沖縄の２型糖尿病男性の骨強度に影響を及ぼすライフスタイル

JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Heel bone strength is related to lifestyle factors in Okinawan men with type 2 diabetes mellitus

Michiko Gushiken[1]*, Ichiro Komiya[2], Shinichiro Ueda[3], Jun Kobayashi[1]

[1]Departments of Maternal and Child Nursing, School of Health Sciences, Faculty of Medicine, [2]Department of Community Healthcare System, and [3]Department of Clinical Pharmacology and Therapeutics, Graduate school of Medicine, University of the Ryukyus, Okinawa, Japan

Keywords
Heel bone stiffness, Male, Type 2 diabetes mellitus

***Correspondence**
Michiko Gushiken
Tel.: +81-98-895-3331 (ext. 2643)
Fax: +81-98-895-1432
E-mail address: boshi@med.u-ryukyu.ac.jp

J Diabetes Invest 2015; 6: 150–157

doi: 10.1111/jdi.12285

ABSTRACT

Aims/Introduction: Although male diabetic patients have an increased risk of fracture, there is little information about this in the literature. The association between heel bone stiffness and the lifestyle of male patients with diabetes was evaluated.

Materials and Methods: The study included 108 participants with type 2 diabetes mellitus patients and 168 age-adjusted, healthy male volunteers. None of the participants had a history of osteoporosis or other severe diseases. Heel bone stiffness was examined by quantitative ultrasound, and each participant completed a health interview survey questionnaire. Bone stiffness was taken as an indicator of bone strength. Stepwise regression analysis was used to investigate associations between bone stiffness and lifestyle-related factors, such as sunlight exposure, intake of milk or small fish, regular exercise, cigarette smoking, consumption of alcohol, and number of remaining teeth.

Results: Bone stiffness showed a significant negative association with cigarette smoking [standardized coefficient (SC) = –0.297, *F*-value (*F*) = 10.059] and age (SC = –0.207, *F* = 7.565) in diabetic patients. Bone stiffness showed a significant negative association with age (SC = –0.371, *F* = 12.076) and height (SC = –0.193, *F* = 7.898), as well as a significant positive association with sunlight exposure (SC = 0.182, *F* = 9.589) and intake of small fish (SC = 0.170, *F* = 7.393) in controls.

Conclusions: These findings suggest that cigarette smoking and age are negatively associated with bone stiffness in Okinawan male patients with type 2 diabetes mellitus.

INTRODUCTION

The prevention of bone fractures is an important goal in a society with increasing longevity. It is recognized that patients with type 2 diabetes mellitus are increasing worldwide, and a meta-analysis has shown that diabetic patients have a higher hip fracture risk than people without diabetes[1–3]. Hip fractures are related to chronic pain and disability, loss of independence, decreased quality of life, and increased mortality.

Although osteoporosis is often thought to be a disease of women, studies show that osteoporotic fractures also result in substantial morbidity, mortality and costs in men[4–6]. It has been reported that mortality during the first 3 months after hip fracture is higher in men than in women, and more than one-third of men who developed a hip fracture died within 1 year[7,8].

Received 1 March 2013; revised 15 July 2014; accepted 19 August 2014

However, as the increased fracture risk in men is not sufficiently well known, bone density examinations are infrequent in outpatient clinics. Limited data are available on the relationship between lifestyle and bone status in male patients with type 2 diabetes mellitus[1,6]. Evidence for the benefit of preventive interventions, such as health education on diabetic patients' quality of life, on relieving the burden on caregivers and on decreasing the costs of fractures, is lacking.

METHODS

Data Selection

Heel bone stiffness was measured in 154 male patients with type 2 diabetes mellitus aged 30–83 years who visited the outpatient clinic of the Ryukyu University Hospital. Patients with type 1 diabetes, impaired glucose tolerance (IGT) and slowly progressive insulin-dependent diabetes mellitus (SPIDDM) were excluded. Patients with conditions that could affect bone

metabolism, such as osteomalacia, compression fracture, rheumatoid arthritis, thyroidectomy, gastrectomy, duodenectomy, kidney disease, nephrectomy and adrenalectomy, as well as those on medications that affect bone metabolism, were also excluded from the analysis.

The background characteristics of the type 2 diabetes mellitus patients, including blood pressure, retinopathy and nephropathy, were assessed. Nephropathy was classified according to the kidney disease improving global outcomes 2012 criteria[9]. Patients with nephropathy grades 3b, 4 and 5 who have an estimated glomerular filtration rate (e-GFR) of <44 mL/min/1.73 m^2 were also excluded from the analysis. Thus, 108 male patients with type 2 diabetes mellitus were ultimately selected for the present study.

