Journal of Diabetes and Its Complications 33 (2019) 107324

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Bone mineral density in patients with longstanding type 1 diabetes: Results from the Canadian Study of Longevity in Type 1 Diabetes

Omar N. Alhuzaim [a,b,1], Evan J.H. Lewis [c,1], Leif E. Lovblom [c], Marina Cardinez [c], Daniel Scarr [c], Genevieve Boulet [c], Alanna Weisman [b,c], Julie A. Lovshin [b,d], Yuliya Lytvyn [d], Hillary A. Keenan [e], Michael H. Brent [f], Narinder Paul [g], Vera Bril [h], David Z.I. Cherney [d], Bruce A. Perkins [b,c,*]

[a] Obesity, Endocrine and Metabolism Center, King Fahad Medical City, Riyadh, Saudi Arabia
[b] Division of Endocrinology and Metabolism, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[c] Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
[d] Division of Nephrology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[e] Research Division, Joslin Diabetes Center, Boston, MA, USA
[f] Department of Ophthalmology and Vision Sciences, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[g] Joint Department of Medical Imaging, Division of Cardiothoracic Radiology, University Health Network, Toronto, Ontario, Canada
[h] The Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Krembil Neuroscience Centre, Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 11 October 2018
Received in revised form 13 December 2018
Accepted 14 December 2018
Available online 22 December 2018

Keywords:
Bone
Bone mineral density
Fragility fracture
Type 1 diabetes
Diabetes complications

ABSTRACT

Aim: It is currently unclear if longstanding type 1 diabetes (T1D) affects bone mineral density (BMD).
Methods: BMD measured by dual-energy X-ray absorptiometry and history of fragility fracture was determined in 75 T1D participants with ≥50 years of diabetes duration and 75 age- and sex-matched non-diabetic controls. BMD T-scores were determined for the lumbar spine (LS), total hip (TH) and femoral neck (FN).
Results: T1D participants had median diabetes duration of 54 [52, 58] years, 41 (55%) were females, and mean A_{1c} was 7.3 ± 0.8%. T1D females had higher LS T-scores compared to female controls (−0.3 ± 1.2 vs. −1.1 ± 1.4, p = 0.014), lower FN T-scores (−1.5 ± 1.0 vs. −1.2 ± 0.9, p = 0.042) and more fragility fractures (7 (17%) vs. 1 (2%), p = 0.021). In T1D, higher A1c was associated with higher adjusted odds of fragility fracture (p = 0.006). T1D males and controls showed no difference in BMD or fractures.
Conclusions: There were no substantial differences in T-score between T1D and matched controls; however, T1D females showed higher BMD at the LS and possibly paradoxically higher fragility fractures compared to matched controls. These findings suggest that lower T-scores may not be associated with a history of fragility fracture in females with longstanding T1D and that other factors should be investigated.

1. Introduction

Longstanding type 1 diabetes (T1D) is associated with increased risk of diabetes-associated complications from chronic exposure to hyperglycemia. While it is generally known that diabetes is associated with altered bone metabolism, investigation of changes in bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) suggests that T1D is associated with lower BMD at one or more sites compared to matched non-diabetic controls.[1–6] It is thought that reductions in BMD might occur early on in the natural history of T1D[4,7–9]; however, there has been limited investigation of bone health in longstanding T1D. To date a study from the Joslin Medalist cohort is the first to reported no difference in BMD compared to controls.[10]

While associations between diabetes complications and reduced BMD have been identified, the risk factors associated lower BMD and subsequent fracture risk in T1D is not completely understood.[8,11–13]

Conflicts of interest: B.A.P. has received speaker honoraria from Medtronic Inc., Johnson and Johnson, Roche, Glaxo Smith Kline Canada, Novo Nordisk and Sanofi; has received research grant support from Medtronic and Boehringer-Ingelheim; and serves as a consultant for Neurometrix. D.Z.I.C. has received speaker honoraria from Janssen, AstraZeneca, Boehringer-Ingelheim, Lilly and Merck and has received research grant support from AstraZeneca, Merck and Boehringer-Ingelheim. E.J.H.L. is part owner and President of Nutarniq Corp., which researches and develops targeted nutritional therapies for chronic diseases and disease complications. J.A.L. has received grants from Sanofi and Merck, and speaking honorarium and/or consulting fees from Novo Nordisk, Eli Lilly, Merck, and AstraZenca. The remaining authors have no relevant disclosures.

* Corresponding author at: Endocrinology and Metabolism, Department of Medicine, University of Toronto; Lunenfeld-Tanenbaum Research Institute, Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, L5209-60 Murray Street Box 16, Toronto, Ontario M5T3L9, Canada.
E-mail address: bruce.perkins@sinaihealthsystem.ca (B.A. Perkins).
[1] Co-first authors.

https://doi.org/10.1016/j.jdiacomp.2018.12.009
1056-8727/

Furthermore, there are conflicting reports on the impact of poor glycemic control on BMD.[4,5,11,14–16] As such, the mechanisms behind increased risk of fragility fracture in T1D has not yet been determined, although several factors have been suggested, including poor glycemic control[1,17,18] and presence of diabetes-related complications including retinopathy and neuropathy.[17,19]

Though T1D is generally seen as a risk factor for fracture, it is presently not known with certainty if longstanding T1D affects bone health.[20] In this light, we aimed to report on BMD, the incidence of fragility fractures and associated factors as an exploratory analysis in the Canadian Study of Longevity in Type 1 Diabetes.

