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BONE HEALTH IN SUBJECTS WITH TYPE 1 DIABETES FOR MORE THAN 50 YEARS

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Abstract

Aims—Few data regarding prevalence of and risk factors for poor bone health in aging individuals with long-standing T1D are available. In this study we aim to describe the prevalence of bone fragility and to identify factors associated with low bone density in individuals with long term T1D.

Methods—We examined the prevalence of non-vertebral fractures in 985 subjects enrolled in the Joslin 50-Year Medalist Study, and measured bone mineral density (BMD) by dual-energy X-ray absorptiometry at the femoral neck, lumbar spine and radius in a subset (65 subjects, mean age 62.6 years, duration 52.5 years, HbA1c 7.1%) with no significant clinical or demographic differences from the rest of the cohort.

Results—Medalists have low prevalence of fractures (0.20% hip and 0.91% wrist) and normal Z-score values (spine +1.15, total hip +0.23, femoral neck −0.01, radius +0.26; $p > 0.05$ for differences vs 0 at all sites). A significant relationship was found between lower BMD and higher total cholesterol, triglycerides and LDL levels, but not HbA1c. Low BMD at the femoral neck was associated with cardiovascular disease after adjustment for confounding factors: prevalence risk ratio (RR) [95% CI] of 4.6 [1.2–18.1], $p = 0.03$ of CVD. No other diabetic vascular complication was found to be associated with low BMD.

Conclusions—These are the first data regarding bone health in aging individuals with T1D for more than 50 years. The low rates of non-vertebral fractures and the normal Z-score suggest the long T1D diabetes duration did not increase the risk of bone fractures in Medalists compared to

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non-diabetic peers. Additionally, the association with cardiovascular disease, demonstrates the BMD differences in group is likely not due to glycemic control alone.

Keywords

bone fractures; osteoporosis; low bone mass; type 1 diabetes; ageing; bone mineral density

INTRODUCTION

Several studies have demonstrated increased bone fragility among those with diabetes documenting up to a 6.3 fold increase risk of osteoporotic fractures compared to those without diabetes [1]. These findings highlight bone fragility as an important diabetic complication. Poor glycemic control, insulin deficiency, decreased IGF1 and amylin are all involved in bone metabolism impairment and may contribute to poor skeletal health in those with type 1 diabetes (T1D) [2, 3]. Despite declining skeletal health being thought of as an age-related condition, most studies in those with T1D have been conducted in those less than 40 years of age, with a primary focus on young adults [4–8]. Studies including the Scottish Linkage Study, the Pittsburgh Epidemiology of Diabetes Complications, the Swedish Registry and the Australian Registry [9–12] showed that rates of cardiovascular mortality are decreasing among those with T1D, leading to increases in longevity. This increase in the number of individuals aging with T1D represents a disproportionate increase in risk of fragility fractures due to the age-related decline of BMD and due to the documented pathological effects of T1D on bone [13]. The study presented here, despite being a pilot study, is a harbinger of what is to come as the number of individuals with T1D grows and their longevity increases. Indeed, we aim to provide insight on bone fragility, markers of bone turnover and factors associated with skeletal health in a subset of individuals with duration of T1D significantly longer than previously studied, and who are in the age range that is at highest risk for fragility fractures. To accomplish this, we enrolled individuals from the Joslin 50-Year Medalists, a unique cohort of subjects who have had insulin dependent diabetes since time of diagnosis 50 years or longer. Due to their age and extreme T1D duration this population provides a unique opportunity to study the effects of long term T1D on skeletal health in the context of age.

Materials and Methods

Study population and procedures

Details of the 50-Year Medalist Study and its methods have been extensively described elsewhere [14–16]. In brief, participants are Caucasian with 50 or more years of documented insulin dependence and are subsequently awarded the Joslin 50-Year Medal. The Medalist Study took place between April 2005 and December 2015. Bone mineral density (BMD) testing by dual-energy X-ray absorptiometry (DXA) took place between October 2011 and June 2012, assessing each individual meeting inclusion criteria as they presented to the study to avoid sampling bias. To participate in the Medalist Study individuals must present three forms of documentation of insulin dependence since time of diagnosis or original medical record. All individuals were assessed at the Joslin Diabetes Center in Boston, MA by clinical exam, electrocardiogram, and standard laboratory measures. The Medalist Study has

extensively characterized over 985 individuals (455 males and 530 females) with mean T1D duration of 55 years. Informed consent was obtained from all subjects prior to participation in the study. The Joslin Committee on Human Studies approved the study protocol.

Medalists were asked to report significant medical events including all fractures [17]. Data about all-cause hip and wrist fractures occurring at any age were collected by questionnaires. Between October 2011 and June 2012, 65 consecutive subjects meeting inclusion criteria (31 men and 34 post-menopausal women) presenting to the same study site received DXA scans. History of Cushing's disease, long-term (>6 months) steroid use, hypogonadism (premature menopause, anorexia, pituitary dysfunction), hypo- and hyperparathyroidism and/or alcoholism were considered as exclusion criteria for this study. Urine and blood specimens were collected on the same day of the DXA scan after an 8-hour fast. Cardiovascular disease was defined as self-reported as history of coronary artery bypass surgery, angioplasty, coronary stent placement, myocardial infarction, or angina [16]. Peripheral neuropathy was assessed using the Michigan Neuropathy Screening Index a score ≥ 2 was considered positive [18]. An albumin-to-creatinine ratio (ACR) >30 mg/g and an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m² was considered positive for nephropathy [19]. Diabetic retinopathy was diagnosed using seven-standard field fundus photography and graded according the Early Treatment Diabetic Retinopathy Study [20].

