ARTICLES

Bone Health and Type 2 Diabetes Mellitus: A Systematic Review

Erin Gorman, Anna M. Chudyk, Kenneth M. Madden, Maureen C. Ashe

ABSTRACT

Purpose: To systematically review the literature related to bone health in older adults with type 2 diabetes mellitus (T2DM).
Methods: We conducted a systematic review of the literature from January 2005 until February 2010, using keywords related to T2DM and bone-health imaging technology in older adults (aged $\geq$ 60 years) to search PubMed, OVID MEDLINE, Ageline, CINAHL, Embase, and PsycINFO.
Results: We found a total of 13 studies that met the inclusion criteria for this review. The majority of the studies used dual X-ray absorptiometry (DXA) and showed either higher or similar areal bone mineral density (aBMD) for older adults with T2DM relative to healthy controls. Studies using more advanced imaging suggested that there may be differences in bone geometry between older adults with and without T2DM.
Conclusions: Older adults with T2DM have similar or higher aBMD at the hip relative to older adults without T2DM, despite previous literature reporting an increased risk of low-trauma fractures. Recent studies with advanced imaging have suggested that there may be differences in bone geometry between older adults with T2DM and those without. Health professionals, especially physiotherapists, should be aware of the increased risk and include assessment of fall risk factors and exercise prescription for fall prevention for older adults with T2DM.

Key Words: bone-mineral density, older adults, systematic review, type 2 diabetes mellitus

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RÉSUMÉ

Objectif : Procéder à une revue systématique de la documentation concernant la santé osseuse chez les personnes âgées souffrant de diabète sucré de type 2.
Méthode : Nous avons procédé à une revue systématique de la documentation scientifique parue de janvier 2005 à février 2010, en utilisant des mots clés liés au diabète sucré de type 2 et aux technologies d'imagerie pour la santé osseuse chez les personnes âgées ($\geq$ 60 ans) pour une recherche dans les bases de données PubMed, OVID MEDLINE, Ageline, CINAHL, Embase, et PsycINFO.
Résultats : Nous avons répertorié en tout 13 études qui comportaient les critères d'inclusion de cette revue systématique. La majorité des études utilisaient la méthode d'absorptiométrie à rayons X à double énergie (DEXA) et démontraient une densité minérale osseuse surfacique (DMOs) similaire ou plus élevée chez les personnes âgées avec diabète sucré de type 2 relativement aux mesures de contrôle saines. Les études ayant recours à une imagerie plus avancée suggéraient qu'il pouvait y avoir des différences dans la géométrie osseuse des aînés avec et sans diabète sucré de type 2.
Conclusions : Les personnes âgées avec diabète sucré de type 2 ont une densité minérale osseuse surfacique à la hanche similaire ou plus élevée que les personnes âgées sans ce type de diabète, malgré le fait que la documentation publiée auparavant rapportait un risque plus élevé de fractures à faible traumatisme chez les personnes souffrant de cette maladie. Les études récentes avec technologie d'imagerie plus avancée suggèrent qu'il pourrait y avoir des différences dans la géométrie osseuse des personnes âgées avec diabète sucré de type 2 et celles qui ne souffrent pas de cette maladie. Les professionnels de la santé, et surtout les physiothérapeutes, devraient être sensibles aux risques accrus des aînés diabétiques et procéder à une évaluation des facteurs de risques de chutes et prescrire des exercices visant à réduire de tels risques.

Mots clés : aînés, densité minérale osseuse, diabète sucré de type 2, personnes âgées, revue systématique

The authors have no conflicts of interest to declare.

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INTRODUCTION

Adults with type 2 diabetes mellitus (T2DM) are at increased risk for low-trauma hip fracture[1,2] (from a fall at standing height or less[3]), which can have serious health consequences and places significant strain on the health care system.[4] In Canada, 964,074 adults 65 years of age and older have diabetes, and of these approximately 90% have T2DM.[5] Because physiotherapists manage health-related concerns for older adults with T2DM, including providing exercise testing and prescription,[6] it is essential for them to understand the complications that older adults with T2DM may experience, including an increased risk of hip fracture.[1,2] The underlying mechanism for the increased fracture risk in T2DM has not been determined; postulated underlying mechanisms include changes in bone mass or bone quality and increased risk of falls.[7] It is therefore important to investigate mechanisms in order to develop effective screening strategies and preventive measures. As physiotherapists are trained to treat older adults with low bone mass (including osteoporosis) and those with a high risk of hip fractures,[8] they have an ideal opportunity to implement prevention strategies.

The increase in fracture risk for older adults with T2DM has been investigated by looking at bone health using areal bone mineral density (aBMD) from dual X-ray absorpiometry (DXA), commonly used in diagnosing osteoporosis.[3] A previous systematic review in this area[1] found higher aBMD in people with T2DM than in people without T2DM, as measured by DXA. Although the majority of studies have shown higher aBMD, there have been some discrepancies in the findings that could be attributed to differences in body mass index (BMI), disease duration, gender, and comorbidities. In addition, aBMD is limited by its two-dimensional nature, which may be influenced by body size and composition, and is unable to distinguish between cortical and trabecular bone compartments.[9] There may be differences in bone geometry that cannot be seen by DXA but that contribute to the increased risk of hip fracture. Advances in bone-imaging technology such as quantitative computed tomography (QCT) and peripheral QCT (pQCT) can distinguish bone compartments and estimate bone strength—a measure of the load or stress that a bone can take before breaking.[10] These advanced imaging technologies may thus allow for better understanding of differences in bone related to T2DM.

