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Hyperglycemic status is associated with an elevated risk of osteoporotic fracture in community-dwelling elderly Japanese men: The Fujiwara-kyo osteoporosis risk in men (FORMEN) cohort study

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ABSTRACT

Purpose: Patients with type 2 diabetes mellitus have an increased fracture risk. However, population-based studies on the association between glycemic status and fracture risk are scarce, and none have targeted a Japanese population. In addition, patients in the lowest category of hemoglobin A1c (HbA1c) do not always show the lowest risk. This study aimed to clarify the association between glycemic status and fracture risk in community-dwelling elderly Japanese men.

Methods: A total of 1992 men aged ≥65 years completed baseline measurements including fasting plasma glucose (FPG), HbA1c, bone density, and an interview regarding past disease history. Osteoporotic fractures (OPFs) that occurred during the 5-year follow-up period were determined through interviews. An OPF at the spine, hip, proximal humerus, or distal radius was defined as a major OPF (MOF).

Results: After excluding participants who had a history of type 1 diabetes mellitus and thiazolidinedione therapy, 1951 men were analyzed. Men with hyperglycemia in the diabetic range had a significantly higher risk of OPF compared with those with normoglycemia, after adjusting for confounding factors including insulin therapy (hazard ratio (HR): 2.76, 95% confidence interval (CI): 1.17, 6.50 in FPG ≥ 126 mg/dl; HR: 2.49, 95% CI: 1.07, 5.77 in HbA1c ≥ 6.5%). An elevated risk of MOF was observed in participants in the prediabetic HbA1c category (HR: 2.15, 95% CI: 1.00, 4.62 in 5.7% ≤ HbA1c < 6.5%) in addition to those in the diabetic category. The intermediate glycemic status group showed intermediate risk, suggesting that the association was linear.

Conclusions: Hyperglycemia was associated linearly with elevated fracture risk in community-dwelling elderly men. MOF risk may be elevated in Japanese elderly men with prediabetic glycemic status.

1. Introduction

The numbers of patients with type 2 diabetes mellitus (T2DM) and osteoporosis are increasing along with the growth of the elderly population. This places great public health and economic burdens on our society [1,2]. Many prospective cohort studies and their meta-analyses have reported that T2DM is associated with an elevated risk of non-traumatic fracture in elderly men and women [3–5]. Fractures have come to be accepted as one of the complications for patients with either type 1 diabetes mellitus (T1DM) or T2DM [6–8]. However, no population-based study on this topic has been conducted in Japan, despite more than ten million patients having T2DM in the country [9]. Moreover, characteristics of T2DM in Japanese patients differ from those in Caucasian patients in terms of higher insulin resistance [10],

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lower insulin secretion [10–12], lighter body weight [13], and fewer coronary heart diseases as complications [14,15] and causes of death [16]. This suggests the possibility of a racial/ethnic difference in the association between hyperglycemia and fracture risk.

In addition, patients with inadequately controlled T2DM whose glycated hemoglobin A1c (HbA1c) levels exceed 7.5% [17] or 9% [18,19] show a significantly higher risk of fracture. Interestingly, patients in the lowest category of HbA1c did not always show the lowest risk. Conway et al. [18] reported that HbA1c levels of 6.5%–6.9% were associated with the lowest risk of fracture in elderly patients with T2DM. Similarly, patients with HbA1c levels of < 6.0% showed a 20% higher risk compared to those with HbA1c levels of 6.0%–6.9% in a study from Taiwan [19]. The reason for this J-shaped relationship between HbA1c levels and fracture risk in patients with T2DM is unclear. Several studies suggest that insulin therapy [20–22] or tight glycemic control [23] may increase fracture risk due to an increase in falls from hypoglycemic events. In addition, patients with early stage T2DM [24] and patients with impaired glucose tolerance (IGT) [25] had decreased fracture risk compared with non-diabetics probably due to an increase in body mass index (BMI) and bone mineral density (BMD). While many population-based studies have reported T2DM-related increases in fracture risk [17,20,22,25–28], only a few have investigated the association between glycemic status and fracture risk [17,25,27], fewer studies have examined the fracture risk in people in prediabetic stages [25], and no study has been conducted among a Japanese population.