Biochemical assays

HbA1c was determined by high-performance liquid chromatography (Tosoh G7 and 2.2, Tokyo, Japan). Lipid profiles were determined by standard enzymatic methods (Roche Diagnostics, Indianapolis, IN; Denka Seiken, Tokyo, JP; and AsahiKasei, Tokyo, JP). High-sensitivity C-reactive protein (hsCRP) was determined by nephelometric methods; creatinine, calcium and albumin by spectrophotometry; intact parathyroid hormone (PTHrP), 25-OH vitamin D, estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG), testosterone by immunoassay; IGF1 by liquid chromatography; urine ACR by turbidimetric methods, (Quest Diagnostics, Wallingford, CT). The following serum bone turnover markers were evaluated: Collagen Type 1 C-Telopeptide (CTX) and total osteocalcin, by electrochemiluminescent immunoassay, Bone-Specific Alkaline Phosphatase by immunoenzymatic assay,

Areal bone mineral density (BMD)

Areal BMD of the lumbar spine, femoral neck, total hip and one-third distal radius was measured by DXA (Hologic QDR Elite Fan Beam X-Ray Densitometer; model number 4500A with a Delphi Upgrade, Waltham, MA). T- and Z-scores were automatically computed by the Hologic software on the basis of male and female reference values (NHANES reference set for hip and Hologic reference dataset for lumbar spine). A single trained technician performed all scans and analyses. According to the World Health Organization diagnostic criteria, normal BMD was defined as T-score values ≥ -1.0 SD, "low bone mass" or "osteopenia" as T-score values < -1.0 SD and > -2.5 SD, and osteoporosis as T-score values ≤ -2.5 SD [21].

Statistical analysis

Two sets of analyses were done, one to examine protection from low bone mineral density (T-score values $< -1.0SD$), and a second to examine characteristics associated with lower bone mineral density in regions known to have a higher cortical/cancellous bone ratio (one-third distal radius and femoral neck). Variables were tested for normality using the Shapiro-Wilk test. Values are expressed as mean $\pm$ SD and medians [range] for continuous variables and as proportions for categorical variables (%) depending on distribution. Comparisons were done using Student's t-test, Kruskal-Wallis, and chi-square depending on distribution. Generalized linear models were used to calculate prevalence risk ratios adjusted for covariates. Those factors significant at $p < 0.1$ were tested in the final model with main effect and outcome. Effect modification was tested in the standard ways. Two-tailed p-value < 0.05 was considered statistically significant. All statistical analyses were performed using *Stata/IC 12.1* software (StataCorp, College Station, TX, USA).

RESULTS

Clinical population

Among the Medalists, mean ($\pm$ SD) age was 66.0 ± 7.6 years (67.3 ± 7.9 in males and 64.9 ± 7.2 in females), disease duration was 54.7 ± 5.7 years and BMI 26.2 ± 4.7 kg/m². The Medalists had a mean HbA1c of $7.2 \pm 0.9\%$ ($55.2 \pm xx$ mmol/mol), triglycerides of 75.0 ± 37 mg/dl, total cholesterol of 161.4 ± 32.7 mg/dl, HDL of 65.1 ± 19.9 mg/dl, LDL of 81.1 ± 23.8 mg/dl and eGFR of 69.6 ± 20.3 ml/min/1.73m². The study population had a CVD prevalence of 39.9% and proliferative diabetic retinopathy (PDR) was diagnosed in 46.4%. Diabetic nephropathy affected 12.5%, and 69.8% were found to have diabetic neuropathy. Data regarding bone fractures were available for all 985 subjects enrolled in the 50-Year Joslin Medalist Study at the time of analysis. History of hip and wrist fractures was reported by 11 subjects (1.12%). More specifically, 9 subjects (0.91%; 4 males and 5 females) had a previous wrist fracture and 2 male subjects (0.20%) reported history of hip fracture.

Areal BMD

Clinical and biochemical features of the 65 subjects who underwent DXA scans are reported in Table 1 (medication use in Supplementary Table 1). There were no significant differences in demographic and clinical features between the primary Medalist cohort and those who underwent the DXA scan. Overall, this subgroup has good glycemic control, HbA1c $7.1 \pm 1.0\%$ (54.1 ± 10.9 mmol/mol), total cholesterol 168.0 ± 36.2 mg/dl, triglycerides 75.4 ± 32.7 mg/dl, HDL 65.7 ± 20.8 mg/dl, LDL 86.8 ± 25.0 mg/dl, and vitamin D levels (35 ± 9 ng/ml). Only one subject had a detectable fasting serum c-peptide, the remaining 64 had had undetectable levels.

Results of the DXA scans are reported in Table 2. The cohort showed comparable or better BMD by Z-score to age, gender and race-matched population. Mean Z-scores were 1.15 ± 1.61 at the lumbar spine ($p < 0.001$ for difference vs 0), 0.23 ± 0.87 at the total hip ($p = 0.040$), -0.01 ± 0.85 at the femoral neck ($p = 0.97$) and 0.26 ± 1.35 at one-third distal radius ($p = 0.13$). The cumulative prevalence of osteoporosis using any of spine, total hip and femoral neck BMD measurements was 4.6%. When the one-third distal radius was

considered in addition to the other diagnostic sites, the prevalence of osteoporosis increased to 16.9%. The proportion of subjects with a T-score -2.5 at the one-third distal radius was 15.4%, 3.1% at the femoral neck and 1.5% at the lumbar spine. The prevalence of low bone mineral density, osteopenia, was 66.2% considering all standard diagnostic sites (lumbar spine, total hip and femoral neck) (Table 2).