Heel bone stiffness was also examined in 185 age-adjusted healthy volunteers who underwent the local resident medical health check-up; 168 male participants aged 30–83 years satisfied the selection criteria (Figure 1).

Coding Procedures

The face-to-face baseline interviews were carried out using a semistructured questionnaire.

The associations between lifestyle factors and heel bone stiffness were examined. The lifestyle factors were daily dietary calcium intake, habitual exercise, sunlight exposure, cigarette smoking and consumption of alcohol. Dietary calcium intake was estimated by a semiquantitative food frequency questionnaire. Daily dietary intake of a glass of milk or small fish was divided into five frequencies: one to two times a day, once a day, once in 2–3 days, once a week and none at all. Sunlight exposure was divided into three categories: mostly indoors, outdoors for shopping or commuting and mostly working outdoors. Habitual exercise was assessed by regular exercise currently and regular exercise at 20 years-of-age. Cigarette smoking was divided into two categories: currently smoking, smoked in the past or never smoked. Consumption of alcohol was divided into three categories: drink daily, drink sometimes and never drank (Table 1).

Participants' characteristics, which included age, height, weight and body mass index (BMI), were investigated from their medical records. Diabetic status, such as diabetes duration, levels of glycated hemoglobin [HbA_{1c}; National Glycohemoglobin Standardization Program (NGSP)], treatment, blood pressure, retinopathy and nephropathy, were also studied in the type 2 diabetes mellitus group[10].

Bone Parameters

Heel bone stiffness was measured using quantitative ultrasound (QUS; AchillesA-1000 PLUS; Lunar Corp., Madison, WI,

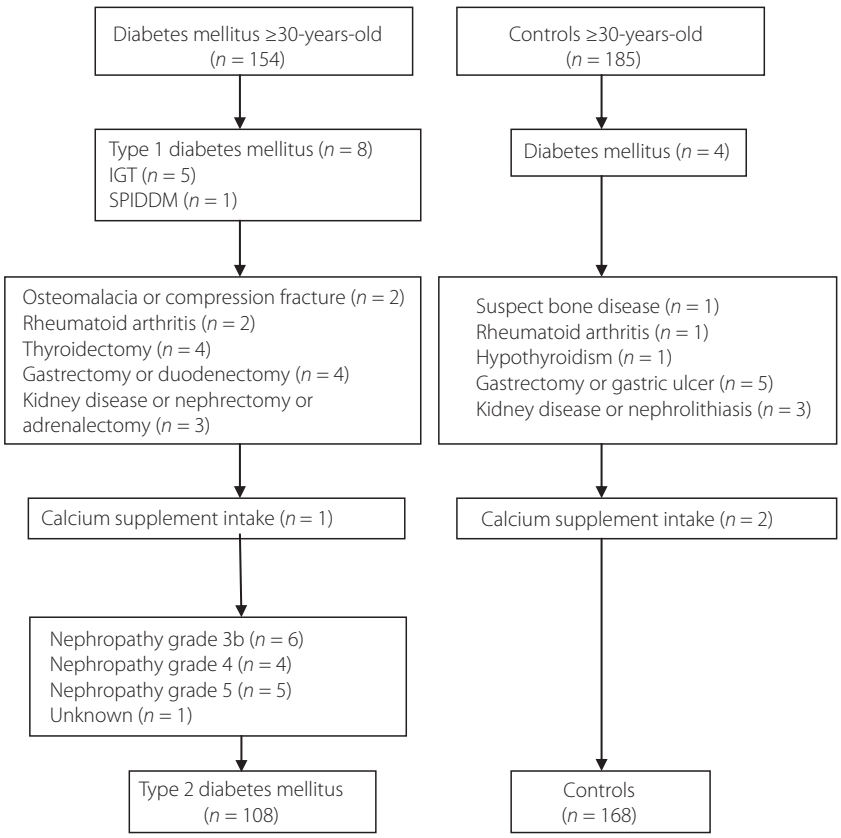

Figure 1 | Case-finding protocol. IGT, impaired glucose tolerance; SPPDM, slowly progressive insulin-dependent diabetes mellitus.