The finding of higher or similar aBMD in older adults with T2DM relative to the general age-matched population seems contradictory to the increased risk of hip fracture, and this suggests possible underlying causes. First, fractures occur as a result of impaired bone health and increased fall risk,[11] and previous studies have suggested that older adults with T2DM have an elevated fall risk.[12] Second, previous studies using other bone-health indicators (such as bone turnover markers), as well as animal studies, have suggested that the T2DM disease process may have a negative impact on bone.[13–15] For example, the increased blood-glucose levels and impaired glycemic control caused by T2DM have been associated with an increased accumulation of advanced glycation end products (AGEs) in bone collagen[16] and impaired calcium deposition and mineralization,[17] which are thought to affect bone strength.

The objective of this systematic review, therefore, was to compare bone health (e.g., bone mineral density, geometry) in older adults (aged ≥ 60 years) with and without T2DM by updating the literature and including studies that used advanced bone-imaging technology to provide a better understanding of bone health in older adults with T2DM.

METHODS

Data Sources and Search

The objective of this systematic review was to investigate the bone health of older adults with T2DM using imaging. We searched the published peer-reviewed literature from January 2005 through February 4, 2010, using PubMed, Ovid MEDLINE, Ageline, CINAHL, Embase, and PsycINFO. We chose to start the search in 2005 in order to update and expand upon the work done by Vestergaard, who completed a systematic review in this area that included articles published before 2005.[1] We did not include articles prior to 2005 because this previous review[1] comprehensively assessed the literature on T2DM and aBMD. Instead, we extended Vestergaard's review by including all studies that investigated bone health for older adults with T2DM, using DXA as well as other modalities such as QCT, pQCT, high-resolution pQCT (HR-pQCT), and quantitative ultrasound (QUS). We extended the previous search strategy by including more recent imaging (QCT, pQCT, HR-pQCT) that permits the three-dimensional assessment of bone; we also searched the reference lists of articles included for full-text review, electronically searched key journals (*Journal of Bone and Mineral Research, Osteoporosis International, Journal of Bone and Joint Surgery,* and *Diabetes and Diabetes Care*), and searched for articles that cited the included articles using the Web of Science. To ensure that pre-2005 articles using modalities other than DXA (including QCT, pQCT, HR-pQCT, and QUS) were not overlooked, we also performed an exploratory search of the databases listed above. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Our search strategy was [*bone* and *bones (MeSH)* or *bone density (MeSH)* or "*bone density*" or "*bone mineral density*" or "*bone geometry*" or "*bone quality*" or "*bone*

structure" or "*bone mass*" or *osteoporo** or *pQCT* or "*peripheral quantitative computed tomography*" or *QCT* or "*quantitative computed tomography*" or *DXA* or *DEXA* or "*dual energy X-ray absorptiometry*" or *ultrasound* or *HR-pQCT* or *Xtreme CT*] AND [*Type 2 Diabetes Mellitus (MeSH)* or *diabetes*]. If the MeSH option was not available, we used the equivalent subject heading if available. We limited our search to English language, human studies, the years 2005–2010, and adults aged ≥ 60 years.

Study Selection

We included all studies that assessed BMD (aBMD by DXA or volumetric BMD (vBMD) by QCT, pQCT, or HR-pQCT) or other bone-imaging outcomes (e.g., estimates of bone strength, structure, quality, geometry) of the lower extremity in older adults (mean age ≥ 60 years) with T2DM and compared the results with a healthy control group. We did not include any studies that reported bone-turnover markers only or in which the population was selected based on the presence of complications associated with increased fracture risk. Only studies not included in the previous systematic review[1] were included in our study. All articles retrieved from the search were first reviewed independently for relevance by two reviewers (AMC, EG), based on title and abstract. Articles that were not included were assigned a reason for exclusion (not relevant, population not older adults, no healthy control group, etc.). Articles obtained for full-text review were assessed independently by two reviewers (AMC, EG), and inclusion in the review was then decided by consensus. A third reviewer (MCA) resolved any discrepancies that arose.

Data Extraction and Quality Assessment

Data were extracted independently for all included articles by two reviewers (AMC, EG) and then checked by a third reviewer (MCA). Discrepancies were resolved through discussion among all three reviewers. Only published results were used, and the outcomes reported were extracted as stated in the articles; we used baseline data for prospective studies. We extracted data on the population; diabetes duration; haemoglobin A_{1C} level (HbA_{1C}), a measure that reflects glycemic control over the preceding months ($HbA_{1c} < 7\%$ is considered to indicate good glycemic control);[19] and bone-imaging outcomes. We also looked within each study for variables that could potentially have an impact on bone health and consequently bias the outcome; we report adjusted results when available, and whether they were adjusted for age and BMI. Note that the models may have adjusted for other variables that were not included and are beyond the scope of this review.

The methodological quality of all included articles was assessed using a checklist modified from the Newcastle–Ottawa Quality Assessment Scale (NOS).[20,21] The checklist included items evaluating the representativeness of the study group, selection of the comparison group, ascertainment of exposure, comparability of cohorts on the basis of the design or analysis, and assessment of outcome. We did not include questions related to follow-up of cohort studies (demonstration that outcome of interest was not present at start of study, follow-up was long enough for outcomes to occur, and follow-up of cohorts was adequate). Items were given a score of 0 or 1, except for the comparability of cohorts, where there was a possibility of 0, 1, or 2, and the scores were summed to produce an overall quality score (/6). Two reviewers (AMC, EG) independently rated the quality of the studies and then came to a consensus on the final score for each one. A third reviewer (MCA) resolved any discrepancies that arose.