Features of Medalists with normal BMD

To identify factors associated with preservation of BMD we further compared clinical and biochemical features of those with normal BMD at all sites ($n=10$) to those with low bone mass in at least one site ($n=55$). No differences in gender (50% vs 47% males, $p=0.874$), age (64.1 ± 6.1 vs 63.7 ± 7.1 years, $p=0.865$), age at diagnosis (11.2 ± 5.9 vs 10.0 ± 6.1 years, $p=0.473$) and disease duration (52.6 ± 2.5 vs 52.5 ± 3.2 years, $p=0.592$) were found between Medalists with normal and low BMD, respectively. Individuals with normal BMD showed a better lipid profile with lower total cholesterol, triglycerides and LDL levels, but no significant differences in HDL levels, this was independent of the use of anti-hyperlipidemics (adjusted $p=0.008$, $p=0.049$ and $p=0.020$, respectively) [Figure 1]. The presence of CVD, proliferative retinopathy, diabetic nephropathy and neuropathy did not differ between those with normal and low BMD [Table 3]. Those with normal BMD did not differ in IGF1 (97.0 ± 22.8 vs 98.3 ± 4.6 pg/ml, $p=0.814$), PTHi (25.7 ± 10.8 vs 28.6 ± 14.7 pg/ml, $p=0.679$), vitamin D (36.8 ± 9.1 vs 34.4 ± 9.5 ng/ml, $p=0.516$), calcium (9.1 ± 0.2 vs 8.9 ± 0.6 mg/dl, $p=0.158$), bone alkaline phosphatase (11.6 ± 3.1 vs 10.8 ± 4.2 mcg/L, $p=0.300$), total osteocalcin (15.1 ± 6.8 vs 17.2 ± 10.4 ng/ml, $p=0.666$) and CTx levels (201.9 ± 58.1 vs 264.8 ± 178.7 pg/ml, $p=0.364$) from those with lower levels of BMD. As well, no differences in sex hormones were found between the two groups (Supplementary Table 2).

Features by low bone mass in cortical sites

Since the higher prevalence of osteoporosis at the one-third distal radius could suggest a greater effect of T1D at sites composed of a greater proportion of cortical bone, we compared traits between those with and without low bone mass at sites with higher cortical/cancellous bone ratio, specifically the femoral neck and one-third distal radius. Table 4 shows subjects with normal T-scores did not differ in clinical and biochemical features from those with T-score < -1.0 SD at both sites. However, as expected, subjects with low bone mass/osteoporosis at the femoral neck showed a trend towards higher level of bone turnover markers (total osteocalcin and CTx) than those with normal femoral neck T-score (Table 4).

Complications

No differences were found in the crude prevalence of the microvascular diseases retinopathy, nephropathy or neuropathy. A borderline difference was found in the prevalence of CVD between those with and without low bone mass at the femoral neck (9.0% vs 27.9%, $p=0.07$) [Table 3], but not at other skeletal sites. Adjusted models of CVD and BMD at the femoral neck demonstrated cholesterol as a significant confounder with the association climbing to a prevalence risk ratio (PRR) [95% CI] of 4.6 [1.2–18.1] of CVD in the presence of low BMD ($p=0.03$ with adjustment) [Figure 2]. Subjects with normal and low femoral neck T-score did

not differ in presence of hypertension ($p=0.60$), smoking status ($p=0.54$), use of lipid lowering agents ($p=0.77$) or antiplatelet medications ($p=0.41$).

DISCUSSION

Our results found an unexpectedly low prevalence of fractures in a large cohort of aging people with T1D with greater than 50 years duration [1, 22]. Accordingly, we showed an unexpectedly low prevalence of osteoporosis and BMD values comparable to non-diabetic peers, as shown by normal Z-scores, in a subgroup of subjects from the same cohort. Indeed, despite their median age of 63 years, only 4.6% of the Medalists were affected by osteoporosis, compared to 10.3% reported in US adults 50 years or older [23] and to 14% in individuals with between 9 to 20 years of T1D [24]. Despite a lower than expected prevalence of osteoporosis, osteopenia was present in 66.2% of the Medalists compared to 43.9% of US adults. While reports in young adults with shorter duration T1D showed they have lower BMD than their non-diabetic peers [25], studies in those with longer duration T1D have results consistent with our findings. Ingberg et al. did not find any significant reduction in terms of lumbar or femoral BMD in males and females [age range 33–55 years] affected by T1D for 33 years [range 28–37] [7]. Similarly, Lunt et al. measured lumbar spine and femoral neck BMD in 99 women (median age 42 years) with long-standing T1D (median disease duration 27 years) and found similar values to those of healthy volunteers [26].

Several factors could explain our results. As we studied older adults having relatively few complications they may have been protected by endogenous factors or better glycemic control throughout their time with diabetes [14, 16, 27]. It is also possible that due to consistent care for their diabetes, these individuals were more diligent regarding diet and other risk factors for skeletal health decline. BMI in the defined normal range and mean values of vitamin D above 30 ng/ml were seen in both those with lower and higher BMD. It has also been proposed that long term exogenous insulin therapy can recover the bone loss seen within the initial years of T1D diagnosis. These individuals with 50 or more years may have recovered initial bone deficit and benefited through exogenous insulin use. As several reports have showed islet transplantation to have positive effects on diabetes complications, especially macrovascular [28, 29], data regarding skeletal health are lacking. This restoration of endogenous insulin production in those T1D may ameliorate declines in skeletal health due to insulin deficiency. Moreover, other strategies to sustain beta-cell function in T1D, such as immunotherapies alone or in combination with other agents [30], should also be studied in terms of bone protection.