Table 1 | Screening factors and the 15 factors analyzed

Questionnaire
I. Check for diseases related to bone status*
Thyroid or parathyroid gland diseases, gastrectomy, kidney disease, RA, osteoporosis and prescribed calcium supplement
II. Age and physique status
1. Age
2. Height
3. Weight
4. BMI
III. Lifestyle-related factors
Daily calcium intake from diet
5. Glass of milk intake
1–2 times a day, once a day, once in 2–3 days, once a week, none at all
6. Small fish intake: smelts (semi-dried) or sardines (niboshi)
1–2 times a day, once a day, once in 2–3 days, once a week, none at all
Usual lifestyle and exercise
7. Regular exercise currently
8. Regular exercise at 20 years-of-age
9. Sunlight exposure
Mostly indoors, outdoors for or shopping or commuting, mostly working outdoors
Preferences
10. Cigarette smoking: smoking currently, smoked in the past or never smoked
11. Consumption of alcohol: drink daily, drink sometimes, never drank
Remaining no. teeth
12. No. remaining teeth
Patients' medical history
IV. Diabetes status
13. Presumed diabetes duration
14. Glycated hemoglobin
15. Treatment
16. Blood pressure
17. Retinopathy
18. Nephropathy

*BMI, body mass index; RA, rheumatoid arthritis. These were excluded from the analysis.

USA). QUS is recommended for infants and pregnant women, because it does not involve X-rays. Its low cost and portability could make QUS an especially valuable osteoporosis detection tool wherever cost or instrument inaccessibility renders dual-energy X-ray absorptiometry (DXA) difficult or impossible[11]. The theoretical foundation of QUS is based on the variation in the speed of the ultrasound wave (SOS), in units of m/s, and its attenuation along its transmission path, at frequencies of 0.4–1.0 MHz. Ultrasound waves pass faster in bone with higher density. In addition, as ultrasound passes through bone, it undergoes attenuation, with a consequent loss of transmitted acoustic energy. The slope of attenuation as a function of frequency [the broadband ultrasound attenuation (BUA), in units of dB/MHz] is lower in more porous and less microstructurally intact bone. Aside from SOS and BUA, the most common derived variable is 'bone stiffness,' a linear combination of SOS and BUA[12]. The investigation was carried out from 1999 to 2000.

Statistical Analysis

In the descriptive analysis of baseline characteristics, the data are expressed as means ± SD. The Pearson product-moment correlation coefficient and regression analysis were used to compare aging and bone stiffness in both groups. Levine's test, Student's *t*-test and the chi square-test were used to compare both groups. One-way analysis of variance (ANOVA) was carried out to compare classification factors and bone stiffness in the type 2 diabetes group. Stepwise regression analysis was carried out to compare lifestyle factors and bone stiffness. All statistical analyses were carried out using SPSS version 17 (SPSS, Chicago, IL, USA).

Ethical Considerations

Informed consent was obtained from all participants. It was explained that no additional fee would be charged for the heel QUS, and that being enrolled in the investigation would not affect their medical care. After the heel QUS was measured, the participants were immediately given an explanation of the measured value, with appropriate health advice.

RESULTS

Participants' Characteristics

Overall, 108 male patients with type 2 diabetes mellitus and 168 male healthy controls were selected for the present study. The average age was 59.7 ± 10.0 years (range 30–80 years) in type 2 diabetes mellitus patients and 60.5 ± 11.7 years (range 30–83 years) in controls. The average height was 162.1 ± 5.5 cm (range 152–178 cm) in type 2 diabetes mellitus patients and 160.6 ± 6.2 cm (range 147–177 cm) in controls. Weight was 65.3 ± 8.8 kg (range 46–88 kg) and 63.8 ± 9.0 kg (range 45–94 kg), and BMI was 24.8 ± 2.8 kg/m^2 (range 19–33 kg/m^2) and 24.7 ± 2.8 kg/m^2 (range 18–34 kg/m^2), respectively. These parameters, except for height, were almost identical in the two groups.

The mean duration of illness of type 2 diabetes mellitus patients was 12.7 ± 8.2 years (range 0.8–32 years), and the mean glycated hemoglobin (HbA_{1c}; NGSP) was 8.0 ± 1.8% (5.6–13.8%)[10]. They were treated with diet (n = 32), insulin injections (n = 23) or oral hypoglycemic agents (n = 53), with patients taking several antidiabetic agents, such as sulfonylureas (n = 44), α-glycosidase inhibitors (n = 14), biguanides (n = 12) or others (n = 1).

The average bone stiffness was 87.8 ± 14.8% in type 2 diabetes mellitus patients and 87.9 ± 14.7% in controls. In normal weight (BMI <25 kg/m^2) participants, the average bone stiffness was 83.7 ± 16.3% in type 2 diabetes mellitus patients and 88.6 ± 14.9% in controls, whereas in overweight (BMI ≥25 kg/

m^2) participants, it was 90.2 ± 13.8% in type 2 diabetes mellitus patients and 87.2 ± 14.4% in controls. Fractures occurred in 10 (9.3%) type 2 diabetes mellitus patients and 12 (7.1%) controls (Table 2).