Statistical Analysis

We calculated the consistency between reviewers for the quality assessment. Kappa values were calculated for interrater reliability for each of the five checklist items. Intra-class correlation coefficients (ICC) were calculated for overall score rating between the two reviewers for each article included in the systematic review. We used Stata Software, version 11 (StataCorp, College Station, TX), to calculate reliability statistics.

We proposed to pool results from single studies by meta-analysis where this was found to be both clinically and statistically appropriate. Pooled estimates of effect were provided if there were at least three studies assessing identical bone-imaging outcome measures in the same anatomical site and if statistical heterogeneity (defined as $p < 0.10$ and $I^2 > 75\%$[22]) was not present. Statistical heterogeneity was assessed using the χ^2 test and the I^2 statistic. Since our outcome variables were continuous and were measured on the same scale across studies, we proposed to use the mean difference between the outcome variables for older adults with and without T2DM to calculate summary statistics of effect and 95% confidence intervals, where appropriate.[22] We used Comprehensive Meta-Analysis Software, version 2.2.050 (Biostat, Englewood, NJ), to create forest plots.

RESULTS

The search strategy retrieved a total of 1,526 studies; of these, 13 were included in this review (see Figure 1). As mentioned above, this study is an update of a previous systematic review by Vestergaard;[1] since the previous search was limited to studies that used DXA, we performed an exploratory search for articles published before 2005 that used other modalities such as QCT, pQCT, HR-pQCT, and QUS, but this search yielded no new articles that were determined to be relevant to the current systematic review. As a result, only the 13

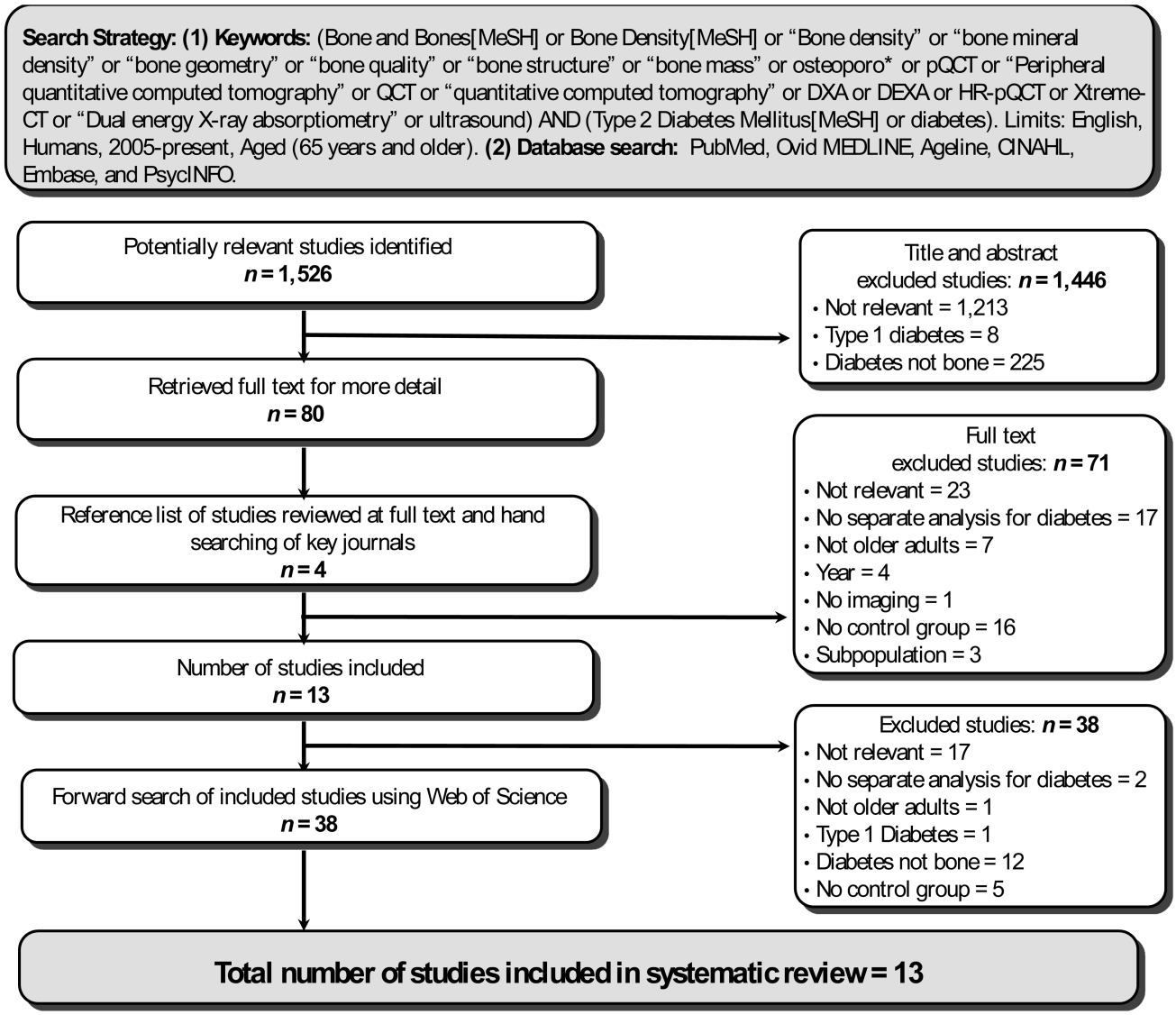

Figure 1 Flow diagram of studies considered for inclusion in the systematic review

studies yielded by the initial search were considered relevant for inclusion: six that investigated the bone health of women, two that investigated the bone health of men, and five that included both men and women. The mean age of study participants ranged from 62 to 77 years for older adults with T2DM and from 60 to 77 years for control groups. The duration of T2DM reported ranged from 6.5 to 13.5 years, and BMI ranged from 22.9 to 33.1 kg/m^2 for older adults with T2DM and from 22.0 to 33.6 kg/m^2 for control groups. Demographic information was extracted only for those participants with bone-imaging data. The majority of these studies used DXA to compare the bone health of older adults with and without T2DM; there were two studies that used QUS, one that used pQCT, and one that used QCT. Eight of the studies were cross-sectional, four were prospective cohorts, and one was a retrospective cohort; only baseline data are presented for cohort studies. The studies included were from Turkey, the United States, Croatia, China, Spain, Australia, and Japan and included different ethnic groups (see Table 1).

