [47•, 59•].

Predictors of Bone Deficits in T1D

There is little consensus as to the clinical determinants of the observed deficits in BMD, bone size, and bone microarchitecture within T1D participants. Similar to the fracture literature, the presence of a T1D-related complication including retinopathy, nephropathy, or other microvascular disease has emerged as a predictor of skeletal deficits in several studies [24, 47•, 49, 59•]. The reported effect of glycemic control on bone outcomes, however, has varied widely, with a negative association seen in some studies [28, 30, 35, 37, 41, 60] but not others [14, 23, 29, 32, 33, 39, 40]. Better glycemic control has been shown to be associated with reduced risk of other T1D-related complications in clinical trials and long-term follow-up studies [22, 61]; so, it is unclear why hyperglycemia has not emerged as a consistent predictor of skeletal deficits. One possibility is insufficient inclusion of participants with very good or very poor glycemic control in study samples. This could be the result of selection bias, or simply reflect the lower prevalence of extreme HbA1c levels in the modern T1D population. Future studies specifically powered to identify an effect of glycemic control on skeletal outcomes may help clarify this relationship.

Bone Quality

Impaired bone quality may contribute to the increased skeletal fragility observed in T1D. Advanced glycation endproducts (AGEs) are the product of non-enzymatic reactions between proteins and sugar [62]. One such reaction results in the formation of abnormal cross-links between type 1 collagen fibers in bone. The accumulation of excessive AGEs in the skeleton may alter bone strength and increase susceptibility to fracture. Measurable AGEs include pentosidine, which can be measured by high-performance liquid chromatography in urine, serum, or bone tissue. Small cross-sectional studies have identified higher bone and serum pentosidine levels in T1D adults with prevalent fracture compared to those with no history of fracture [63, 64]. Reference point indentation (RPI) is an emerging technique that aims to provide an in vivo assessment of bone quality in humans. A recent study identified utilizing RPI in adults with type 2 diabetes identified altered bone material strength compared to controls [65]. No clinical studies using RPI to investigate bone quality in T1D have yet been published.

Markers of Bone Turnover and Bone Mineral Metabolism

Multiple clinical studies have attempted to identify the effects of T1D on bone turnover by analyzing serum and urine markers of bone formation [osteocalcin (OCN), bone-specific alkaline phosphatase, procollagen type 1 amino terminal propeptide (P1NP)] and bone

resorption [C-terminal cross-linked telopeptide of type I collagen (CTX), N-terminal cross-linked telopeptide of type I collagen, tartrate resistance acid phosphatase]. A meta-analysis published in 2014 identified lower OCN levels in T1D participants; analysis of other turnover markers was not possible due to insufficient or heterogeneous data [66]. A finding of low bone formation markers in association with T1D has been reported in most [35, 38, 47•, 50, 67, 68•, 69, 70], but not all studies [29]. Results for bone resorption markers have been variable, with most studies reporting normal levels [35, 38, 50, 70, 71], and others finding lower [47•, 59•, 72], or in one case higher levels [69] in T1D participants compared to controls. A cross-sectional study in adults identified an inverse relationship between non-fasting glucose and P1NP and CTX [73], and a longitudinal study in children found an inverse relationship between HbA1c and OCN and CTX [67], suggesting a negative effect of hyperglycemia on bone turnover. Sclerostin levels were found to be higher in T1D participants compared to controls in one [70], but not another study [72].

Bone turnover markers are affected by age, sex, growth velocity, and diurnal patterns. Participant heterogeneity or failure to account for these characteristics may contribute to the lack of consistency between studies regarding the effect of T1D on bone turnover. Histomorphometric data from bone biopsies might help clarify the effect of T1D on bone turnover; unfortunately, such data in T1D participants are extremely limited. The largest study included transiliac samples from 18 adult T1D participants without diabetes-related complications and found no difference in structural or dynamic parameters compared to matched controls [74]. A second study from the same authors found higher degree of mineralization in bone samples analyzed by microradiography in five T1D participants with fracture history compared to non-fracturing T1D or healthy controls [64]. Future studies in larger and more diverse T1D cohorts could be helpful in clarifying the effects of T1D on bone formation and mineralization.