Finally, the Joslin 50-Year Medalist cohort is documented to have low rates of diabetic vascular complications (45.6% PDR, 12.5% diabetic nephropathy, 40.5% CVD) [16, 27]. As shown by Miao et al. [31] there is a strong association between vascular complications and rate of fractures in T1D. Similarly, Shanbhogue et al. recently described an association between the presence of vascular complications of T1D and deficit in bone microarchitecture and volumetric BMD [32]. These findings show a similar pattern to that of the Medalists, protection from vascular complications and preservation of skeletal health. This is supported by our findings of a strong and independent association between CVD and

low BMD at the femoral neck, which remained with adjustment. Indeed femoral neck could be particularly vulnerable to vessel occlusion because of the monolateral end-arterial blood supply [33]. Accordingly, a worse lipid profile was associated with low BMD in this group. Epidemiological studies have associated dyslipidemia with osteoporosis in postmenopausal women [34] and it has recently been shown that people with isolated high levels of LDL have lower BMD [35]. Moreover, both *in vitro* and *in vivo* studies show dyslipidemia and products of lipid oxidation may decrease BMD by inhibiting osteoblast and stimulating osteoclast differentiation through the induction of macrophage-colony stimulating factor and tartrate resistant acid phosphatase [36, 37].

We also found the prevalence of osteoporosis increases by almost four times if the one-third radius is considered among the sites used for diagnosis together with the hip and the spine. This could suggest a preferential involvement of the cortical bone compartment, even though we cannot further speculate on this finding as we did not investigate bone microarchitecture. However, in line with these findings, it has recently been shown that cortical rather than trabecular bone microarchitecture is negatively affected by diabetes, particularly higher fasting glucose, especially at the radius [32, 38–40].

We acknowledge our study has some limitations. Self-report of fractures may result in underestimates of fragility fractures. Degenerative changes in spine anatomy and aortic calcification, which are common in older adults, may have overestimated BMD at the lumbar spine [41]. Additionally, as this is a cross-sectional study, causal associations cannot be made. However, for factors such as HbA1c, we have previously shown a strong correlation ($r^2=0.51$) between current and historical glycemic control in the 50-Year Medalists [16]. The lack of an internal control group did not allow the evaluation of the lipid-effect on BMD in subjects without diabetes compared to Medalists. As the exclusion of subjects with a previous diagnosis of osteoporosis would have introduced a selection bias, those currently using osteoporosis medications were included. Eight subjects were on medication for osteoporosis and the adjustment for this confounder did not modify our results. Finally, even with adjustment for known confounders, there may be unidentified factors influencing the bone health of this population. While the “extreme disease duration” of this population could limit the generalizability of our results, the study of people like Medalists is necessary to study the effects of long term T1D. This extraordinary population enables us to identify patterns and factors in a growing portion of the population, which could potentially heavily burden the healthcare system. As these individuals have escaped the primary causes of early death amongst those with diabetes, namely CVD [16], this suggest a bias for better glycemic control, and other factors which protect against vascular disease.

In conclusion, this study provides the first data on fracture history and bone density in a large sample of aging individuals with T1D with more than 50 years of the disease. We found BMD is not on average lower in the Medalists, based on Z-scores. Thus, the 50-Year Medalists may serve as a unique model to identify factors which may protect T1D patients from the development of bone fragility, a common but under recognized complication of diabetes, particularly among those with life-long insulin dependence. In the Medalists, a good lipid profile is associated with favorable BMD values, suggesting that in T1D with

reasonable glycemic control, there may be an association between cardiovascular disease and skeletal health decline. Additional prospective studies are needed to confirm these observations and to further elucidate potential mechanisms contributing to skeletal health in those with longstanding T1D.

Statement of Human Rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Statement of Informed Consent

Informed consent was obtained from all patients for being included in the study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

ACR	Albumin-to-Creatinine Ratio
BMD	Bone Mineral Density
CTx	Collagen Type 1 C-Telopeptide
CVD	Cardiovascular Disease
DXA	Dual-energy X-ray Absorptiometry
eGFR	Estimated Glomerular Filtration Rate
FSH	Follicle-Stimulating Hormone
hsCRP	High-sensitivity C-reactive protein
LH	Luteinizing Hormone
PDR	Proliferative Diabetic Retinopathy
PTHi	intact Parathormone,