2. Materials and methods

2.1. Study design

The present study is an analysis of baseline data collected from the Canadian Study of Longevity in Type 1 Diabetes, and represents a cross-sectional study of adults living with T1D for ≥50 years. The first objective of the main study was to establish a baseline mail-based national registry to determine factors associated with the development of complications associated with longstanding disease duration[21–23]; the second was to phenotype complications in a portion of these individuals in hospital (along with age- and sex-matched controls).[24–28] Between February 2015 and September 2016, 75 participants with ≥50 years of T1D and 75 age- and sex-matched non-diabetic controls participated in phase 2 of the study. Participants underwent extensive phenotyping procedures over the course of 2 visits set 2–4 weeks apart.[21] Participant search criteria from the registry for the second phase included those living in the Greater Toronto Area (i.e. proximity to the University Health Network and Mount Sinai Hospital in Toronto, Ontario, Canada where the study was conducted), or a willingness to travel for two requisite study days. Non-diabetic controls were sex-matched 1:1 and age-matched within five years of a T1D participant. These matched controls were typically spouses, family or friends of study participants. Exclusion criteria common to both non-diabetic controls and T1D participants were specific to phenotyping procedures which were not the focus of this manuscript and included 1) any current eye infection, corneal damage, severe movement disorder, or proparacaine allergy to preclude safe corneal confocal microscopy examination and 2) blood pressure >140/90 mm Hg to preclude angiotensin II infusion procedures. The purpose of the current exploratory analysis was to characterize BMD as measured by DXA and to describe the prevalence of bone fragility facture among longstanding T1D participants as compared to age-and sex-matched non-diabetic controls. All participants provided written informed consent, and the study and its procedures were approved by the institutional ethics board at the University Health Network and Mount Sinai Hospital in Toronto, ON, Canada.

2.2. Study procedures and diabetes complication definitions

Participants underwent review of medical history, physical exam, BMD, and completed an additional questionnaire specific to bone health. On day two, participants underwent objective neurological testing including nerve conduction study and corneal nerve fibre length (CNFL) testing, renal hemodynamic function study and coronary artery calcification scoring at Cardiac CT Unit. Blood samples were collected for biochemical analysis of standard clinical parameters including: A_{1c}, lipid profile, calcium, parathyroid hormone (PTH), phosphate, alkaline phosphatase, electrolytes, serum creatinine, estimated glomerular filtration rate (eGFR), spot albumin/creatinine ratio (ACR), thyroid stimulating hormone (TSH) and estradiol using standard University Health Network procedures analyzed on Abbott Architect Chemistry Analyzer (Abbott, Illinois USA).

Diabetic neuropathy was defined according to Toronto consensus criteria (abnormal nerve conduction study in two nerves, plus the presence of neuropathic signs and/or symptoms). Diabetic nephropathy was defined based on the presence of albuminuria according to an albumin-to-creatinine ratio (ACR) >2 mg/mmol as well as stage 3 chronic kidney disease (CKD3) by an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) Study Equation. Presence of diabetic retinopathy, and its classification as proliferative (PDR) or non-proliferative (NPDR), was diagnosed based on wide-field retinal scanning (Optos Tx200, Optos, Dunfermile Scotland UK) and interpretation by a retinal specialist (M.H.B.). Cardiovascular disease (CVD) was defined based on the presence of history of myocardial infarction, coronary artery disease (CAD), stroke, or peripheral vascular disease.

2.3. Bone mineral density

BMD was measured at the lumbar spine (LS), total hip (TH) and femoral neck (FN) by DXA using a Hologic (Discovery QDR, model: Discovery A (S/N 85675) bone densitometer. BMD values were expressed in T-scores and Z-score in relation to the male and female reference population (Hologic reference for the spine site, NHANES reference for TH and FN). The coefficient of variance for the DXA was 0.20% at LS. One trained technician performed all DXA measurements and analyses any abnormal scans due to potential fractures or deformities were excluded. World Health Organization criteria for classification of "low bone mass" or osteopenia and osteoporosis were used according to the T-score values, where normal indicating T-score of −1.0 SD or above, "low bone mass" or osteopenia is T-score less than −1 and greater than −2.5 SD, and osteoporosis when the T-score is less than or equal to −2.5 SD. Insulin pumps were disconnected from patients who were using them at the time of the DXA measurement.