As noted above, the quality of the studies was rated using the modified NOS checklist, for a total score out of 6. The consistency between raters for individual questions was 0.83 for item 1, 0.76 for item 2, 0.69 for item 3, 0.40 for item 4, and 1.0 for item 5 (ICC = 0.773, $p < 0.001$). The quality scores for the included articles ranged from 1 to 6, with a median score of 4.

Eleven of the included studies used DXA to determine aBMD (T2DM $n = 4813$, control $n = 12693$)[23–33] at either the total hip or the femoral neck site. Of these DXA studies, seven controlled for age[23,27,29–33] and four for

Table 1 Summary and quality assessment of studies included in the systematic review ($n = 13$)

*Study Country Study Design*** Quality Score*	*Population*					*Imaging Reported Region*	*Outcome (mean ± SD) or (mean, 95% CI)*	*Statistical Comparison*
	n	*Age*	*Gender (F/M)*	*BMI (kg/m^2)*	*Diabetes Duration (years)*			
Women								
Anaforoglu (2009)[23] Turkey Cross-sectional 5/6	T2DM: 206 Control: 61	T2DM: 61.9 ± 8.6 Control: 60.1 ± 9.3	T2DM: 206/0 Control: 61/0	T2DM: 30.4 ± 5.1 Control: 28.0 ± 4.5	T2DM: 10.3 ± 8.2 –	DXA Femoral Neck, Total Hip	T2DM: FN aBMD 0.77 ± 0.11 Total Hip aBMD 0.92 ± 0.13 Control: FN aBMD 0.73 ± 0.12 Total Hip aBMD 0.89 ± 0.13	*t*-test; Mann-Whitney *U*-test Age matched and adjusted for BMI and calcium intake No significant difference between groups
Bonds (2006)[25****] USA Prospective cohort 4/6	T2DM: 469 Control: 5915	Not reported Not reported	T2DM: 469/0 Control: 5951/0	Not reported Not reported	Not reported –	DXA Hip*	T2DM: Hip aBMD 0.90 ± 0.16 Control: Hip aBMD 0.84 ± 0.14	ANOVA Corrected for multiple scanners T2DM higher aBMD ($p < 0.01$)
Hadzibegovic (2008)[26] Croatia Retrospective 2/6	T2DM: 130 Control: 166	T2DM: 67(45–80) Control: 67(41–84)	T2DM: 130/0 Control: 166/0	T2DM: 29.3 ± 4.5 Control: 28.3 ± 4.1	Not reported –	DXA Femoral Neck	T2DM: FN aBMD 0.870 ± 0.132 Control: FN aBMD 0.832 ± 0.134	*t*-test T2DM higher aBMD ($p < 0.05$)
Shan (2009)[27] China Cross-sectional 5/6	T2DM: 1042 Control: 919	T2DM: 62.2 ± 7.1 Control: 61.2 ± 8.2	T2DM: 1042/0 Control: 919/0	T2DM: 23.6 ± 3.4 Control: 23.5 ± 3.3	T2DM: 6.6 ± 6.1 –	DXA Femoral Neck, Total Hip	T2DM: FN aBMD0.641 ± 0.111 Total hip aBMD 0.711 ± 0.125 Control: FN aBMD 0.644 ± 0.11 Total hip aBMD 0.715 ± 0.128	ANOVA Age matched No significant difference between groups
Sosa (2009)[28] Spain Prospective cohort 1/6	T2DM: 111 Control: 91	T2DM: 71.5 ± 5.0 Control: 69.9 ± 4.2	T2DM: 111/0 Control: 91/0	T2DM: 33.1 ± 4.1 Control: 33.6 ± 4.7	Not reported –	DXA Femoral Neck QUS Calcaneus	T2DM: FN aBMD 0.757(0.733–0.781) SOS 1537(1531–1543) Control: FN aBMD 0.733(0.707–0.759) SOS 1532(1526–1538)	*t*-test DXA: No significant differences between groups ($p = 0.189$) QUS SOS: No significant differences between groups ($p = 0.249$)
Tao (2008)[29] China Cross-sectional 4/6	T2DM: 76 Control: 86	T2DM: 64.1 ± 9.3 Control: 66.5 ± 6.5	T2DM: 76/0 Control: 86/0	T2DM: 24.2 ± 3.8 Control: 24.1 ± 4.1	T2DM: 10.1 ± 7.3 –	DXA Femoral Neck, Total Hip QUS Midshaft tibia	T2DM: FN aBMD 0.80 ± 0.13 Total Hip aBMD 0.87 ± 0.14 SOS 3815 ± 148 Control: FN aBMD 0.74 ± 0.12 Total Hip aBMD 0.80 ± 0.13 SOS 3845 ± 139	*t*-test Adjusted for age and BMI DXA FN and Total Hip higher in T2DM ($p < 0.001$) QUS SOS: No significant differences between groups ($p > 0.05$)