SHBG Sex Hormone Binding Globulin

T1D Type 1 Diabetes

References

1. Janghorbani M, Van Dam RM, Willett WC, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. *Am J Epidemiol*. 2007; 166:495–505. DOI: 10.1093/aje/kwm106 [PubMed: 17575306]
2. Maddaloni E, D'Onofrio L, Lauria A, et al. Osteocalcin levels are inversely associated with HbA1c and BMI in adult subjects with long-standing type 1 diabetes. *J Endocrinol Invest*. 2014; 37:661–6. DOI: 10.1007/s40618-014-0092-7 [PubMed: 24859912]
3. McCabe LR. Understanding the pathology and mechanisms of type 1 diabetic bone loss. *J Cell Biochem*. 2007; 102:1343–57. DOI: 10.1002/jcb.21573 [PubMed: 17975793]
4. Onder A, Cetinkaya S, Tunc O, Aycan Z. Evaluation of bone mineral density in children with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab*. 2013; 26:1077–81. DOI: 10.1515/jpem-2012-0369 [PubMed: 24114897]
5. Joshi A, Varthakavi P, Chadha M, Bhagwat N. A study of bone mineral density and its determinants in type 1 diabetes mellitus. *J Osteoporos*. 2013; 2013:397814. doi: 10.1155/2013/397814 [PubMed: 23607045]
6. Miazgowski T, Czekalski S. A 2-year follow-up study on bone mineral density and markers of bone turnover in patients with long-standing insulin-dependent diabetes mellitus. *Osteoporos Int*. 1998; 8:399–403. DOI: 10.1007/s001980050082 [PubMed: 9850345]
7. Ingberg C-M, Palmér M, Aman J, et al. Body composition and bone mineral density in long-standing type 1 diabetes. *J Intern Med*. 2004; 255:392–8. [PubMed: 14871464]
8. Strotmeyer ES, Cauley JA, Orchard TJ, et al. Middle-aged premenopausal women with type 1 diabetes have lower bone mineral density and calcaneal quantitative ultrasound than nondiabetic women. *Diabetes Care*. 2006; 29:306–311. DOI: 10.2337/diacare.29.02.06.dc05-1353 [PubMed: 16443878]
9. Livingstone SJ, Levin D, Looker HC, et al. Estimated life expectancy in a Scottish cohort with type 1 diabetes, 2008–2010. *JAMA*. 2015; 313:37–44. DOI: 10.1001/jama.2014.16425 [PubMed: 25562264]
10. Miller RG, Secrest AM, Sharma RK, et al. Improvements in the life expectancy of type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complications study cohort. *Diabetes*. 2012; 61:2987–92. DOI: 10.2337/db11-1625 [PubMed: 22851572]
11. Petrie D, Lung TWC, Rawshani A, et al. Recent trends in life expectancy for people with type 1 diabetes in Sweden. *Diabetologia*. 2016; 59:1167–76. DOI: 10.1007/s00125-016-3914-7 [PubMed: 27044338]
12. Huo L, Shaw JE, Wong E, et al. Burden of diabetes in Australia: life expectancy and disability-free life expectancy in adults with diabetes. *Diabetologia*. 2016; 59:1437–45. DOI: 10.1007/s00125-016-3948-x [PubMed: 27075450]
13. Keenan HA, Maddaloni E. Bone Microarchitecture in Type 1 Diabetes: It Is Complicated. *Curr Osteoporos Rep*. 2016; doi: 10.1007/s11914-016-0338-8
14. Keenan HA, Costacou T, Sun JK, et al. Clinical factors associated with resistance to microvascular complications in diabetic patients of extreme disease duration: the 50-year medalist study. *Diabetes Care*. 2007; 30:1995–7. DOI: 10.2337/dc06-2222 [PubMed: 17507696]
15. Keenan HA, Sun JK, Levine J, et al. Residual insulin production and pancreatic β -cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes*. 2010; 59:2846–53. DOI: 10.2337/db10-0676 [PubMed: 20699420]
16. Sun JK, Keenan HA, Cavallerano JD, et al. Protection from retinopathy and other complications in patients with type 1 diabetes of extreme duration: the joslin 50-year medalist study. *Diabetes Care*. 2011; 34:968–74. DOI: 10.2337/dc10-1675 [PubMed: 21447665]
17. Martin LM, Leff M, Calonge N, et al. Validation of self-reported chronic conditions and health services in a managed care population. *Am J Prev Med*. 2000; 18:215–8. [PubMed: 10722987]

18. Feldman EL, Stevens MJ, Thomas PK, et al. A practical two-step quantitative clinical and electrophysiological assessment for the diagnosis and staging of diabetic neuropathy. *Diabetes Care*. 1994; 17:1281–9. [PubMed: 7821168]
19. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009; 150:604–12. [PubMed: 19414839]
20. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991; 98:823–33. [PubMed: 2062515]
21. Kanis JA, Melton LJ, Christiansen C, et al. The diagnosis of osteoporosis. *J Bone Miner Res*. 1994; 9:1137–41. DOI: 10.1002/jbmr.5650090802 [PubMed: 7976495]
22. Weber DR, Haynes K, Leonard MB, et al. 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; doi: 10.2337/dc15-0783
23. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014; 29:2520–6. DOI: 10.1002/jbmr.2269 [PubMed: 24771492]
24. Kemink SA, Hermus AR, Swinkels LM, et al. Osteopenia in insulin-dependent diabetes mellitus; prevalence and aspects of pathophysiology. *J Endocrinol Invest*. 2000; 23:295–303. [PubMed: 10882147]
25. Bridges MJ, Moochhala SH, Barbour J, Kelly CA. Influence of diabetes on peripheral bone mineral density in men: a controlled study. *Acta Diabetol*. 2005; 42:82–6. DOI: 10.1007/s00592-005-0183-1 [PubMed: 15944841]
26. Lunt H, Florkowski CM, Cundy T, et al. A population-based study of bone mineral density in women with longstanding type 1 (insulin dependent) diabetes. *Diabetes Res Clin Pract*. 1998; 40:31–8. [PubMed: 9699088]
27. He ZH, D'Eon SA, Tinsley LJ, et al. Cardiovascular disease protection in long-duration type 1 diabetes and sex differences. *Diabetes Care*. 2015; 38:e73–4. DOI: 10.2337/dc15-0017 [PubMed: 25908159]
28. Fiorina P, Folli F, Maffi P, et al. Islet transplantation improves vascular diabetic complications in patients with diabetes who underwent kidney transplantation: a comparison between kidney-pancreas and kidney-alone transplantation. *Transplantation*. 2003; 75:1296–301. DOI: 10.1097/01.TP.0000061788.32639.D9 [PubMed: 12717219]
29. Bassi R, Fiorina P. Impact of Islet Transplantation on Diabetes Complications and Quality of Life. *Curr Diab Rep*. 2011; 11:355–363. DOI: 10.1007/s11892-011-0211-1 [PubMed: 21748256]
30. Pozzilli P, Maddaloni E, Buzzetti R. Combination immunotherapies for type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2015; 11:289–297. DOI: 10.1038/nrendo.2015.8 [PubMed: 25688000]
31. Miao J, Brismar K, Nyrén O, et al. Elevated hip fracture risk in type 1 diabetic patients: a population-based cohort study in Sweden. *Diabetes Care*. 2005; 28:2850–5. [PubMed: 16306544]
32. Shanbhogue VV, Hansen S, Frost M, et al. Bone Geometry, Volumetric Density, Microarchitecture, and Estimated Bone Strength Assessed by HR-pQCT in Adult Patients With Type 1 Diabetes Mellitus. *J Bone Miner Res*. 2015; 30:2188–99. DOI: 10.1002/jbmr.2573 [PubMed: 26096924]
33. Bagger YZ, Rasmussen HB, Alexandersen P, et al. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se? *Osteoporos Int*. 2007; 18:505–12. DOI: 10.1007/s00198-006-0255-2 [PubMed: 17109061]
34. Makovey J, Chen JS, Hayward C, et al. Association between serum cholesterol and bone mineral density. *Bone*. 2009; 44:208–13. DOI: 10.1016/j.bone.2008.09.020 [PubMed: 18983946]
35. Yerges-Armstrong LM, Shen H, Ryan KA, et al. Decreased bone mineral density in subjects carrying familial defective apolipoprotein B-100. *J Clin Endocrinol Metab*. 2013; 98:E1999–2005. DOI: 10.1210/jc.2013-2471 [PubMed: 24106285]
36. Parhami F, Garfinkel A, Demer LL. Role of lipids in osteoporosis. *Arterioscler Thromb Vasc Biol*. 2000; 20:2346–8. [PubMed: 11073836]
37. Parhami F, Jackson SM, Tintut Y, et al. Atherogenic diet and minimally oxidized low density lipoprotein inhibit osteogenic and promote adipogenic differentiation of marrow stromal cells. *J Bone Miner Res*. 1999; 14:2067–78. DOI: 10.1359/jbmr.1999.14.12.2067 [PubMed: 10620066]