2.4. Definition of fragility fracture

We supplemented the first and second study phase data with a questionnaire focused on bone health in which participants were asked to report risk factors for osteoporosis, history of osteoporosis medications use, calcium and vitamin D supplement use, history of exposure to glucocorticoids for longer than 3 months, use of hormonal replacement therapy and testosterone therapy as well as family history of osteoporosis or fractured hip. Questions concerning fragility fracture in adult life (>18 years old), defined as spontaneous fractures or fracture after a fall from standing position, were specified according to their locations (excluding skull, hands/fingers and feet/toes fractures) along with non-fragility fractures. All questionnaires were reviewed by study staff for accuracy. The questionnaire is included as Supplemental material.

2.5. Statistical analysis

Statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute, Cary, NC). Comparisons of characteristics between T1D and controls – both the total study population and stratified by sex - were made using the Student's *t*-test, the Wilcoxon rank sum test, or the χ^2-test. In particular, prevalence of fragility fractures was compared using the χ^2-test. T-scores were the variable chosen a priori for the primary comparison of BMD (g/cm^2) and differences in Z-score are presented in Supplemental Table 1. Confounders, also chosen a priori, included body mass index (BMI), calcium and vitamin D supplement use, **osteoporosis medication use**, and current alcohol consumption. An α-level of 0.05 was used for tests of statistical significance.

3. Results

The characteristics of T1D participants and the control group are shown in Table 1. T1D participants reported higher use of calcium supplements (40 (53%) vs. 26 (35%), p = 0.021) and vitamin D (59 (79%) vs. 47 (63%), p = 0.031) compared to the control group; however the intake of these supplements was not different between groups (calcium (600 mg [342–683] vs. 500 mg [333–800], p = 0.79, and vitamin D (1000 IU [1000–1600] vs. 1000 IU [1000−2000] p = 0.59)). Low BMI (<18.5) was present in 0 (0%) T1D participants and 1 (1%) control. Self-reported fragility fracture history tended to be higher in T1D participants compared to controls (9 (12%) vs. 3 (4%), p = 0.071) with T1D females having more fragility fractures compared to female controls (7 (17%) vs. 1 (2%), p = 0.021).

Differences in BMD (g/cm^2) and T-score between T1D and controls and as stratified by sex are presented in Table 2, unadjusted and with adjustments made for BMI, bone supplement use, osteoporosis medication use, and current alcohol consumption. This data is presented graphically in Fig. 1 with additional details including Z-scores presented in Supplemental Table 1. The LS skeletal health of females with T1D was reflected in higher in overall T-scores. However, at the FN, T1D females had a lower proportion of normal (11 (27%) vs. 14 (33%)) and osteopenia-range (22 (54%) vs. 27 (63%)) T-scores compared to controls. Accordingly, T1D females also had higher proportion of osteoporosis-range T-scores (8 (20%) vs. 2 (5%)); no difference was found in scores at the TH. Males with and without T1D did not differ significantly in BMD at any of the measured sites. Sensitivity analyses excluding participants with eGFR <60 ml/min/1.73 m^2 and those on osteoporosis medication did not change these conclusions.

To explore factors associated with low bone density in longstanding T1D, we compared T1D participants with normal bone density (defined by a T-score ≥ −1.0 at least one site, n = 20) to those with low bone density (defined by a T-score < −1.0 in at least one site, n = 55, Supplemental Table 2). Univariate analysis showed that there were no differences in age, sex, duration of diabetes or use of calcium and vitamin D supplementation. Compared to those with normal bone density, participants with low bone density had lower BMI (p = 0.005) and lower daily insulin dose (p = 0.017). The presence of diabetes-related

Table 1
Characteristics of the participants with longstanding type 1 diabetes and the age- and sex-matched controls, shown as combined cohorts and stratified by sex.