(Continued)

Table 1 (Continued)

*Study Country Study Design*** Quality Score*	*Population*					*Imaging Reported Region*	*Outcome (mean ± SD) or (mean, 95% CI)*	*Statistical Comparison*
	n	*Age*	*Gender (F/M)*	*BMI (kg/m^2)*	*Diabetes Duration (years)*			
Men								
Petit (2009)[35] USA Prospective cohort 5/6	T2DM: 190	T2DM: 76.9 ± 4.8	T2DM: 0/190	T2DM 29.9 ± 4.5	Not reported	pQCT Tibia (4%, 66%)	T2DM: 4% Tibia Total vBMD Model 1—305(298–312) Model 2—303 (296–310) BSI Model 1—120 (115–125) Model 2—116 (111–121) T2DM 66% Tibia Section Modulus Model 1—3386 (3304–3468) Model 2—3298 (3219–3377)	Linear regression models Model 1 adjusts for age, race and tibia length Model 2 adjusts for age, race, tibia length and body weight 4%-Model 1: T2DM had higher total and BSI ($p < 0.05$) Model 2: T2DM had lower total area ($p < 0.05$) Model 2: 66% tibia T2DM had lower total area and section modulus ($p < 0.05$)
	Control: 981	Control: 77.3 ± 5.2	Control: 0/981	Control: 27.6 ± 3.8	–		Control 4% Tibia Total vBMD Model 1—297 (294–300) Model 2—297 (294–300) BSI Model 1—114 (112–116) Model 2—115 (113–117) Control 66% Tibia Section Modulus Model 1—3375 (3340–3411) Model 2—3392 (3358–3426)	
Yaturu (2009)[30] USA Cross-sectional 3/6	T2DM: 550 Control: 550	T2DM: 67.2 ± 0.4 Control: 67.5 ± 0.4	T2DM: 0/550 Control: 0/550	T2DM: 31.1 ± 0.2 Control: 31.0 ± 0.1	Not reported –	DXA Femoral Neck	T2DM: FN aBMD 0.882 ± 0.009 Control: FN aBMD 0.952 ± 0.08	*t*-test Age, BMI, smoking and alcohol history matched FN aBMD was significantly lower in T2DM ($p < 0.01$)
Women and Men								
Broussard (2008)[31] USA Cross-sectional 3/6	T2DM: 962	T2DM: F: 64.7 ± 0.5 M: 64.0 ± 0.7	T2DM: 512/450	T2DM: BMI ≥ 30 F: 54.1% M: 41.6%	Not reported	DXA Total Hip	T2DM: Total Hip aBMD F: 0.848 ± 0.010 M: 1.008 ± 0.010	Logistic regression Adjusted for age and race/ethnicity Both men and women with T2DM had higher BMD ($p < 0.001$)
	Control: 3967	Control F: 62.6 ± 0.3 M: 62.0 ± 0.3	Control: 1993/1974	Control: BMI ≥ 30 F: 27.4% M: 22.6%	–		Control: Total Hip aBMD F: 0.810 ± 0.004 M: 0.954 ± 0.006	

(Continued)

Table 1 (Continued)

Study Country *Study Design**** *Quality Score*	*Population*					*Imaging* *Reported* *Region*	*Outcome* *(mean ± SD) or* *(mean, 95% CI)*	*Statistical Comparison*
	n	*Age*	*Gender* *(F/M)*	*BMI* *(kg/m^2)*	*Diabetes* *Duration* *(years)*			
Melton (2008)[34] USA Cross-sectional 5/6	T2DM: 49	T2DM: 72.2 ± 11.6	T2DM: 28/21	T2DM: 29.8 ± 6.2	T2DM: Median 6.5	QCT Femoral Neck	T2DM: F: aBMD 0.68 ± 0.15, Cortical vBMD 573 ± 76, Ratio** 1.6 ± 0.3 M: aBMD 0.69 ± 0.15, Cortical vBMD 522 ± 69, Ratio** 1.1 ± 0.2	Logistic regression Age matched and adjusted for BMI Women with T2DM had higher aBMD and cortical vBMD ($p < 0.05$) No significant differences between groups for men
	Control: 49	Control: 72.2 ± 11.6	Control: 28/21	Control: 27.6 ± 4.6	–		Control: F: aBMD 0.57 ± 0.11, Cortical vBMD 522 ± 67, Ratio** 1.8 ± 0.3 M: aBMD 0.65 ± 0.14, Cortical vBMD 526 ± 72, Ratio** 1.1 ± 0.4	
Rakic (2006)[32] Australia Prospective cohort 3/6	T2DM: 194	T2DM: F: 65.5 ± 9.6 M: 66.0 ± 9.1	T2DM: 86/108	T2DM: F: 31.9 ± 6.1 M: 29.0 ± 4.4	T2DM: F: 9.1 (7.1–11.9) M: 8.7 (6.9 –12.7)	DXA Femoral Neck, Total Hip	T2DM: F: FN aBMD 0.808 ± 0.153 Total Hip aBMD 0.993 ± 0.173 M: FN aBMD 0.851 ± 0.128 Total Hip aBMD 1.060 ± 0.156	General linear modelling Adjusted for age and BMI For women Total Hip ($p = 0.006$) and FN aBMD ($p = 0.026$) were higher for T2DM For men Total Hip ($p = 0.88$) and FN BMD ($p = 0.34$) no significant differences
	Control: 194	Control: F: 64.8 ± 11.1 M: 66.3 ± 9.6	Control: 86/108	Control: F: 25.1 ± 3.5 M: 25.9 ± 3.0	–		Control: F: FN aBMD 0.722 ± 0.103 Total Hip aBMD 0.848 ± 0.118 M: FN aBMD 0.802 ± 0.129 Total Hip aBMD 1.013 ± 0.158	