38. Patsch JM, Burghardt AJ, Yap SP, et al. Increased cortical porosity in type 2 diabetic postmenopausal women with fragility fractures. *J Bone Miner Res.* 2013; 28:313–24. DOI: 10.1002/jbmr.1763 [PubMed: 22991256]
39. Yu EW, Putman MS, Derrico N, et al. Defects in cortical microarchitecture among African-American women with type 2 diabetes. *Osteoporos Int.* 2015; 26:673–679. DOI: 10.1007/s00198-014-2927-7 [PubMed: 25398431]
40. Farr JN, Drake MT, Amin S, et al. In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. *J Bone Miner Res.* 2014; 29:787–95. DOI: 10.1002/jbmr.2106 [PubMed: 24123088]
41. Kinoshita H, Tamaki T, Hashimoto T, Kasagi F. Factors influencing lumbar spine bone mineral density assessment by dual-energy X-ray absorptiometry: comparison with lumbar spinal radiogram. *J Orthop Sci.* 1998; 3:3–9. [PubMed: 9654549]

Figure 1. Normal T-score is associated with better lipid profile

Subjects with T-score ≥ -1.0 SD at all sites showed lower levels of total cholesterol, triglycerides and LDL than subjects with T-score < -1.0 SD. No significant differences were found in HDL levels. Bars are for standard deviation.

Figure 2. Prevalence risk ratio of diabetic complications associated with T-score < -1.0SD at femoral neck

*Adjusted for total cholesterol; other complication estimates not significant in bivariate or multivariate models

Table 1

Study sample features.

	Overall (n=65)		Males (n=31)		Females (n=34)	
	Mean ± SD	Median [range]	Mean ± SD	Median [range]	Mean ± SD	Median [range]
Age, years	63.8 ± 6.9	63 [52–81]	65.9 ± 7.0	65 [52–81]	61.8 ± 6.4	61 [53–79]
Age at diagnosis, years	10.2 ± 6.0	10 [0–25]	10.9 ± 6.5	11 [2–25]	9.5 ± 5.6	9 [0–21]
Disease duration, years	52.5 ± 3.1	51 [50–67]	53.4 ± 3.9	52 [50–67]	51.6 ± 1.8	51 [50–56]
BMI, Kg/m ²	26.6 ± 5.0	25.8 [18.0–43.9]	27.8 ± 4.5	27.2 [20.6–42.5]	25.6 ± 5.3	24.6 [18.0–44.0]
Waist to hip ratio	0.9 ± 0.1	0.9 [0.8–1.1]	1.0 ± 0.1	1.0 [0.9–1.1]	0.9 ± 0.1	0.9 [0.8–1.1]
HbA1c, % (mmol/mol)	7.1 ± 1.0 (54.1 ± 10.9)	7 [5.2–11.5] (53.0 [33.3–102.2])	7.0 ± 1.1 (53.0 ± 12.0)	6.9 [5.2–11.5] (51.9 [33.3–102.2])	7.2 ± 0.9 (55.2 ± 9.8)	7.2 [5.6–9.4] (55.2 [37.7–79.2])
Insulin dose, IU/kg	0.48 ± 0.20	0.45 [0.48–0.20]	0.56 ± 0.24	0.52 [0.23–1.30]	0.42 ± 0.14	0.42 [0.14–0.72]
eGFR, ml/min/1.73m ²	76.2 ± 19.2	79.8 [18.6–101.1]	78.2 ± 16.9	83.2 [40.6–101.1]	74.4 ± 21.2	78.0 [18.6–100.8]
Total cholesterol, mg/dl	168.0 ± 36.2	163 [93–292]	156.6 ± 30.4	159 [93–219]	178.3 ± 38.4	168 [115–292]
Triglycerides, mg/dl	75.4 ± 32.7	70 [33–209]	74.8 ± 34.8	71 [33–209]	75.8 ± 31.1	68 [36–182]
HDL, mg/dl	65.7 ± 20.8	63 [23–136]	58.7 ± 18.7	58 [23–111]	72.0 ± 20.0	69.5 [31–136]
LDL, mg/dl	86.8 ± 25.0	85 [43–162]	82.9 ± 23.5	79 [51–154]	90.4 ± 26.1	87.5 [43–162]
hsCRP, mg/L	0.8 ± 1.3	0.2 [0.1–5.8]	1.0 ± 1.3	0.6 [0.1–5.5]	0.6 ± 1.3	0.2 [0.1–5.8]
Corrected calcium, mg/dl	8.9 ± 0.5	9.0 [6.9–10.3]	8.7 ± 0.6	8.8 [6.9–9.4]	9.1 ± 0.4	9.1 [8.4–10.3]
Vitamin D, ng/ml	35 ± 9	32 [17–53]	33 ± 9	32 [17–53]	35.9 ± 9.6	33 [17–51]
Bone Alkaline Phosphatase, mcg/L	10.9 ± 4.0	9.9 [5.6–25.9]	10.0 ± 3.4	9.5 [5.6–23.3]	11.7 ± 4.3	10.9 [6.7–25.9]
Total osteocalcin, ng/ml	16.9 ± 9.9	14.0 [4.0–67]	15.6 ± 5.4	14.5 [7.0–29.0]	18.0 ± 12.7	14.0 [4.0–67.0]
CTX, pg/ml	254.9 ± 166.8	230 [14.0–1119.0]	226.3 ± 91.3	224.0 [73.0–412.0]	280.6 ± 211.6	241.5 [14–1119]
PTHr, pg/ml	28.1 ± 14.2	26 [7–71]	29.9 ± 12.2	28.5 [7–57]	26.6 ± 15.8	23 [8–71]
IGF1, pg/ml	98.1 ± 32.5	91 [15–223]	100.4 ± 26.5	90 [64–156]	96.0 ± 37.5	91 [15–223]