Table 3 shows the background characteristics of the type 2 diabetes mellitus patients. Blood pressure was classified according to the standard 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement[13]. Diabetic retinopathy was graded as no diabetic retinopathy (NDR), simple diabetic retinopathy, preproliferative diabetic retinopathy (pre-PDR) and proliferative diabetic retinopathy (PDR) according to the diagnostic classification by Davis *et al.*[14] Nephropathy was classified based on cause, GFR stage and albuminuria stage according to the Kidney Disease: Improving Global Outcomes 2012 criteria[9].

Age-Related Bone Loss

Heel bone stiffness decreased with age in both groups, but it was significantly associated with age only in controls. The regression slope was flatter in type 2 diabetes mellitus than in controls. Furthermore, from the 30 s to the 40 s, heel bone stiffness was lower in type 2 diabetes mellitus patients than in controls (type 2 diabetes mellitus, stiffness = –0.19 × age + 98.5, $r = 0.12$, $P = 0.20$; controls, stiffness = –0.33 × age + 107.9, $r = 0.26$, $P = 0.01$; Figure 2).

Lifestyle Factor Effects

Table 4 shows that 108 type 2 diabetes mellitus patients and 168 control subjects were included in categorical comparisons that included age, height, weight, BMI, intake of a glass of milk or small fish intake as part of the daily diet, regular exercise currently or at 20 years-of-age, sunlight exposure, cigarette smoking, consumption of alcohol and the number of remaining teeth.

Weight and BMI had no significant correlations with heel bone stiffness in both groups. However, age had significant negative associations with bone stiffness in both groups [type 2 diabetes mellitus, standardized coefficient (SC) = –0.207, *F*-value (*F*) = 7.565; controls, SC = –0.371, $F = 12.076$]. Furthermore, cigarette smoking was significantly negatively associated with heel bone stiffness in type 2 diabetes mellitus only (SC = –0.297, $F = 10.059$). In contrast, sunlight exposure and small fish intake were significantly associated with heel bone stiffness in controls only (sunlight exposure, SC = 0.182, $F = 9.589$; small fish intake, SC = 0.170, $F = 7.393$).

Duration of diabetes, HbA_{1c} and treatment were not associated with heel bone stiffness.

DISCUSSION

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased

Table 2 | Characteristics of type 2 diabetes mellitus patients and controls

	Type 2 diabetes mellitus patients ($n = 108$)	Controls ($n = 168$)	*P*-value
Age, years (range)	59.7 ± 10.0 (30–80)	60.5 ± 11.7 (30–83)	0.553
Height, cm (range)	162.1 ± 5.5 (152–178)	160.6 ± 6.2 (147–177)	0.044*
Weight, kg (range)	65.3 ± 8.8 (46–88)	63.8 ± 9.0 (45–94)	0.161
BMI, kg/m^2 (range)	24.8 ± 2.8 (19–33)	24.7 ± 2.8 (18–34)	0.704
Duration of diabetes, years (range)	12.7 ± 8.2 (0.8–32)		
HbA_{1c} (%) (NGSP)	8.0 ± 1.8 (5.6–13.8)		
Therapeutic modality	Diet ($n = 32$)		
	Insulin ($n = 23$)		
	OHA† ($n = 53$)		
	Sulfonylurea ($n = 44$)		
	α-Glucosidase inhibitor ($n = 14$)		
	Biguanide ($n = 12$)		
	Others ($n = 1$)		
Bone stiffness (%)	87.8 ± 14.8	87.9 ± 14.7	0.673
Normal weight (BMI <25 kg/m^2)	83.7 ± 16.3 ($n = 51$)	88.6 ± 14.9 ($n = 88$)	0.078
Overweight (BMI ≥25 kg/m^2)	90.2 ± 13.8 ($n = 57$)	87.2 ± 14.4 ($n = 80$)	0.227
History of fracture	10 (9.3%)	12 (7.1%)	0.401
Smoking currently	26 (24.1%)	42 (25.0%)	0.157
Smoked in the past or never smoked	82 (75.9%)	124 (73.8%)	0.157
Unknown	–	2 (1.2%)	

BMI, body mass index; HbA_{1c}, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program. Results are expressed as means ± SD (range). Analysis using Levene's test, Student's *t*-test or the chi square-test. *$P < 0.05$. †Oral hypoglycemic agents (OHA), some patients took more than one drug. No patients took pioglitazone.