	Total cohort		Females		Males	
	Controls n = 75	T1D n = 75	Controls n = 43	T1D n = 41	Controls n = 32	T1D n = 34
Clinical characteristics						
Female sex, n (%)	43 (57%)	41 (55%)	–	–	–	–
Age (years)	65 ± 8	66 ± 8	64 ± 8	65 ± 8	66 ± 8	67 ± 8
Diabetes duration (years)	–	54 [52, 58]	–	53 [52, 57]	–	55 [52, 58]
Age at diagnosis (years)	–	10 [6, 17]	–	10 [6, 17]	–	10 [5, 16]
Daily insulin dose (units)	–	35.6 ± 13.2	–		–	
Current smoking, n (%)	3 (4%)	3 (4%)	1 (3%)	0 (0%)	2 (6%)	3 (9%)
Current alcohol consumption, n (%)	46 (65%)	59 (80%)*	25 (63%)	34 (83%)*	21 (68%)	25 (76%)
BMI (kg/m^2)	27.3 ± 5.4	26.6 ± 3.8	27.2 ± 6.6	26.8 ± 4.7	27.3 ± 3.4	26.3 ± 2.5
Biochemical characteristics						
A_{1c} (%)	5.7 ± 0.4	7.3 ± 0.8**	5.7 ± 0.3	7.5 ± 1.0**	5.7 ± 0.5	7.2 ± 0.6**
Total cholesterol (mmol/l)	4.89 ± 0.94	3.87 ± 0.77**	5.27 ± 0.89	4.06 ± 0.76**	4.37 ± 0.76	3.63 ± 0.72**
HDL (mmol/l)	1.39 ± 0.38	1.65 ± 0.45**	1.54 ± 0.38	1.79 ± 0.47*	1.19 ± 0.27	1.48 ± 0.36**
LDL (mmol/l)	2.80 ± 0.77	1.86 ± 0.54**	3.07 ± 0.69	1.92 ± 0.52**	2.44 ± 0.74	1.79 ± 0.56**
Triglycerides (mmol/l)	1.52 ± 1.00	0.78 ± 0.39**	1.42 ± 0.91	0.77 ± 0.42**	1.66 ± 1.11	0.79 ± 0.37**
ALP (U/l)	71 ± 17	75 ± 22	73 ± 19	75 ± 24	68 ± 14	76 ± 20
Calcium (mmol/l)	2.31 ± 0.10	2.32 ± 0.10	2.33 ± 0.10	2.35 ± 0.10	2.28 ± 0.10	2.29 ± 0.10
PTH (pmol/l)	4.8 [3.6, 6.8]	4 [3.4, 7.0]	4.8 [3.6, 6.8]	4.9 [3.1, 7.5]	4.3 [3.6, 6.7]	4.8 [3.5, 6.1]
Estradiol (pmol/l)	37 [37, 39]	41.5 [37, 64]**	37 [37, 39]	43 [37, 66]**	–	–
$eGFR_{MDRD}$ (ml/min/1.73 m^2)	84 ± 14	72 ± 17**	80 ± 12	67 ± 15**	91 ± 14	78 ± 18**
Presence of complications						
Retinopathy						
None	–	12 (16%)	–	5 (12%)	–	7 (21%)
NPDR	–	24 (32%)	–	13 (32%)	–	11 (32%)
PDR	–	39 (52%)	–	23 (56%)	–	16 (47%)
Neuropathy	–	65 (89%)	–	33 (83%)	–	32 (97%)
Nephropathy	–	8 (11%)	–	5 (12%)	–	3 (9%)
Cardiovascular disease	–	15 (20%)	–	10 (24%)	–	5 (15%)
Presence of condition which may cause secondary osteoporosis[a]	7 (11%)	17 (23%)	4 (11%)	11 (28%)	3 (11%)	6 (18%)
Risk of falls	5 (8%)	6 (9%)	4 (12%)	5 (13%)	1 (5%)	1 (4%)
Use of medications						
Osteoporosis medications	9 (12%)	9 (12%)	8 (19%)	8 (20%)	1 (3%)	1 (3%)
Vitamin D supplement	49 (65%)	59 (79%)	33 (77%)	38 (93%)*	16 (50%)	21 (62%)
Calcium supplement	26 (35%)	41 (55%)*	20 (47%)	27 (66%)	6 (19%)	14 (38%)*
Steroids	5 (8%)	4 (5%)	4 (11%)	4 (10%)	1 (4%)	0 (0%)
HRT (post menopause)	12 (31%)	12 (30%)	12 (31%)	12 (30%)	0 (0%)	0 (0%)
Testosterone	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (7%)	0 (0%)
Fracture history						
Fragility fracture history in adult life	3 (4%)	9 (12%)	1 (2%)	7 (17%)*	2 (6%)	2 (6%)
Any fracture history	32 (43%)	40 (53%)	18 (42%)	27 (66%)*	14 (44%)	13 (38%)

T1D, type 1 diabetes mellitus; ALP, alkaline phosphatase; PTH, parathyroid hormone; $eGFR_{MDRD}$, estimated glomerular filtration rate by the Modification of Diet in Renal Disease Study equation; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; HRT: hormone replacement therapy. Risk of falls was determine from self-reported questionnaire.

[a] Includes the following conditions: graves, primary hyperparathyroidism, rheumatoid arthritis, malabsorption, chronic lung disease, chronic liver disease.

* p < 0.05.

** p < 0.01.

Table 2
Unadjusted and adjusted[a] differences in bone mineral density in participants with longstanding type 1 diabetes and the age- and sex-matched controls, shown as combined cohorts and stratified by sex.