Table 2

Bone mineral density in adults with longstanding Type 1 diabetes.

		Overall (n=65)		Males (n=31)		Females (n=34)	
		Mean $\pm$ SD, %	Median [range]	Mean $\pm$ SD, %	Median [range]	Mean $\pm$ SD, %	Median [range]
Lumbar spine	BMD (g/cm ²)	1.068 $\pm$ 0.170	1.039 [0.788–1.693]	1.079 $\pm$ 0.200	1.070 [0.788–1.693]	1.057 $\pm$ 0.137	1.038 [0.800–1.367]
	Z-score (SD)	1.15 $\pm$ 1.61	1.2 [–1.8–6.5]	0.69 $\pm$ 1.88	0.6 [–1.8–6.5]	1.59 $\pm$ 1.17	1.65 [–0.7–4.1]
	T-score (SD)	–0.00 $\pm$ 1.542	–0.1 [–2.8–5.5]	–0.10 $\pm$ 1.82	–0.2 [–2.8–5.5]	0.093 $\pm$ 1.24	–0.1 [–2.2–2.9]
	T-score <–1.0 SD	22.5		32.3		11.8	
	T-score –2.5 SD (%)	1.5		3.2		0	
Total hip	BMD (g/cm ²)	0.908 $\pm$ 0.123	0.924 [0.658–1.258]	0.950 $\pm$ 0.134	0.962 [0.681–1.258]	0.867 $\pm$ 0.099	0.883 [0.658–1.061]
	Z-score (SD)	0.23 $\pm$ 0.87	0.3 [–1.9–2.2]	0.04 $\pm$ 0.89	0.2 [–1.9–1.9]	0.41 $\pm$ 0.83	0.6 [–1.2–2.2]
	T-score (SD)	–0.58 $\pm$ 0.84	–0.5 [–2.3–1.5]	–0.56 $\pm$ 0.88	–0.5 [–2.3–1.5]	–0.61 $\pm$ 0.82	–0.5 [–2.3–1.0]
	T-score <–1.0 SD (%)	33.9		32.3		35.3	
	T-score –2.5 SD (%)	0		0		0	
Femoral neck	BMD (g/cm ²)	0.738 $\pm$ 0.110	0.731 [0.515–1.026]	0.770 $\pm$ 0.121	0.756 [0.586–1.026]	0.707 $\pm$ 0.089	0.702 [0.515–0.918]
	Z-score (SD)	–0.01 $\pm$ 0.85	–0.1 [–1.7–2.1]	–0.09 $\pm$ 0.91	–0.1 [–1.5–1.8]	0.08 $\pm$ 0.78	0 [–1.7–2.1]
	T-score (SD)	–1.23 $\pm$ 0.84	–1.3 [–3.0–0.7]	–1.17 $\pm$ 0.89	–1.3 [–2.5–0.7]	–1.28 $\pm$ 0.79	–1.3 [–3.0–0.6]
	T-score <–1.0 SD (%)	66.2		67.7		64.7	
	T-score –2.5 SD (%)	3.1		0		5.9	
One-third distal radius	BMD (g/cm ²)	0.691 $\pm$ 0.110	0.694 [0.495–0.982]	0.771 $\pm$ 0.083	0.788 [0.562–0.982]	0.618 $\pm$ 0.076	0.615 [0.495–0.819]
	Z-score (SD)	0.26 $\pm$ 1.35	0.30 [–3.4–4.1]	0.14 $\pm$ 1.45	0.3 [–3.4–4.1]	0.37 $\pm$ 1.3	0.3 [–1.7–3.4]
	T-score (SD)	–1.06 $\pm$ 1.4	–0.9 [–4.6–2.7]	–0.97 $\pm$ 1.43	–0.7 [–4.6–2.7]	–1.14 $\pm$ 1.31	–1.2 [–3.3–2.3]
	T-score <–1.0 SD (%)	47.7		41.9		52.9	
	T-score –2.5 SD (%)	15.4		9.7		20.6	
Three-points low bone mass [*]		66.2		71.0		61.8	
Three-points osteoporosis [*]		4.6		3.2		5.9	
Four-points low bone mass ^{**}		67.7		71.0		64.7	
Four-points osteoporosis ^{**}		16.9		12.9		20.6	

Low bone mass and osteoporosis are defined as T-score <–1.0SD and >–2.5SD and T-score –2.5SD respectively.