Table 3 | Background characteristics of type 2 diabetes mellitus patients

Characteristic	Classification	*n* (%) *n* = 108	Stiffness (%) mean ± SD	*P*-value*
Blood pressure	Normal pressure (120–139 mmHg/80–89 mmHg)	54 (50.0)	87.2 ± 15.4	0.323
	Hypertension (≥140 mmHg/90 mmHg or under treatment)	51 (47.2)	88.1 ± 15.1	
	Hypotension (<120 mmHg/80 mmHg)	3 (2.8)	69.7 ± 7.2	
Retinopathy	No diabetic retinopathy	56 (51.9)	87.6 ± 14.8	0.453
	Simple diabetic retinopathy	28 (25.9)	85.3 ± 16.8	
	Preproliferative diabetic retinopathy	7 (6.5)	89.3 ± 10.8	
	Proliferative diabetic retinopathy	10 (9.3)	85.0 ± 18.4	
	Unknown	7 (6.5)	91.6 ± 14.6	
Nephropathy	Grade 1 (normal or high: GFR ≥90 mL/min/1.73 m^2)	61 (56.5)	87.4 ± 15.4	0.379
	Grade 2 (mildly decreased: GFR 60–89 mL/min/1.73 m^2)	36 (33.3)	85.1 ± 16.0	
	Grade 3a (mildly or moderately decreased: GFR 45–59 mL/min/1.73 m^2)	11 (10.2)	93.0 ± 11.9	

GFR, glomerular filtration rate; SD, statdard deviation. Results are means ± SD. No patients were undergoing dialysis or receiving vitamin D treatment. *$P < 0.05$, analysis using analysis of variance, with no significant differences.

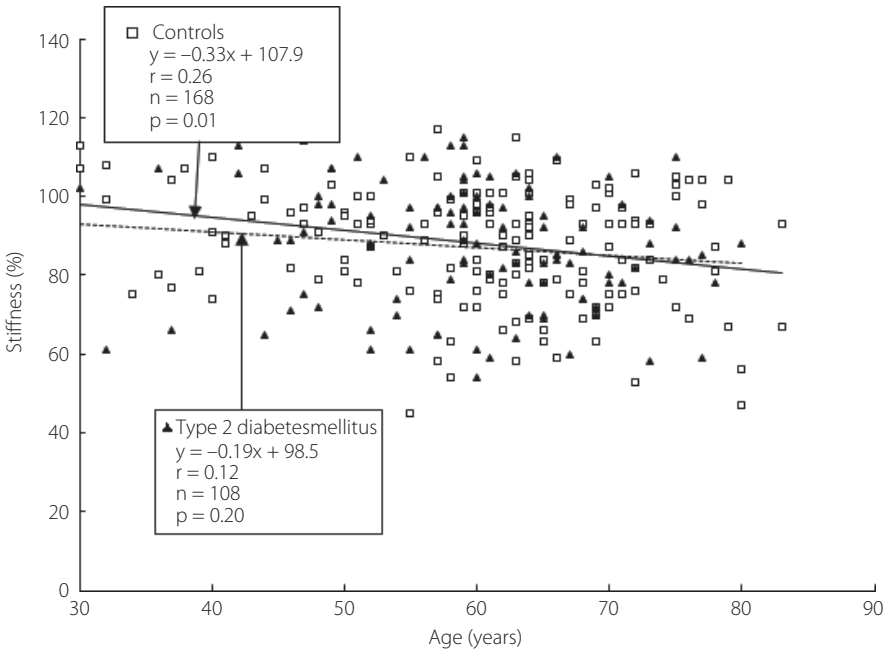

Figure 2 | Relationship between age and heel bone stiffness on quantitative ultrasound.

fracture risk. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume, and in any given individual it is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation and mineralization. A fracture occurs when a failure-inducing force is applied to osteoporotic bone[15].

QUS methods have been introduced in recent years for the assessment of skeletal status in osteoporosis. Current evidence supports the use of QUS techniques for the assessment of fracture risk in elderly women. This has been best established for water-based calcaneal QUS systems. The rules of physics describe the relationships among mechanical properties, 3-D bone architecture and velocity or attenuation of transmitted ultrasonic waves. QUS parameters could allow one to assess the mechanical properties of cortical and trabecular bone, which in turn are important determinants of whole bone stiffness and fracture risk[16].