This study examined community-dwelling elderly Japanese men to clarify whether hyperglycemia and higher fracture risk are associated in this population, and whether the J-shaped relationship between glycemic status and fracture risk is observed in community-dwelling elderly people after allowing for anti-diabetic treatments including insulin use.

2. Materials and methods

2.1. Study setting

The Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study is an ancillary study of a larger prospective cohort study, the Fujiwara-kyo study, which aims to provide a scientific basis for comprehensive strategies to prevent frailty, increase the number of healthy life years, and enhance the functioning and quality of life of elderly men and women in Japan. The FORMEN study evaluates bone health in male participants of the Fujiwara-kyo study. Details of the Fujiwara-kyo and FORMEN studies have been described elsewhere [29].

2.2. Study participants

Participants of the Fujiwara-kyo study enrolled voluntarily in four cities of Nara Prefecture, Japan. Participants were included if they were aged ≥65 years at enrollment, living at home, able to walk without assistance from another person, and able to provide self-reported information and written informed consent. Of the 4427 participants of the Fujiwara-kyo study, 2012 men completed the FORMEN baseline study, and were invited to the follow-up surveys conducted 5 years later to identify the outcome, i.e., osteoporotic fractures.

The study protocol of the Fujiwara-kyo study was approved by the Medical Ethics Committee of Nara Medical University. The protocol of the FORMEN study was approved by the Ethics Committee of Kindai University Faculty of Medicine (#19-032).

2.3. Identification of outcome

Trained nurses determined the site of fracture, time of fracture event, situation in which the fracture occurred, and X-ray diagnosis of the fracture (yes/no) from interviews conducted during the follow-up surveys. The same information was obtained in supplemental postal and telephone surveys conducted just after the follow-up surveys for those who did not participate in the follow-up surveys. Osteoporotic fracture (OPF) was defined as a fracture at any skeletal site other than the head, finger, lower thigh, and foot that occurred after baseline without strong external force and was diagnosed by a medical doctor with radiographs. Major OPF (MOF) included an OPF at the spine, hip, proximal humerus, or distal radius. In cases of multiple fractures, the first fracture during the follow-up period was adopted as the outcome.

We validated this method using 21 incident fractures identified during the first two years of follow-up. Of these, 19 cases provided consent for us to contact the attending surgeon in order to confirm the occurrence, date, and skeletal site of the fracture. All surgeons responded to our inquiries and confirmed the occurrence of all self-reported fractures, that differences between the self-reported date and real date of fracture events were within six months, and that the self-reported fracture site seldom differed from the correct site. We concluded that the false positive rate for fracture detection using the present method was extremely low (0% in this pilot study) and that the margin of error in fracture dates and skeletal sites would be acceptable.

2.4. Medical history and lifestyle factors

Participants completed a questionnaire survey consisting of 250 items that covered medical history of fracture, malignant diseases, hypertension, diabetes mellitus, coronary heart disease, dyslipidemia, asthma, kidney disease, prostate disease, and medications due to these diseases. Participants were asked to bring current prescriptions of medications to the baseline visit, and interviewers recorded the names and doses of the medications including insulin, thiazolidinediones (TZD), and other anti-diabetic drugs.

T1DM was defined as either physician-diagnosed T1DM or insulin-dependent diabetes mellitus, or physician-diagnosed diabetes mellitus diagnosed at younger than 40 years of age. T2DM was defined as either physician-diagnosed T2DM or non-insulin-dependent diabetes mellitus, or physician-diagnosed middle age or older-onset diabetes mellitus without specification of type 1 or type 2.

2.5. Laboratory measurements

We drew blood from each participant after an overnight fast and obtained plasma and serum samples for the following conventional biochemical tests: FPG, HbA1c, serum insulin (FSI), creatinine, triglycerides, and cholesterol.