	Total cohort			Females				Males			
	Controls (n = 75)	T1D (n = 75)	Unadjusted p-value	Controls (n = 43)	T1D (n = 41)	Unadjusted p-value	Adjusted p-value[b]	Controls (n = 32)	T1D (n = 34)	Unadjusted p-value	Adjusted p-value
Lumbar spine											
BMD (g/cm^2)	0.99 ± 0.16	1.04 ± 0.16	0.067	0.93 ± 0.16	1.01 ± 0.14	**0.015**	**0.022**	1.06 ± 0.14	1.06 ± 0.19	0.93	0.41
T-score	−0.8 ± 1.4	−0.3 ± 1.4	**0.041**	−1.1 ± 1.4	−0.3 ± 1.2	**0.007**	**0.014**	−0.3 ± 1.2	−0.3 ± 1.6	0.92	0.38
Femoral neck											
BMD (g/cm^2)	0.76 ± 0.12	0.72 ± 0.13	**0.041**	0.71 ± 0.10	0.68 ± 0.11	0.13	0.056	0.82 ± 0.11	0.77 ± 0.13	0.068	0.64
T-score	−1.1 ± 0.9	−1.4 ± 1.0	**0.022**	−1.2 ± 0.9	−1.5 ± 1.0	0.12	**0.042**	−0.8 ± 0.7	−1.2 ± 0.9	0.053	0.70
Total hip											
BMD (g/cm^2)	0.93 ± 0.14	0.91 ± 0.13	0.25	0.88 ± 0.14	0.86 ± 0.12	0.54	0.27	1.01 ± 0.11	0.96 ± 0.13	0.14	0.74
T-score	−0.4 ± 1.0	−0.6 ± 0.9	0.22	−0.5 ± 1.1	−0.7 ± 1.0	0.60	0.25	−0.2 ± 0.7	−0.5 ± 0.8	0.13	0.81
Combined											
Normal T-scores	28 (37%)	20 (27%)	0.36	10 (23%)	11 (27%)	0.91	0.91	18 (56%)	9 (26%)	**0.036**	0.21
Low bone mass in at least one site	38 (51%)	43 (57%)		25 (58%)	22 (54%)			13 (41%)	21 (62%)		
Osteoporosis in at least one site	9 (12%)	12 (16%)		8 (19%)	8 (20%)			1 (3%)	4 (12%)		

Data are mean ± SD or n (%). T-scores in the normal range defined as values ≥ −1, in the low bone mass range as −1 > T-score values ≥ −2.5, and in the osteoporosis range is defined as values < −2.5. Bold p-values indicate p-value < 0.05.

[a] Adjusted analysis accounted for participants' BMI, bone supplement use, osteoporosis medication use, and current alcohol consumption.

[b] In a sensitivity analysis of the female participants in which we excluded the 8 (19%) of controls and 9 (20%) of T1D participants exposed to osteoporosis medications (antiresorptive agents other than estrogen, anabolic agents), results were unchanged.

complications (retinopathy, neuropathy, nephropathy and CVD) was similar between those with normal bone density and low bone density. In multivariable logistic regression using a forward selection model, BMI and PTH were identified as the factors most strongly associated with low bone density (adjusted OR 0.73 and 1.41 for every 1 unit increase in BMI and PTH, respectively).

We used univariate and multivariate regression to explore factors associated with fracture history in the T1D population (Supplemental Table 3). For any fracture history, female sex and a history of macrovascular disease were associated with higher odds of having any fracture history (adjusted OR 2.90 for female sex and 7.30 for macrovascular disease). For fragility fracture history, A1c was associated with higher odds of fragility fracture (adjusted OR 4.13 for every 1% increase is A1c).

4. Discussion

In individuals with longstanding T1D, we showed that females with T1D had higher BMD at the LS and lower BMD at the FN compared to age- and sex-matched controls. Males with T1D were not different from age- and sex-matched controls for BMD at all sites. While females with T1D reported higher fragility fractures, it appeared that BMD was not associated with fragility fractures in longstanding T1D. The reported incidence of fragility fracture in the present study is consistent with other studies investigating bone health in T1D postmenopausal women and adults ≥50 years of age with insulin-dependent diabetes.[29] This is in contrast to recent findings from the Joslin Medalist Study, that reported a low prevalence of self-reported non-vertebral fractures in participants with ≥50 years of T1D but also did not find an association with BMD.[10] We acknowledge that the comparison of fragility fractures between T1D and controls in this study is susceptible to information bias; however, this bias should be non-differential information bias since both groups were treated the same and were equally likely to have errors in recall. While we might be missing some of the magnitude of fragility fractures, it is important to interpret the results given our unique population.

BMD and bone micro-architecture are primary contributors to fragility fracture risk.[30] The lack of association between BMD and fragility fracture in our study suggests that T1D participants may have abnormal bone quality as a result of altered bone architecture as has been previously suggested.[31] Further investigation of bone architecture in the long duration cohorts are ongoing and will be important to provide a more comprehensive understanding of the changes in bone health that increases fragility fracture risk. Exploratory analysis of our data suggests that A_{1c} was the only independent variable associated with history of fragility fracture, irrespective of low BMD. This is consistent with previous studies that reported glycemic control was positively associated with fractures but not bone density in patients with T1D.[18]

We observed no difference in blood calcium concentration between T1D and controls despite mixed evidence on the impact of drugs used in the management of T1D and related complications on bone metabolism.[32] The T1D cohort reported higher use of calcium and vitamin D supplements, which might have been related to the observed LS BMD results. These findings also might represent the successful knowledge translation efforts of calcium and vitamin D supplementation to maintain BMD in post-menopausal females.