(Continued)

Table 1 (Continued)

*Study Country Study Design*** Quality Score*	*Population*					*Imaging Reported Region*	*Outcome (mean ± SD) or (mean, 95% CI)*	*Statistical Comparison*
	n	*Age*	*Gender (F/M)*	*BMI (kg/m^2)*	*Diabetes Duration (years)*			
Register (2006)[33] USA Cross-sectional 6/6	T2DM: 775	T2DM: 62.6 ± 9.0	T2DM: 410/365	T2DM: 32.2 ± 6.5	T2DM: 11.7 ± 7.6	DXA Total Hip	T2DM: M: Total Hip aBMD 1.027 ± 0.009 F: Total Hip aBMD 0.954 ± 0.008	General estimating equation Adjusted for age For women Total Hip was higher in T2DM ($p < 0.001$) There were no significant differences for the men ($p = 0.37$)
	Control: 106	Control: 60.0 ± 10.3	Control: 73/33	Control: 28.9 ± 6.0	–		Control: M: Total Hip aBMD 1.000 ± 0.029 F: Total Hip aBMD 0.891 ± 0.016	
Yamamoto (2009)[24] Japan Cross-sectional 3/6	T2DM: 298	T2DM: F: 67.5 ± 9.8 M: 66.0 ± 8.1	T2DM: 137/161	T2DM: F: 24.5 ± 4.5 M: 22.9 ± 3.0	T2DM: F:13.5 ± 9.9 M:12.5 ± 9.3	DXA Femoral Neck	T2DM: F: FN aBMD 0.641 ± 0.120 M: FN aBMD 0.748 ± 0.119	*t*-test FN aBMD was higher for T2DM in men and women ($p < 0.01$)
	Control: 698	Control: F: 65.9 ± 8.3 M: 67.6 ± 8.8	Control: 622/76	Control: F: 22.0 ± 3.0 M: 22.1 ± 3.2	–		Control: F: FN aBMD 0.602 ± 0.102 M: FN aBMD 0.692 ± 0.103	

BMD = bone-mineral density (g/cm2); aBMD = areal BMD; vBMD = volumetric BMD; BMI = body mass index (kg/m2); BSI = bone strength index; BUA = broadband ultrasound attenuation (dB/mHz); DXA = dual energy X-ray absorptiometry; FN = femoral neck; pQCT = peripheral quantitative computed tomography; QCT = quantitative computed tomography; QUI = quantitative ultrasound index; QUS = quantitative ultrasound; SOS = speed of sound (m/s); T2DM = type 2 diabetes mellitus; M = male; F = female

* Study reported BMD measurement site as the hip. This was interpreted as total hip.

** Ratio (fall load / flexural rigidity)

*** Baseline data presented for prospective and retrospective cohort studies.

**** Demographic information was extracted only for participants with bone-imaging data.

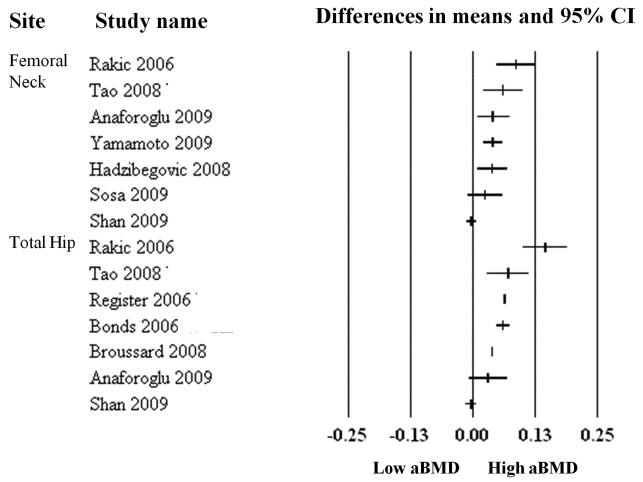

Figure 2 Forest plot of mean differences of areal bone-mineral density for women with and without T2DM

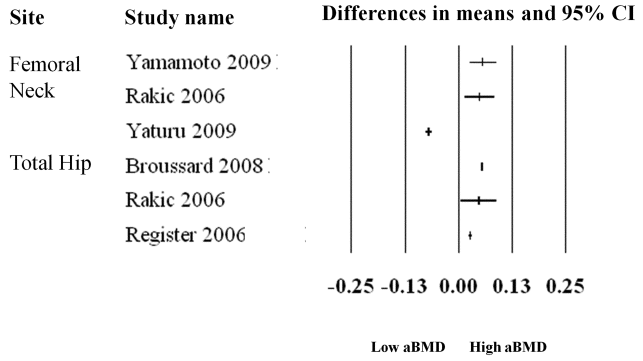

Figure 3 Forest plot of mean differences of areal bone-mineral density for men with and without T2DM

BMI.[23,29,30,32] Women with T2DM had a significantly higher aBMD at the total hip in five studies,[25,29,31–33] of which two controlled for age[31,33] and two controlled for both age and BMI;[23,29] two studies showed no significant difference,[23,27] both of which controlled for age and one of which also controlled for BMI.[23] Femoral neck aBMD was significantly higher for older women with T2DM in four studies,[24,26,29,32] two of which controlled for both age and BMI.[29,32] Femoral neck aBMD did not show a significant difference in three studies,[23,27,28] of which two controlled for age[27,28] and one controlled for both age and BMI.[23] For men, aBMD at the total hip site did not differ significantly between those with T2DM and healthy controls in two studies[32,33] (one of which controlled for age and BMI,[33] while the other controlled for age only[32]) and was significantly lower for those with T2DM in one study, which controlled for age.[31] Areal BMD at the femoral neck was significantly higher for men with T2DM in one study,[24] which did not adjust for age or BMI; was not significantly different in another study,[32] which adjusted for both age and BMI; and was significantly lower in a third study,[30] which adjusted for both age and BMI. The DXA results are displayed in separate forest plots for women (Figure 2) and men (Figure 3). We were unable to combine these results by meta-analysis because there was significant heterogeneity between the studies ($I^2 > 75\%$). No other summary of effects could be calculated for the studies that used advanced imaging, as there were too few such studies available.