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Low BMD at lumbar spine, total hip or femoral neck;
*
** Low BMD at lumbar spine, total hip, femoral neck or one-third distal radius.

Table 3

Prevalence of chronic complications of diabetes by T-score overall and at cortical sites

	Subjects with normal T-score (n=10)	Subjects with osteoporosis / low bone mass (n=55)	Femoral Neck T-score > -1.0 SD (n=22)	Femoral Neck T-score < -1.0 SD (n=43)	1/3 Radius T-score > -1.0 SD (n=34)	1/3 Radius T-score < -1.0 SD (n=31)
Cardiovascular diseases	20.0 %	21.8 %	9.0 %	27.9 %	20.6 %	22.6 %
Proliferative diabetic retinopathy	66.7 %	35.6 %	37.5 %	42.1 %	50.0 %	29.2 %
Diabetic nephropathy	10 %	17.4 %	4.6 %	20.9 %	20.6 %	9.7 %
Diabetic neuropathy	80.0 %	64.1 %	66.7 %	66.7 %	64.7 %	69.0 %

Table 4

Population features by T-score at cortical sites.

	Femoral Neck T-score (n=22)	-1.0 SD (n=43)	Femoral Neck T-score SD (n=43)	T-score < -1.0	p-value	1/3 Radius T-score (n=34)	-1.0 SD (n=31)	1/3 Radius T-score < -1.0 SD (n=31)	p-value
Gender, % male	45.5	48.8			0.796	52.9	41.9		0.375
Age, years	63.9 ± 6.6	63.7 ± 7.2			0.928	63.1 ± 7.4	64.5 ± 6.4		0.421
Age at diagnosis, years	11.3 ± 6.0	9.6 ± 6.0			0.269	10.2 ± 6.4	10.2 ± 5.6		0.911
Duration, years	51.9 ± 1.9	52.8 ± 3.5			0.466	52.3 ± 3.2	52.7 ± 3.0		0.340
BMI, kg/m ²	26.4 ± 4.9	26.7 ± 5.2			0.954	27.7 ± 5.9	25.3 ± 3.6		0.145
Waist to hip ratio	0.90 ± 0.08	0.90 ± 0.08			0.970	0.92 ± 0.10	0.87 ± 0.06		0.086
Insulin dose, UI/Kg	0.47 ± 0.14	0.49 ± 0.23			0.691	0.47 ± 0.18	0.50 ± 0.22		0.927
HbA1c, % (mmol/mol)	7.1 ± 0.8 (54.1 ± 8.7)	7.1 ± 1.1 (54.1 ± 12.0)			0.921	7.0 ± 0.9 (53.0 ± 9.8)	7.3 ± 1.1 (56.3 ± 12.0)		0.346
eGFR, ml/min/1.73m ²	79.7 ± 15.9	74.4 ± 20.7			0.406	74.7 ± 18.3	77.9 ± 20.4		0.344
Total cholesterol, mg/dl	159.3 ± 37.1	172.4 ± 35.4			0.170	162.6 ± 32.7	173.9 ± 39.5		0.210
Triglycerides, mg/dl	71.4 ± 31.3	77.4 ± 33.6			0.305	72.6 ± 32.9	78.4 ± 32.9		0.454
HDL, mg/dl	63.2 ± 17.3	66.9 ± 22.5			0.505	60.9 ± 18.7	70.9 ± 22.1		0.054
LDL, mg/dl	81.7 ± 26.4	89.5 ± 24.1			0.142	87.1 ± 24.4	86.6 ± 26.0		0.655
hsCRP, mg/L	0.6 ± 0.9	0.9 ± 1.5			0.611	0.6 ± 1.1	1.0 ± 1.5		0.693
Corrected Calcium, mg/dl	9.0 ± 0.43	8.8 ± 0.6			0.625	8.9 ± 0.5	8.8 ± 0.6		0.253
25-OH Vitamin D, ng/ml	33.8 ± 9.8	35.2 ± 9.1			0.604	35.6 ± 9.2	33.8 ± 9.5		0.468
Bone Alkaline Phosphatase, mcg/L	10.8 ± 2.9	11.0 ± 4.4			0.626	10.9 ± 3.1	11.0 ± 4.8		0.691
Total osteocalcin, ng/ml	13.6 ± 6.5	18.4 ± 10.9			0.053	17.1 ± 11.1	16.6 ± 8.8		1.0
C-Telopeptide, pg/ml	206.6 ± 123.6	277.2 ± 180.4			0.093	255.0 ± 190.9	254.7 ± 141.1		0.707
PTHr, pg/ml	24.7 ± 8.6	29.7 ± 16.0			0.369	28.0 ± 16.7	28.3 ± 11.3		0.525
IGF1, pg/ml	95.5 ± 24.13	99.5 ± 36.2			0.821	97.2 ± 31.2	99.1 ± 34.2		0.601