A role for altered bone mineral metabolism as a contributor to impaired skeletal health in T1D is another active area of research. Several studies have identified a high prevalence of vitamin D insufficiency and deficiency in T1D patients [75, 76]. Early in the disease course, however, it does not appear that the prevalence of low vitamin D in T1D is out of proportion to the general population. A registry study conducted in US children found that 36 % of T1D participants were deficient in vitamin D; however, the prevalence was similar to what was reported in similarly aged children from the nationally representative National Health and Nutrition Examination Survey [77•]. A cross-sectional study performed in 1803 children (907 T1D) found no difference between 25(OH) vitamin D levels at diagnosis in T1D participants compared to their non-T1D siblings [78]. Few studies have investigated the effects of T1D on vitamin D metabolism in humans. One study in young adults with T1D found no relationship between HbA1c and either 25(OH) vitamin D, $1,25(OH)_2$ vitamin D, or $24,25(OH)_2$ vitamin D [79]. Urinary vitamin D binding protein excretion was higher in T1D patients compared to controls, and related to hyperglycemia and urinary microalbumin excretion [80], a finding which could contribute to low-vitamin D levels in patients with poorly controlled or long-standing disease.

Parathyroid hormone (PTH) is the principal regulator of whole body calcium status through its actions to activate vitamin D and increase calcium resorption from bone. It may also have

anabolic effects on the skeleton [81]. PTH levels have been found to be lower in T1D participants compared to controls in some studies [70, 79] and higher in others [72, 82]. A tri-sodium-citrate calcium clamp study performed in 15 adult T1D participants and 19 matched controls suggested that T1D participants had a lower set-point for PTH secretion, but normal PTH responsiveness to hypocalcemia [83]. PTH secretion is influenced by whole body calcium and magnesium status and renal function, all of which are potential confounders of a relationship between PTH and T1D. Excess urinary calcium excretion has been described in association with T1D in cross-sectional studies conducted in both adults and children [84–90]. A relationship between glycemic control and urinary calcium excretion was found in some studies, [84–86] but not in others [88–90]. Hypercalciuria is a known risk factor for low BMD and fracture risk in other conditions [91]; however, the potential impact of excess urinary calcium excretion on calcium balance, bone accrual, or skeletal fragility in T1D is not known.

Conclusion

Skeletal health is impaired in T1D. Population-based studies have clearly shown that patients with T1D have an increased risk of fracture compared to the general population. In addition to increased fracture risk, the other characteristics of T1D-related bone disease include mild to modest deficits in bone density, size, and structure and abnormalities in bone turnover markers that are consistent with impaired bone formation. There is emerging evidence that bone quality is impaired in T1D, a finding which may explain the apparent paradox of high fracture risk out of proportion to degree of BMD deficit. The adverse skeletal effects begin to manifest early in the disease course and extends to both males and females of all ages. The presence of a diabetes-related complication such as microvascular disease has emerged as a potential risk factor for impaired bone health; however, the role for glycemic control and other predictors remains uncertain. Longitudinal data are needed to better define the natural history of T1D-related bone disease. Targeted investigation of the effects of T1D on bone accrual during childhood and adolescence and on bone loss after menopause may be especially useful in designing clinical interventions to identify, treat, and ultimately prevent fracture in high-risk individuals.

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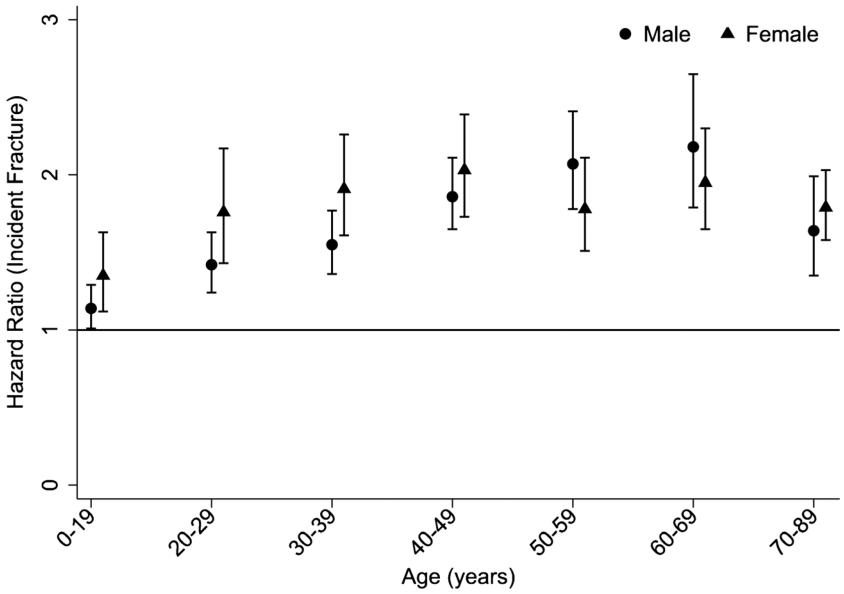

Fig. 1.