Two studies used QUS[28,29]; both investigated women only (T2DM $n = 187$, control $n = 177$). Sosa et al.[28] investigated the calcaneus, while Tao et al.[29] investigated bone health at the midshaft tibia. No significant differences were found in the speed of sound (SOS) at the calcaneus or the midshaft tibia, regardless of whether variables such as age and BMI were controlled for[29] or not.[28]

Quantitative CT was used in one study,[34] which assessed aBMD and cortical vBMD at the femoral neck of both men and women (T2DM $n = 49$, control $n = 49$); participants were age matched, and the results were adjusted for BMI. Women with T2DM had higher aBMD and vBMD than controls, but there were no significant differences between men with and without T2DM. When the results were combined for men and women, this study found a higher vBMD, aBMD, and cortical vBMD for persons with T2DM. There were no significant differences between groups in the load-to-strength ratio, which is the relationship between the load that is encountered with a fall at the hip and the estimated strength of the bone (as the ratio increases, fracture risk also rises).

Peripheral QCT of the distal and proximal tibia was used in one study of men only (T2DM $n = 190$, control $n = 981$).[35] This study found a significantly higher total vBMD, trabecular vBMD, and bone strength index (BSI) in participants with T2DM at the distal end of the tibia (4% site) after adjusting for age, race, and tibia length. When body weight was also accounted for, however, the only significant finding was a lower total cross-sectional area for men with T2DM. At the midshaft tibia (66% site), men with T2DM had significantly lower total area and section modulus (an estimate of bone strength) only after adjusting for age, race, tibial length, and body weight.

DISCUSSION

The present systematic review found that studies using DXA observed higher or similar aBMD for older adults with T2DM relative to controls, and that there is limited evidence to suggest that there may be differences in the bone geometry of older adults with T2DM that may not be captured by DXA. DXA provides a global view of bone health but is limited in its ability to sepa-

rate bone compartments and estimate bone strength. The majority of studies included in this review used DXA to investigate bone health, and all but one[30] showed either no significant difference or higher aBMD for older adults with T2DM. This finding is consistent with those of previous reviews.[1,36] Vestergaard[1] found a significantly higher hip aBMD for individuals with T2DM; 13 of the included articles looked specifically at older adults, and these studies were consistent with this trend.[37–49] In our review, the two studies using QUS[28,29] showed no significant differences between older adults with T2DM and healthy controls; however, studies using advanced imaging (pQCT and QCT) showed mixed findings for older adults with T2DM, suggesting that there may be changes in bone geometry.[34,35] Although further research with advanced imaging is needed to determine what mechanism is at work, the previously reported increased risk of fracture among individuals with T2DM[1,2] is not congruent with the DXA results documented in this review, which suggests that DXA results alone may not provide enough information to determine fracture risk for older adults with T2DM. This finding may have important clinical implications for health care professionals and is especially noteworthy for physiotherapists who may be involved in the care of older adults with T2DM and/or work in the area of fall and fracture prevention.

The bone health of older adults with T2DM may be influenced by many factors; for example, BMI was found to be a major determinant of aBMD for T2DM.[1] Shan et al.[27] performed an analysis with sub-groups based on BMI classifications (underweight, normal weight, and overweight/obese) and found that among individuals with T2DM, those who were obese had the highest aBMD, while those who were underweight had the lowest aBMD of all groups, relative to healthy controls. However, there is some evidence to suggest that body mass may affect the accuracy of DXA scan images; in particular, increased BMI may lead to overestimation of aBMD.[50] Because over 65% of adults with T2DM have metabolic syndrome,[51] which is characterized by abdominal obesity, this possibility should be considered when interpreting the results of DXA scan images. Only four of the DXA studies reviewed here controlled for BMI,[23,29,30,32] and all but one[30] showed a similar trend of higher or similar aBMD in older adults with T2DM. Body size was also controlled for in the QCT[34] and pQCT[35] studies. Petit et al. performed two linear regression models, one with and one without adjustment for body size; results differed between the two models.[35] Among studies that did not control for BMI, three found significant differences in BMI between control and T2DM groups; in all three studies, T2DM groups had a higher BMI.[24,31,33] However, three other studies produced mixed results: Broussard and Magnus[31] found higher aBMD in the T2DM group; Register et al.[33] reported higher aBMD for women with T2DM, but no significant difference for men; and Yamamoto et al.[24] found higher aBMD in older adults with T2DM. The discrepancy in results between studies done with DXA and those using pQCT or QCT may be due to the resolution of the imaging and to the fact that pQCT and QCT are able to distinguish between bone compartments and to estimate bone strength.