FPG levels (mg/dl) were determined by the hexokinase-glucose-6-phosphate dehydrogenase method (L-Type Glu 2, Wako Pure Chemical Industries, Ltd., Osaka, Japan); HbA1c levels (%, National Glycohemoglobin Standardization Program) by the latex aggregation immunoassay (Determiner L HbA1C, Kyowa Medex Co., Tokyo, Japan); and FSI levels (μU/ml) by the chemiluminescent enzyme immunoassay (Lumipulse Presto II/Insulin, Fujirebio Inc., Tokyo, Japan). To estimate insulin resistance and beta-cell function, homeostasis model assessment-insulin resistance (HOMA-IR) and HOMA-b, respectively, were calculated using FPG and FSI values for participants who were not on insulin therapy and whose FPG levels were ≤140 mg/dl [30].

Serum creatinine levels (mg/dl) were measured using an enzymatic method (L-type CRE·M; Wako Pure Chemical Industries, Ltd., Osaka, Japan). To evaluate renal function, estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease Study equation modified for the Japanese population by the Japanese Society of Nephrology as follows: eGFR (ml/min/1.73 m^2) = 194 × serum $Cr^{-1.094}$ × $age^{-0.287}$ [31].

2.6. Bone mass measurements

Areal bone mineral density (aBMD) (g/cm^2) was measured by dual-energy X-ray absorptiometry (DXA) at the lumbar spine in a

posteroanterior projection (QDR4500A, Hologic Inc., Bedford, MA, USA). The region of interest (ROI) was set as the second to fourth vertebrae, in accordance with Japanese guidelines for diagnosing osteoporosis at the time of the survey [32]. We excluded vertebrae with fractures or degenerative changes causing > 1 SD greater aBMD from the immediately adjacent vertebrae, in accordance with the International Society for Clinical Densitometry guidelines for individual vertebrae exclusion [33]. Consequently, the baseline study included data from 1897 men with at least two assessable vertebrae. We scanned the right hip unless the right hip showed significant deformity or had been replaced with an artificial hip. We obtained valid hip aBMD values in 1987 participants.

Short-term precision of aBMD measurements was 1.2% for both the spine and hip, as calculated from five measurements on different days from five male volunteers (age range, 21–41 years) [34]. Quality assurance was conducted using a spine phantom throughout the study period, and no significant drift in measurements was detected.

2.7. Body size measurements

We measured the height (cm) and weight (kg) of participants using an automatic scale and calculated BMI (kg/m^2).

2.8. Statistical analyses

All statistical calculations were performed with SAS software (Version 9.4, SAS Institute, Cary, NC, USA) on a personal computer. Levels of biochemical markers for glucose metabolism were all distributed log-normally; therefore, these values were logarithmically converted and then statistically analyzed. These data are expressed as geometric means and SDs. Participants were classified into three groups, i.e., normoglycemic, impaired fasting glucose/prediabetic, and diabetic categories, by baseline levels of FPG (FPG < 100, 100 ≤ FPG < 126, FPG ≥ 126) or HbA1c (HbA1c < 5.7, 5.7 ≤ HbA1c < 6.5, HbA1c ≥ 6.5), according to guidelines of the American Diabetes Association [35] and the Japan Diabetes Society [36]. Fracture risk in these groups was evaluated with a Cox proportional hazards model including possible confounding factors as covariates. Missing values of aBMD (95 values for spine aBMD, 5 values for hip aBMD) were imputed by values estimated from the multivariate regression equation incorporating age, BMI, and hip aBMD for spine aBMD imputation or spine aBMD for hip aBMD imputation.

3. Results

3.1. Baseline characteristics of participants in glycemic groups

Of the 2012 participants, 4 men with T1DM, 35 with a history of TZD therapy, and 20 with missing test results were excluded. We determined the presence or absence of the outcome in 1951 men subjected to analyses. We identified 200 participants diagnosed at baseline with T2DM. Their median duration of disease was 10.5 years, and 182 men received a pharmaceutical anti-diabetic treatment, including insulin in 17 men.

Table 1 shows the basic characteristics of participants grouped by levels of glycemic index. With higher glycemic status, we observed an increasing trend in weight, BMI, aBMD, and serum triglycerides levels, and a decreasing trend in HDL-cholesterol levels. During the median follow-up of 54.3 months (8480 person-years (PY)), 44 OPFs (5.2/1000 PY) including 34 MOFs (4.0/1000 PY) were identified and showed an increasing trend with an increase in FPG.