Fracture risk is increased in T1D across the lifespan. Crude hazard ratios are shown for incident fracture (all sites) in 30,394 T1D participants compared to 303,872 participants without diabetes. Reprinted with permission from *The American Diabetes Association.* "Copyright ©2015 American Diabetes Association. From: Diabetes Care 2015 Oct. 38(10): 1913–1920

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Table 1

Summary of key fracture epidemiologic studies in type 1 diabetes

Year published	Authors	Data source/country	Sex and sge of participants	Sample size	Fracture outcome	Statistical measure of risk	T1D-related fracture risk[1]
1999	Forsen et al. [4]	NTHS/Norway	M/F 50–74 years	T1D: 51 No DM: 26,895	Incident hip	Relative Risk	M: 4 (0.6,28.2) F: 5.7 (1.8,17.9)
2001	Nicodemus et al. [5]	IWHS/USA	F 55–69 years	T1D: 47 No DM: 30,377	Incident hip	Relative Risk	F: 12.3 (5.1,29.7)
2005	Miao et al. [6]	Swedish Inpatient Register/Sweden	M/F < 65 years	T1D: 24,605 No DM: not stated	Incident hip	Standardized Hospitalization Ratio	M: 7.6 (5.9,9.6) F: 9.8 (7.3,12.9)
2005	Vestergaard, et al.[7]	NHDR/Denmark	M/F all ages	Fracture: 124,655 No fracture: 373,962 Fracture: 10,530 No fracture: 31,535	incident, all sites incident hip	Odds Ratio	M/F: 1.9 (1.8,2.1) M/F 1. (1.3,2.2)
2006	Janghorbani, et al. [8]	Nurse Health Study/USA	F ≥ 30 years	T1D: 292 No DM: 101,343	Incident hip	Relative Risk	F: 7.1 (4.4,11.4)
2006	Ahmed, et al. [9]	Tromso Study/Norway	M/F ≥ 25 years	T1D: 81 No DM: 26,704	Incident non-vertebral	Relative Risk	M: 3.1 (1.3,7.4) F: 3 (0.98,1.4)
					Incident Hip		M: 17.8 (5.6,56.8) F: 8.6 (1.1, 56.5)
2013	Hothersall et al. [10]	SCI-DC/Scotland	M/F 20–84 years	T1D: 21,033 No DM: 3.6 M	Incident hip	Incident Rate Ratio	M: 3.3 (2.5,4.3) F: 3.5 (2.8,4.6)
2014	Fraser et al.[11]	CaMos/Canada	M/F > 50 years	T1D: 98 No DM: 7147	Incident atraumatic, all sites	Hazard Ratio	M/F: 2.5 (1.6-3.9)
2014	Liao et al. [12•]	TNHIRD/Taiwan	M/F ≥ 20 years	T1D: 2992 No DM: 64,942	Incident, all sites	Hazard Ratio	M/F: 1.2 (1.1,1.4)
2015	Weber et al. [13••]	THIN/United Kingdom	M/F < 90 years	T1D: 30,394 No DM: 303,872	Incident, all sites	Hazard Ratio	M: 1.6 (1.5,1.7) F: 1.7 (1.6,1.8)
					Incident hip		M: 2.4 (1.9,2.9)

Year published	Authors	Data source/country	Sex and sge of participants	Sample size	Fracture outcome	Statistical measure of risk	T1D-related fracture risk[1]
							F: 2.3 (2,2.7)

CaMos Canadian Multicenter Osteoporosis Study, *DM* diabetes mellitus, *IWHS* Iowa Women's Health Study, *M* million, *NHDR* National Hospital Discharge Register, *NTHS* Nord Trondelag Health Survey, *SCI-DC* Scottish Care Information-Diabetes Collaboration Database, *THIN* The Health Improvement Network TNHIRD, Taiwan's National Health Insurance Research Database

[1] M/F denotes males and females grouped together for analysis; 95 % confidence intervals displayed in parenthesis; unadjusted outcomes reported if both unadjusted and adjusted outcomes are provided in literature

Curr Osteoporos Rep. Author manuscript; available in PMC 2017 December 01.