Meta-analyses[30,33] indicate that an increase in facture risk may be related to diabetes type. T1D appears to be associated with lower BMD, whereas T2D is associated with higher BMD as a result of differences in BMI in these populations and subsequent differences in bone metabolism. Our data and others[3,30] show that BMI is positively associated with BMD. Future research of BMD, bone architecture and fracture risk should examine the effects physical activity and specifically weight bearing exercises, which have been shown to improve BMD and decrease fracture risk.[34,35] Physical activity is associated with lower A_{1c} and has been shown to attenuate the progression of diabetic neuropathy, which can further reduce the risk of fragility fracture.[36] The incidence of hypoglycemia is a major risk factor for falls and should also be considered in future research[37] alongside the use of pump therapy and continuous glucose monitoring.

This is the first study in long-standing T1D to compared bone health to matched-controls. Our control group is representative of the general population as demonstrated by their Z-scores (Supplemental Table 1). However, these controls might not be truly representative of the general population as they were spouses, family members of friends of the T1D participants. These controls are more frequently exposed to information regarding blood glucose control and related lifestyle practices. This selection of controls provides the most representative control group and a more conservative analysis of the effects of longstanding T1D on bone health and as such, we consider this to be a non-differential sampling bias. We do acknowledge that our study shows an incidence of fractures similar to previous population based studies[38]; however

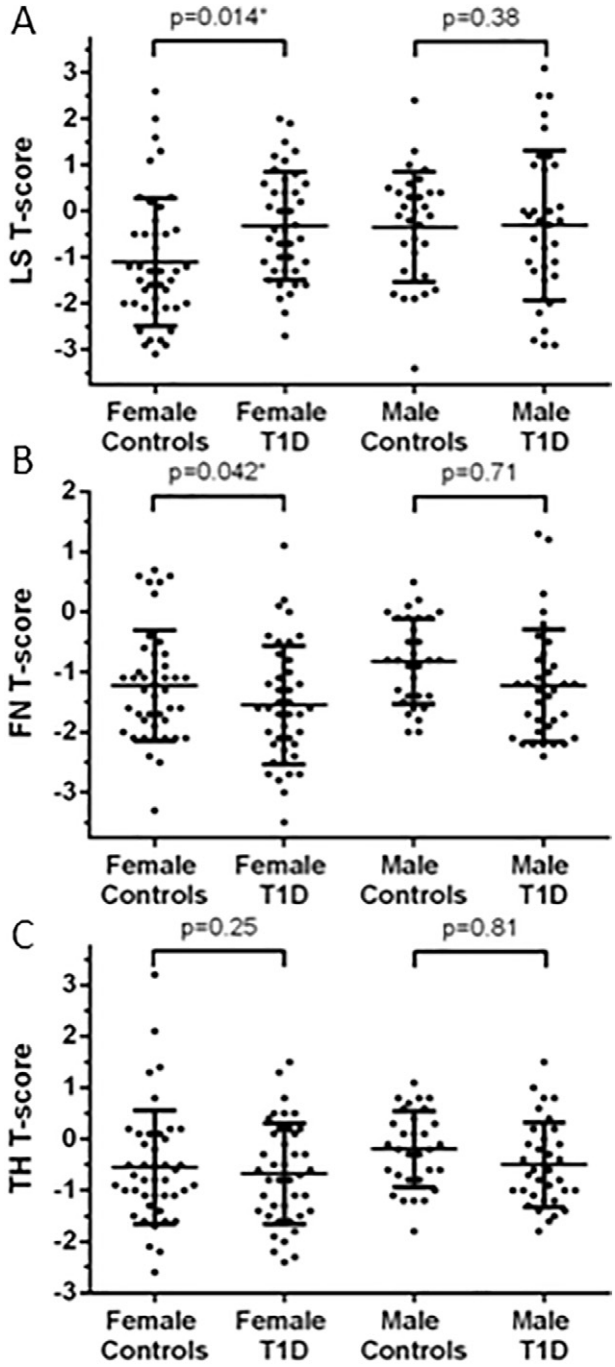

Fig. 1. Comparison of bone mineral density (BMD) between participants with longstanding type 1 diabetes and age- and sex-matched controls. Analysis of BMD is shown in panels A - lumbar spine (LS), B - femoral neck (FN) and C - total hip (TH).

there is a lower prevalence of fragility fractures. This could be the result of participant under reporting, which creates an information bias or measurement bias from the clinical assessment and as such this data should be interpreted with caution.

It is important to note additional limitations of the current study. We used a cross-sectional study design, which allow an association rather than a causality assessment. Current reports of A_{1c} allows us to assess the glucose control over the last three months but not long-term exposure, however others have shown a strong longitudinal association with current and previous glycemic control.[39] Degenerative changes of the spine, vertebral compression fractures and aortic calcifications all can lead to inaccurately higher readings of BMD at the lumbar spine.[40] Our study is subject to selection bias as we are examining participants with ≥50 years T1D and therefore the results presented here might not be applicable to the broader population; however, here we seek to understand the factors associated with skeletal health in this group. For the assessment of calcium and vitamin D supplement use and risk of falls we used self-reported questionnaires that are susceptible to recall bias.