3.2. Age-adjusted HRs of baseline variables on incident osteoporotic fractures

Table 2 shows unadjusted HRs of age and age-adjusted HRs of baseline variables on the incidence of osteoporotic fractures. Participants diagnosed with T2DM did not have a significantly higher risk of either OPF or MOF. However, every 1 SD increase in glycemic index was linearly associated with a significantly higher risk of OPF or MOF, ranging from 38% to 48%. Those receiving insulin therapy had an approximately three-fold greater risk of OPF and MOF compared with non-insulin users. Higher aBMD both at the spine and hip showed a significant protective effect against fracture. Histories of gastrectomy, stroke, and OPF were associated with a significantly higher risk of incident OPF.

3.3. Adjusted HRs for glycemic indices on the incidence of OPF

To evaluate independent effects of glycemic levels on the incidence of OPF and MOF, we adjusted this association for baseline characteristics that showed a significant age-adjusted HR on incident OPF (Table 2); that is, spine and hip aBMD, triglycerides, and history of insulin use, gastrectomy, stroke, and OPF. For aBMD, we used spine aBMD only, as spine and hip aBMD were highly correlated.

Table 3 and Supplemental Table 1 show unadjusted, age-adjusted, age- and aBMD-adjusted, and fully adjusted HRs of OPF and MOF for three categories of glycemic indices. The greatest HRs were observed in the age- and aBMD-adjusted models. After adjusting for all of the above-listed variables, we still observed a positive correlation between glycemic level and HR of incident OPF or MOF. The intermediate glycemic status group showed an intermediate risk for all models. Participants in the prediabetic HbA1c category had a nearly significant elevated risk of MOF ($p = 0.0504$). The so-called J-shaped association between glycemic level and fracture risk was not observed. These results did not change when participants on insulin therapy were excluded from the analysis (Supplemental Table 2). When further excluding all participants on pharmaceutical anti-diabetic therapy, the number of participants in the highest category of glycemic indices decreased by approximately 40%. The association between glycemic status and fracture risk was weakened, but similar tendencies were still observed (Supplemental Table 3).

4. Discussion

In the present study, community-dwelling elderly Japanese men with higher glycemic levels had a significantly higher risk of osteoporotic fractures. This relationship between glycemic status and fracture risk appeared to be linear and remained significant after adjusting for potential confounders including insulin therapy, and even after excluding participants on anti-diabetic therapy.

Many population-based cohort studies have been conducted to examine the association between T2DM and fracture risk. Most [17,20,22,26–28], but not all [24], of these studies reported that people diagnosed with T2DM had a higher risk of fracture. In the present study, however, higher glycemic status was associated with increased fracture risk, whereas a diagnosis of T2DM was not. Even in patients diagnosed with T2DM, fracture risk may decrease when adequate control of T2DM is achieved. As is generally accepted, adequate control of hyperglycemia is important for preventing complications of diabetes and is likely to be similarly important for decreasing osteoporotic fractures.

In the present study, every 1 SD increase in FPG or HbA1c was significantly associated with a 38% to 48% increase in risk of OPF or MOF (Table 2). These linear relationships were also observed in the categorical analysis of glycemic indices (Table 3). This result is not consistent with some previous studies that reported a J-shaped association between these variables [18,19]. These studies examined patients with T2DM, most of whom received pharmaceutical treatment. Tight glycemic control may lead to increased hypoglycemic events, causing falls which in turn increase the number of fractures. In the Rotterdam Study [25], subjects with IGT had a decreased fracture risk compared with non-diabetics, whereas subjects with established

Table 1
Baseline characteristics and incidence rate of fracture during the 5-year follow-up period in participants of the FORMEN Cohort Study grouped by glycemic status at baseline.