Table 2

Studies reporting DXA bone mineral density (BMD) or bone mineral content (BMC) as Z-scores relative to reference population

Year	Authors	Country	Sex	Age (years)	n	Reported Z-score	Prevalence of Z score < −1*
1996	Munoz-Torres et al. [23]	Spain	M/F	30 ± 9	94	LS BMD Z: −0.89 ±1.2 FN BMD Z: −0.99 ±1.2	N/A
1997	Pascual et al. [44]	Spain	M	9.7 ± 4.3	26	LS BMD Z: −0.34 ± 1.1	N/A
			F	11.2 ± 3.8	29	LS BMD Z: 0.07 ± 1.2	
1999	Lunt et al. [43]	New Zealand	F	43 (26–66)	99	LS BMD Z: −0.2 (−0.4-0) FN BMDZ: −0.12 (−0.4-0.1)	N/A
2000	Pastor et al.	Spain	M/F	28.6 ± 8.9	62	LS BMD Z: −0.84 ± 1.3 FN BMD Z: −0.93 ± 1.3	LS or FN: 22%
2000	Rozadilla et al. [26]	Spain	M/F	28.9 ± 8.8	88	LS BMD Z: −0.38 ± 1.1 FN: −0.37 ± 1.1	N/A
2001	Gunczler et al. [50]	Venezuela	M/F	9.5 ± 2.2	23	TB BMD Z: 0.27 ± 0.6[1] LS BMD Z:−0.89 ± 1.2	LS Z: 45%
2001	Lopez-Ibarra et al. [27]	Spain	M/F	28.4 ± 5.4	32	LS BMD Z: −0.61 ± 1.2 FN BMD Z: −0.32 ± 1	N/A
2002	Valerio et al. [28]	Italy	M/F	13.1 ± 1.7	27	LS BMD Z: −0.44 ± 1.02	LS Z: 37%
2004	Ingberg et al. [92]	Sweden	M	43.1 ± 5	18	LS BMD Z: −0.7 ± 1.6 FN BMD Z: −0.7 ± 1.4	N/A
			F	41.2 ± 5	20	LS BMD Z: 0.6 ± 0.9 FN BMD Z: 0.1 ± 0.9	
2006	Leger et al. [31]	France	M	13 (10–16)	73	TB BMC Z:−0.2 (−0.82-0.58) LS BMC Z:−0.02 (−0.44-0.57)	N/A
			F	14 (12–17)	54	TB BMC Z: −0.34 (−0.92-0.54) LS BMC Z: −0.37 (−1.29-0.53)	
2007	Miazgowski et al. [33]	Poland	M	43.6 ± 5.1	36	LS BMD Z: −0.71 ± 1.1 Femur BMD Z: −0.67 ± 0.7	N/A
2009	Hamilton et al. [36]	Australia	M	43.4 ± 15.9	50	LS BMD Z: −0.27 ± 0.2 FN BMD:−0.38 ± 1.1	N/A
			F	37.9 ± 13.8	52	LS BMD Z: 0.31 ± 1.2 FN BMD Z: −0.04 ± 1.3	
2011	Eller-Vainicher et al. [39]	Belarus	M/F	32.8 ± 8.4	175	LS BMD Z: −0.11 ± 1.2 Femur BMD Z: −0.32 ± 1.4	LS Z: 26.3% Femur Z: 33%
2013	Joshi et al. [41]	India	M/F	27.2 ± 11.2	75	TB BMD Z: −1.10 ± 1.5 LS BMD Z: −1.03 ± 1.2	N/A
2013	Zhukouskaya et al. [14]	Belarus	M/F	31.1 ± 8.6	82	LS BMD Z: −0.56 ± 1.3 FN BMD Z: −0.64 ± 1.1	LS Z: 37% FN Z: 30%
2015	Parthasarathy et al. [46]	India	M	11.4 ± 3.6	77	LS BMAD Z: 0 ± 1.1 TB BMC Z:[3] −0.2 ± 1.1	Total Body Z:[3] 22%
			F	10.8 ± 3.9	93	LS BMAD Z: 0 ± 1 TB BMC Z:[3] −0.5 ± 1.1	

[2] Median (interquartile range)

BMAD bone mineral apparent density, *BMC* bone mineral content, *BMD* bone mineral density, *FN* femoral neck, *LS* lumbar spine, *N/A* not available, *TB* total body

[*] 15.9 % of a normally distributed reference population would be expected to have a Z-score of <−1

[1] Mean ± SD, all such values

[3]Adjusted for lean body mass