There are many other variables that may affect aBMD in older adults with T2DM, including the severity, duration, and management of the disease. For example, Vestergaard's systematic review found that diabetes duration was a significant predictor of aBMD, while age and HbA_{1C} levels were not.[1] Disease severity is proposed to affect bone and HbA_{1C} levels, although Vestergaard's review did not show a significant association between HbA_{1C} and either aBMD or fracture risk.[1] Disease duration may also have an effect on hip-fracture risk,[52] possibly because of the prolonged effects of impaired glycemic control; the earlier review found disease duration to be a significant predictor of aBMD.[1] In the present review, seven studies reported HbA_{1C} levels,[23,24,28,29,32–34] of which four performed additional analysis to determine the impact of HbA_{1C} level on aBMD[23,29,32,33]; two studies[32,33] found a negative association between aBMD and HbA_{1C}. Seven of the included studies reported diabetes duration,[23,24,27,29,32–34] of which five did a further analysis to determine the impact of diabetes duration on aBMD.[23,27,29,32,33] Only one study found a significant negative association between duration of disease and aBMD at the total hip and femoral neck.[23] Management of T2DM can include diet and lifestyle modifications, oral anti-diabetic medication, and/or insulin; although medications may influence bone health in T2DM, participants' medications were not consistently reported in the included studies, and this factor is beyond the scope of the present review.

Gender is also an important factor when comparing bone health, and all studies included in this review completed separate analyses for men and women. Women, in general, have higher rates of fracture and lower aBMD than men. This is hypothesized to be the result of men's having larger bones (as a result of differences in sex-hormone production), which increases bending strength.[53] For women, all studies included in this review showed either a higher or a similar aBMD in individuals with T2DM relative to those without T2DM. All but one study[30] included in our review showed either a higher or a similar aBMD for older men with T2DM relative to older men without T2DM; fewer studies have investigated the bone health of men with T2DM. Petit et al.[35] suggested that for men, there may be differences in bone geometry related to the presence of T2DM; they observed decreased total bone area and section modulus in the tibia after adjusting for body size.[35] The other study to use advanced imaging was by Melton et al.,[34]

who investigated both men and women and found no significant differences for men and higher cortical vBMD for women with T2DM relative to healthy controls.

Ethnicity should also be considered when assessing bone health. In the United States, according to population-level data, osteoporosis is more prevalent among white women[54] and men.[55] Araujo et al. reported higher aBMD in black men than in white and Hispanic men;[56] Asian adults have lower aBMD than white adults, and this is thought to be due to their smaller body size.[57] In the present review, only three studies reported the ethnicity of participants[31,33,35]; all were from the United States, and all but Petit et al.'s[35] study found a significantly lower proportion of white older adults in the T2DM group. Broussard and Magnus[31] was the only study to control for ethnicity in their analyses; these authors found that it was not significantly associated with low aBMD. The Health, Aging, and Body Composition (Health ABC) Study compared aBMD in older adults with T2DM between white and black men and women; they found ethnicity to be a significant predictor of total hip aBMD and found that black men with T2DM had the highest aBMD.[58]

Evidence for changes in bone microstructure[34,35] associated with T2DM is found in a number of animal studies.[13–15] Moreover, research suggests that hyperglycemia associated with T2DM can alter bone turnover[59] and may impair vitamin D and calcium metabolism[17]—which can also affect the integrity of bone for older adults with T2DM. Other factors that can affect bone quality include advanced glycation end products (AGEs), which result in changes to bone collagen.[16,60]

Although bone health is a key component of fracture risk, the contribution of falls should also be considered. Studies have shown that older adults with T2DM are at increased risk of falling.[12,25,61] Diabetic complications such as neuropathy and neuromuscular impairment, retinopathy, foot problems, cognitive decline, and multiple medications contribute to this increased risk of falls.[7,62] Despite this increased risk, however, the literature highlights the fact that the higher risk of fractures remains even after the increased fall risk has been accounted for.[25]

Regardless of the mechanism of increased fracture risk, assessing fall risk, promoting exercise, and reducing sedentary behaviour are important for older adults in general, and especially for those with T2DM. Exercise is important for fall prevention (through increasing muscle balance and strength),[63] bone health,[64] and cardiovascular health,[65] and it may help in managing and preventing related T2DM complications.

Limitations

We note several limitations of our review. First, we included only articles written in English. Second, we were limited by the available evidence on bone strength as estimated by advanced imaging (QCT and pQCT). We were also limited by the amount of heterogeneity among the studies, which prevented us from carrying out a meta-analysis on these data. Future research needs to collect and report sample demographics, which may have an impact on bone-imaging outcomes. In particular, BMI; ethnicity; and diabetes severity, duration, and management should be reported and investigated through sub-group analyses when possible. Lastly, this review included only studies that looked at bone health of the lower extremity; we chose this site specifically because it is clinically relevant to the hip. Although some studies looked only at the tibia, we note that the lower limb should have similar loading patterns as the hip.

Conclusion

The results of this study extend the existing knowledge on T2DM and bone health. Areal BMD measured by DXA has limitations, and future research of the bone health of older adults with T2DM should include advanced imaging to investigate bone at the microstructural level. In addition, other risk factors such as BMI and disease progression may influence bone health for older adults with T2DM. Because fracture risk is influenced by both bone health and fall risk, however, clinicians who work with this population should be aware of the potential risk factors and should develop effective strategies to determine the influence of underlying diabetic complications, especially on balance and strength. More prospective studies on fall risk factors and bone health in older adults with T2DM are needed.

KEY MESSAGES

What Is Already Known on This Topic

People with T2DM are at greater risk of hip fracture relative to the healthy population.

What This Study Adds

This study shows that areal BMD may not completely capture bone health in older adults with T2DM and that changes in bone, if any, may be explained through bone microstructure changes related to T2DM.

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