A meta-analysis has suggested that low QUS values are associated with overall fracture risk, low-trauma fractures, and with hip and other fractures in older women; the association is similar to that seen with DXA[17]. BUA is associated with an

Table 4 | Stepwise regression analysis of bone stiffness in type 2 diabetes mellitus patients and controls

	Dependent variable					
	Bone stiffness (%)					
	Type 2 diabetes mellitus			Controls		
Independent variables	Standardized coefficient	*F*-value	*P*-value	Standardized coefficient	*F*-value	*P*-value
Age (years)	–0.207	7.565	0.033	–0.371	12.076	0.000
Height (cm)				–0.193	7.898	0.018
Sunlight exposure				0.182	9.589	0.013
Small fish intake				0.170	7.393	0.023
Cigarette smoking	–0.297	10.059	0.003			
n	108			168		
Significance (*P*)	0.001			0.000		
Adjusted R^2	0.139			0.155		
F-value	7.565			7.393		

Controls: eight factors poorly fitting factors (weight, body mass index, milk intake, regular exercise at 20 years-of-age, regular exercise currently, cigarette smoking, consumption of alcohol and number of remaining teeth). Type 2 diabetes mellitus patients: 13 poorly fitting factors (height, weight, body mass index, milk intake, small fish intake, regular exercise at 20 years-of-age, regular exercise currently, sunlight exposure, consumption of alcohol, number of remaining teeth, diabetes duration, glycated hemoglobin and treatments for diabetes).

increased risk for hip fracture. Intertrochanteric fractures in particular are strongly associated with a low BUA measurement[18]. These indices indirectly describe bone micro-architectural features, such as trabecular spacing, orientation and connectivity, as well as bone density[10]. Additionally, the heel bone is weight-bearing and contains approximately 90% trabecular bone, which has a high metabolic turnover rate and a pattern of bone loss similar to the spine. Bone stiffness might be thought to be almost the same as 'bone strength', which is a combined indicator of 'bone density' and 'bone quality.'

Previous studies reported that diabetic patients had higher bone mineral density (BMD; g/cm^2) than those without diabetes, despite an increased fracture risk[1–3]. This phenomenon might be explained by poor bone quality rather than BMD. Recent studies have suggested that collagen cross-linking, a low level of serum vitamin B_6, and advanced glycation end-products play an important role in bone quality[19,20]. Based on the present definition, both BMD and bone quality, which encompass the structural and material properties of bone, are important factors in the determination of 'bone strength'[15].

In the present study, aging was shown to reduce heel bone stiffness in both groups. The regression slope was flatter in type 2 diabetes mellitus patients than in controls, and from the 30 s to the 40 s, heel bone stiffness was lower in type 2 diabetes mellitus patients than in controls.

These estimates in men were remarkably similar to those in women with type 2 diabetes mellitus[21]. The metabolic effects of poor glycemic control could lead to bone loss in the initial stage of type 2 diabetes mellitus. Based on a previous study, in patients with diabetes, a low bone formation rate retards bone accumulation during growth, and low bone turnover retards age-related bone loss. In the elderly with a long duration of type 2 diabetes mellitus, the low bone turnover delays bone loss, and might eventually result in bone density that exceeds the value expected for age[22].

The present data suggest that cigarette smoking is a significant risk factor for decreased bone strength in type 2 diabetes mellitus. A meta-analysis showed that cigarette smoking produced the greatest increases in hip fracture risk (40%) in men[23]. There is growing evidence that cigarette smoking is a risk factor for the development of type 2 diabetes[24,25]. Cigarette smoking is associated with insulin resistance, and affects calcium and vitamin D metabolism[26,27]. Furthermore, smokers with diabetes have an increased rate of microvascular complications, cardiovascular disease (CVD) and premature death. Therefore, the American Diabetes Association recommends that all patients not smoke[24].

Okinawans have approximately 20% fewer hip fractures than mainland Japanese[28]. It has been found that diabetic osteopenia was higher in northern Japan, Hokkaido and Tohoku regions, than in southern Japan, Kyushu and Chugoku-Shikoku regions[29]. Total mean monthly sunlight exposure in 2000 was 32,235 MJ/m^2 in Okinawa and 27,818 MJ/m^2 in northern areas (Sapporo)[30]. Okinawa is the southernmost point in Japan, and the amount of sunlight exposure per unit is higher than that received in northern areas; therefore, spending time outside allows Okinawan men to have optimal vitamin D levels year round.