5. Conclusion

The present study showed that in a cohort with ≥50 years of T1D, T-scores in females with T1D was lower at the FN and also higher at the LS compared to matched controls despite higher reported fragility fractures, additionally, lower BMD is not associated with presence of fragility fractures in longstanding T1D. This raises the possibility that abnormalities in bone quality and architecture might be related to the risk of fragility facture and should be examined along with lifestyle factors and diabetes complications in future studies.

Acknowledgement

We greatly appreciate our study participants, who have inspired our team and have donated a considerable about of time participating in this study. O.N.A., E.J.H.L. and L.E.L. performed the statistical analysis, with O.N.A. and E.J.H.L. as wrote the manuscript as co-first authors. All authors reviewed the manuscript for scholarly content. D.Z.I.C. and B.A.P. played a principal role in study design. B.A.P. is the senior author and is the guarantor for the content of this study.

Funding statement

We are grateful to the support of JDRF Canada (operating grant 17-2013-312), its Canadian Clinical Trial Network, and to Diabetes Canada for their non-financial support with study advertisement. We acknowledge the contributions of the Menkes Family Foundation for supporting aspects of this research. E.J.H.L. was supported by a Banting and Best Diabetes Centre Post-Doctoral Fellowship funded by Eli Lilly and Company and Boehringer Ingelheim.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2018.12.009.

References

1. Shah V, Harrall K, Shah C, et al. Bone mineral density at femoral neck and lumbar spine in adults with type 1 diabetes: a meta-analysis and review of the literature. Osteoporos Int 2017;28:2601-10.
2. Joshi A, Varthakavi P, Chadha M, Bhagwat N. A study of bone mineral density and its determinants in type 1 diabetes mellitus. J Osteoporos 2018;2013, 397814.
3. Eller-Vainicher C, Zhukouskaya V, Yolkachey Y, et al. Low bone mineral density and its predictors in type 1 diabetic patients evaluated by the classic statistics and artificial neural network analysis. Diabetes Care 2011;34:2186-91.
4. Lopez-Ibarra P, Pastor M, Escobar-Jimenez F, et al. Bone mineral density at time of clinical diagnosis of adult-onset type 1 diabetes mellitus. Endocr Pract 2001;7:346-51.
5. Kemink S, Hermus A, Swinkels L, Lutterman J, Smals A. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. J Endocrinol Invest 2000;23:295-303.
6. Shah V, Shah C, Snell-Bergeon J. Type 1 diabetes and risk of fracture: meta-analysis and review of the literature. Diabetes Med 2015;32:1134-42.
7. Gunczler P, Lanes R, Paoli M, Martinis R, Villaroel O, Weisinger J. Decreased bone mineral density and bone formation markers shortly after diagnosis of clinical type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2001;14:525-8.
8. Campos Pastor M, Lopez-Ibarra P, Escobar-Jimenez F, Serrano Pardo M, Garcia Cervigon A. Intensive insulin therapy and bone mineral density in type 1 diabetes mellitus: a prospective study. Osteoporos Int 2000;11:455-9.
9. Dhaliwal R, Foster N, Boyle C, et al. Determinants of fracture in adults with type 1 diabetes in the USA: results from the T1D Exchange Clinic Registry. J Diabetes Complications 2018;32:1006-11.