Calcium is an essential nutrient for critical biological functions, such as nerve conduction, muscle contraction and structural support of the skeleton. Studies show that, among Japanese women, plants and fish contributed 46.7% of total dietary calcium, whereas 32.4% was derived from milk[31]. Japanese people are accustomed to traditional dishes, such as fish, especially small fish eaten with soft and edible bones, like sardines and smelts. One hundred grams of milk, smelts (semi-dried)

and sardines (niboshi) contain 110, 380, and 2200 mg of calcium per 100 g edible portion, respectively[32]. Smelts are not a common food in Okinawa, but sardines (niboshi) are very commonly eaten. Regarding the data concerning calcium intake in men, the total mean intake was 516 mg/day in Japan and 444 mg/day in Okinawa. As for dried small fish intake in men, total mean intake was 16 g/day in Japan and 5 g/day in Okinawa[33,34]. Therefore, the calcium intake was lower in Okinawan men than in mainland Japanese men.

The positive relationships between small fish intake and sunlight exposure and bone stiffness, which were seen in controls, disappeared in patients with type 2 diabetes mellitus. Patients with diabetes require more calcium intake and sunlight exposure than those without diabetes, because of increased calcium loss from urine with glycosuria or exacerbating diabetic complications, such as kidney failure.

Bone loss appears to be progressive in diabetic patients with chronic kidney disease (CKD). A previous study has noted that patients with initial eGFR 43.8 ± 3.6 mL/min/1.73 m^2 were not on dialysis after 2-year follow up[35]. Another study has reported that parathyroid hormone (PTH) was found to be elevated in more than 20% of CKD grade 3 patients[36]. PTH stimulates the bone metabolism and rotation. PTH increases the phosphate excretion in urine by acting on a proximal renal tubule, PTH also increases reabsorption of calcium with stimulating production of activated vitamin D (1α, $25[OH]_2$ D_3). Therefore, complicating factors are involved in calcium homeostasis and bone metabolism in type 2 diabetes patients with renal failure. Consequently, patients with nephropathy grades 3b, 4 and 5 with an eGFR of <44 mL/min/1.73 m^2 were excluded from the analysis in the present study.

It has also been reported that diabetic retinopathy is associated with fracture risk[37]. The effects of atherosclerosis, or increased advanced glycation end-products, which are often seen in diabetic patients with retinopathy and/or nephropathy, might be involved. The metabolic effects of diabetes on the skeleton are complex. Further study is required to determine whether intervention could prevent the reduction of bone strength and hip fractures in diabetic patients.

Although there are several life factors, cigarette smoking was strongly associated with bone strength in patients with diabetes mellitus; therefore, all patients with diabetes should not smoke.

ACKNOWLEDGMENTS

The authors thank the doctors of the Second Department of the University of the Ryukyus Hospital. This work was supported by the staff in the Outpatient Department and in the Okinawa General Health Service Association. No financial support was provided.

REFERENCES

1. Schwartz AV, Sellmeyer DE, Ensrud KE, *et al.* Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 2001; 86: 32–38.
2. 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: 427–444.
3. Schwartz AV, Vittinghoff E, Bauer DC, *et al.* Association of BMD and FRAX score with risk of fracture in older adults with type 2 Diabetes. *JAMA* 2011; 305: 2184–2192.
4. Qaseem A, Snow V, Shekelle P, *et al.* Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. *Ann Int Med* 2008; 148: 680–684.
5. Liu H, Paige NM, Goldzweig CL, *et al.* Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. *Ann Int Med* 2008; 148: 685–701.
6. Brauer CA, Coca-Perraillon M, Cutler DM, *et al.* Incidence and mortality of hip fractures in the United States. *JAMA* 2009; 302: 1573–1579.
7. Haentjens P, Magaziner J, Colon-Emeric CS, *et al.* Meta-analysis: excess mortality after hip fracture among older women and men. *Ann Int Med* 2010; 152: 380–390.
8. U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. *Ann Int Med* 2011; 154: 356–364.
9. KDIGO. 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150.
10. Kashiwagi A, Kasuga M, Araki E, *et al.* International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program Values. *J Diabetes Invest* 2012; 3: 39–40.
11. Didier H, Marc-Antoine K. Quantitative ultrasound for the detection and management of osteoporosis. *Salud Publica Mex* 2009; 51: 525–537.
12. Tan BK, Price R. Quantitative Ultrasound (QUS). *Aust J Physiother* 2007; 53: 290.
13. World Health Organization, International Society of Hypertension Writing Group. 2013 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens* 2003; 21: 1983–1992.
14. Davis MD, Meyers FL, Bresnick GH, *et al.* Natural evolution. In: L'Esperance FAJr (ed.). Current diagnosis and Management of Chorioretinal Diseases. C.V. Mosby, St Louis, MO, 1977; 179–184.
15. Osteoporosis prevention, diagnosis, and therapy. NIH Consensus Statement Online 2000 March 27-29; 17: 1-36 [accessed on 2012, March 17]. NIH Consensus Statement Web site. Available at: http://consensus.nih.gov/2000/2000Osteoporosis111html.htm.
16. Glüer C-C. Quantitative ultrasound techniques for the assessment of osteoporosis: expert agreement on current status. *J Bone Miner Res* 1997; 12: 1280–1288.