10. Maddaloni E, D'Eon S, Hastings S, et al. Bone health in subjects with type 1 diabetes for more than 50 years. Acta Diabetol 2017;54:479-88.
11. Camurdan M, Cinaz P, Bideci A, Demire F. Role of hemoglobin A1c, duration and puberty on bone mineral density in diabetic children. Pediatr Int 2007;49:645-51.
12. Strotmeyer E, Cauley J, Orchard T, Steenkiste A, Dorman J. Middle-aged premenopausal women with type 1 diabetes have lower bone mineral density and calcaneal quantitative ultrasound than nondiabetic women. Diabetes Care 2006;29:306-11.
13. Rozadilla A, Nolla J, Montana E, et al. Bone mineral density in patients with type 1 diabetes mellitus. Joint Bone Spine 2000;67:215-8.
14. Danielson K, Elliott M, LeCaire T, Binkley N, Palta M. Poor glycemic control is associated with low BMD detected in premenopausal women with type 1 diabetes. Osteoporos Int 2009;20:923-33.
15. Valerio G, del Puente A, Esposito-del Puente A, Buono P, Mozzillo E, Franzese A. The lumbar bone mineral density is affected by long-term poor metabolic control in adolescents with type 1 diabetes mellitus. Horm Res 2002;58:266-72.
16. Leger J, Marinovic D, Alberti C, et al. Lower bone mineral content in children with type 1 diabetes mellitus is linked to female sex, low insulin-like growth factor type I levels, and high insulin requirement. J Clin Endocrinol Metab 2006;91:3947-53.
17. Weber D, Haynes K, Leonard M, Willi S, Benburg M. Type 1 diabetes is associated with an increased risk of fracture across the life span: a population-based cohort study using The Health Improvement Network (THIN). Diabetes Care 2015;38:1913-20.
18. Neuman T, Samann A, Lodes S, et al. Glycaemic control is positively associated with prevalent fractures but not with bone mineral density in patients with Type 1 diabetes. Diabetes Med 2011;28:872-5.
19. Miao J, Brismar K, Nyren O, Ugarlph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. Diabetes Care 2005;28:2850-5.
20. Weber D, Schwartz G. Epidemiology of skeletal health in type 1 diabetes. Curr Osteoporos Rep 2016;14:327-36.
21. Lovshin J, Boulet G, Lytvyn Y, et al. Renin-angiotensin-aldosterone system activation in long-standing type 1 diabetes. JCI Insight 2018;3, e96968.
22. Weisman A, Rovinski R, Farooqi M, et al. Commonly measured clinical variables are not associated with burden of complications in long-standing type 1 diabetes: results from the Canadian Study of Longevity in Diabetes. Diabetes Care 2016;39:e67-8.
23. Weisman A, Lovblom L, Keenan H, et al. Diabetes care disparities in long-standing type 1 diabetes in Canada and the U.S.: a cross-sectional comparison. Diabetes Care 2018;41:88-95.
24. Bjornstad P, Lovshin J, Lytvyn Y, et al. Adiposity impacts intrarenal hemodynamic function in adults with long-standing type 1 diabetes with and without diabetic nephropathy: results from the Canadian Study of Longevity in Type 1 Diabetes. Diabetes Care 2018;41:831-9.
25. Bai J, Lovblom L, Cardinez M, et al. Neuropathy and presence of emotional distress and depression in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. J Diabetes Complications 2017;31:1318-24.
26. Scarr D, Lovblom L, Lovshin J, et al. Lower corneal nerve fibre length identifies diabetic neuropathy in older adults with diabetes: results from the Canadian Study of Longevity in Type 1 Diabetes. Diabetologia 2017;60:2529-31.
27. Boulet G, Halpern E, Lovblom L, et al. Prevalence of insulin pump therapy and its association with measures of glycemic control: results from the Canadian Study of Longevity in Type 1 Diabetes. Diabetes Technol Ther 2016;18:298-307.
28. Bai J, Boulet G, Halpern E, et al. Cardiovascular disease guideline adherence and self-reported statin use in longstanding type 1 diabetes: results from the Canadian study of longevity in diabetes cohort. Cardiovasc Diabetol 2016;25:14.
29. Fraser L, Papaioannou A, Adachi J, Ma J, Thabane L. Fractures are increased and bisphosphonate use decreased in individuals with insulin-dependent diabetes: a 10 year cohort study. BMC Musculoskelet Disord 2014;15:201.
30. Vestergaard P. Discrepancies in bone mineral density and fracture risk in patients with type 1 and type 2 diabetes – a meta-analysis. Osteoporos Int 2007;18:427-44.
31. Keenan H, Maddaloni E. Bone microarchitecture in type 1 diabetes: it is complicated. Curr Osteoporos Rep 2016;14:351-8.
32. Adil M, Khan R, Kalam A, Venkata S, Kandhare A, Sharma M. Effect of anti-diabetic drugs on bone metabolism: evidence from preclinical and clinical studies. Pharmacol Rep 2017;69:1328-40.
33. Janghorbani M, Van Dam R, Willet W, Hu F. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495-505.
34. Zhao R, Zhao M, Xu Z. The effects of differing resistance training modes on the preservation of bone mineral density in postmenopausal women: a meta-analysis. Osteoporos Int 2015;26:1605-18.
35. Hinton P, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. Bone 2015;79:203-12.
36. Balducci S, Iancobellis G, Parisi L, et al. Exercise training can modify the natural history of diabetic peripheral neuropathy. J Diabetes Complications 2006;20:216-23.
37. Shah V, Wu M, Foster N, Dhaliwal R, Al Mukaddam M. Severe hypoglycemia is associated with high risk for falls in adults with type 1 diabetes. Arch Osteoporos 2018;13:66.
38. Shreyasee A, Gabriel S, Achenbach A, Atlinson E, Melton L. Are young women and men with rheumatoid arthritis at risk for fragility fractures? A population-based study. J Rheumatol 2013;40:1669-76.
39. Tinsley L, Kupelian V, D'Eon S, et al. Association of glycemic control with reduced risk for large-vessel disease after more than 50 years of type 1 diabetes. J Clin Endocrinol Metab 2017;102:3704-11.
40. Dawson-Hughes B, Dallal G. Effect of radiographic abnormalities on rate of bone loss from the spine. Calcif Tissue Int 1990;46:280-1.