17. Marín F, González-Macías J, Díez-Pérez A, *et al.* Relationship between bone quantitative ultrasound and fractures: a meta-analysis. *J Bone Miner Res* 2006; 21: 1126–1135.
18. Bauer DC, Gluer CC, Cauley JA, *et al.* Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Int Med* 1997; 157: 629–634.
19. Saito M, Fujii K, Mori Y, *et al.* Role of collagen enzymatic and glycation induced cross-links as a determinant of bone quality in spontaneously diabetic WBN/Kob rats. *Osteoporos Int* 2006; 17: 1514–1523.
20. Saito M, Marumo K. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. *Osteoporos Int* 2010; 21: 195–214.
21. Gushiken M, Maeshiro C, Kuniyoshi M, *et al.* A survey of the bone mineral density in Okinawan female with type 2 diabetes mellitus. *Jpn J Health Hum Ecol* 2003; 69: 57–63 (Japanese)
22. Krakauer JC, Mckenna MJ, Buderer NF, *et al.* Bone loss and bone turnover in diabetes. *Diabetes* 1995; 44: 775–782.
23. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. *Calcif Tissue Int* 2001; 68: 259–270.
24. American Diabetes Association. Standards of medical care in diabetes-2012. *Diabetes Care* 2014; 37: s14–s80.
25. Carole W, Patrick B, William AG, *et al.* Active smoking and the risk of type 2 diabetes. *JAMA* 2007; 298: 2654–2664.
26. Targher G, Alberiche M, Zenere MB, *et al.* Cigarette smoking and insulin resistance in patients with noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1997; 82: 3619–3624.
27. Brot C, Jorgensen NR, Sorensen OH. The influence of smoking on vitamin D status and calcium metabolism. *Eur J Clin Nutr* 1999; 53: 920–926.
28. Ross PD, Norimatsu H, Davis JW, *et al.* A comparison of hip fracture incidence among native Japanese, Japanese Americans, and American Caucasians. *Am J Epidemiol* 1991; 133: 801–809.
29. Imura H, Seino Y, Nakagawa S, *et al.* Diabetic osteopenia in Japanese: a geographic study. *J Jpn Diabetes Soc* 1987; 30: 929–934 (Japanese).
30. The Ministry of Land, Infrastructure, and Transport. Solar and infrared radiation data (Japanese). No date [accessed on 2013, June 21]. The Ministry of Land, Infrastructure, and Transport, Japan Meteorological Agency. Available at: http://www.data.kishou.go.jp/obs-env/radiation/data_rad.html.
31. Zhang Y, Ojima T, Murata C. Calcium intake pattern among Japanese women across five stage of health behavior change. *J Epidemiol* 2007; 17: 45–53.
32. The Ministry of Education, Culture, Sports, Science, and Technology. Standard tables of food composition in Japan: 2010 (Japanese). 2010 [accessed on 2013, June 25]. The Ministry of Education, Culture, Sports, Science, and Technology. Available at: http://www.mext.go.jp/b_menu/shingi/gijyutu/gijyutu3/houkoku/1298713.htm.
33. The Ministry of Health, Labour and Welfare. National Health and Nutrition Survey: 2011 (Japanese). 2013 [accessed on 2013 June 25]. The Ministry of Health, Labour and Welfare. Available at: http://www.mhlw.go.jp/bunya/kenkou/eiyou/dl/h23-houkoku.pdf.
34. The Department of Welfare and Health in Okinawa prefecture. The Okinawa Prefectural Health and Nutrition Survey: 2011 (Japanese). 2013 [accessed on 2013 Jun 25]. The Department of Welfare and Health in Okinawa prefecture. Available at: http://www. kenko-okinawa21.jp/.
35. Rigalleau V, Lasseur C, Raffaitin C, *et al.* Bone loss in diabetic patients with chronic kidney disease. *Diabet Med* 2007; 24: 91–93.
36. Donadio C, Ardini M, Lucchesi A, *et al.* Parathyroid hormone and large related C-terminal fragments increase at different rates with worsening of renal function in chronic kidney disease patients. A possible indicator of bone turnover status? *Clin Nephrol* 2007; 67: 131–139.
37. Ivers RQ, Mitchell P, Cumming RG, *et al.* Diabetes and risk of fracture. *Diabet Care* 2001; 24: 1198–1203.