		Grouped by fasting plasma glucose (FPG, mg/dl)				Grouped by glycated hemoglobin A1c (HbA1c, %)			
	Total	FPG < 100	100 ≤ FPG < 126	FPG ≥ 126	P for trend	HbA1c < 5.7	5.7 ≤ HbA1c < 6.5	HbA1c ≥ 6.5	P for trend
N (%)	1951 (100)	1203 (61.7)	556 (28.5)	192 (9.8)		1178 (60.4)	536 (27.5)	237 (12.1)	
Age (years)	73.0 ± 5.2	72.9 ± 5.2	73.2 ± 5.4	72.9 ± 5.3	p = 0.447	72.9 ± 5.1	73.1 ± 5.5	73.0 ± 5.1	p = 0.713
Height (cm)	162.9 ± 5.7	162.9 ± 5.6	162.6 ± 5.8	163.5 ± 6.0	p = 0.600	162.7 ± 5.7	163.0 ± 5.5	163.5 ± 5.9	p = 0.039
Weight (kg)	60.9 ± 8.5	60.3 ± 8.3	61.6 ± 8.9	62.6 ± 8.4	p < 0.001	60.0 ± 8.1	62.0 ± 9.0	62.6 ± 8.9	p < 0.001
BMI (kg/m^2)	22.9 ± 2.8	22.7 ± 2.7	23.3 ± 2.8	23.4 ± 2.8	p < 0.001	22.6 ± 2.6	23.3 ± 3.0	23.4 ± 2.9	p < 0.001
LS-aBMD (g/cm^2)	1.010 ± 0.189	0.999 ± 0.188	1.020 ± 0.185	1.046 ± 0.198	p < 0.001	1.000 ± 0.186	1.007 ± 0.188	1.064 ± 0.196	p < 0.001
Hip-aBMD (g/cm^2)	0.878 ± 0.127	0.871 ± 0.128	0.889 ± 0.121	0.892 ± 0.133	p = 0.002	0.872 ± 0.125	0.882 ± 0.127	0.901 ± 0.130	p = 0.002
FPG (mg/dl)	100.7 $^{\times}/_{+}$ 1.2	90.2 $^{\times}/_{+}$ 1.1	107.4 $^{\times}/_{+}$ 1.1	167.1 $^{\times}/_{+}$ 1.3	–	93.7 $^{\times}/_{+}$ 1.1	100.8 $^{\times}/_{+}$ 1.2	144.0 $^{\times}/_{+}$ 1.4	p < 0.001
HbA1c (%)	5.3 $^{\times}/_{+}$ 1.1	5.0 $^{\times}/_{+}$ 1.1	5.4 $^{\times}/_{+}$ 1.1	6.7 $^{\times}/_{+}$ 1.2	p < 0.001	4.9 $^{\times}/_{+}$ 1.0	5.5 $^{\times}/_{+}$ 1.0	6.9 $^{\times}/_{+}$ 1.1	–
FSI (mU/l)[A]	4.8 $^{\times}/_{+}$ 2.0	4.0 $^{\times}/_{+}$ 1.9	5.5 $^{\times}/_{+}$ 1.9	10.2 $^{\times}/_{+}$ 2.3	p < 0.001	4.2 $^{\times}/_{+}$ 1.9	5.2 $^{\times}/_{+}$ 2.0	8.0 $^{\times}/_{+}$ 2.3	p < 0.001
HOMA-IR[B]	1.1 $^{\times}/_{+}$ 2.0	0.9 $^{\times}/_{+}$ 1.9	1.5 $^{\times}/_{+}$ 1.9	2.5 $^{\times}/_{+}$ 1.9	p < 0.001	1.0 $^{\times}/_{+}$ 1.9	1.3 $^{\times}/_{+}$ 2.0	1.6 $^{\times}/_{+}$ 2.2	p < 0.001
HOMA-β[B]	50.8 $^{\times}/_{+}$ 1.9	54.3 $^{\times}/_{+}$ 1.9	45.0 $^{\times}/_{+}$ 1.9	40.0 $^{\times}/_{+}$ 1.9	p < 0.001	50.5 $^{\times}/_{+}$ 1.9	52.2 $^{\times}/_{+}$ 2.1	47.4 $^{\times}/_{+}$ 2.2	p = 0.878
Triglyceride (mg/dl)	114.1 $^{\times}/_{+}$ 1.6	112.1 $^{\times}/_{+}$ 1.6	112.7 $^{\times}/_{+}$ 1.6	132.1 $^{\times}/_{+}$ 1.6	p < 0.001	109.2 $^{\times}/_{+}$ 1.6	118.9 $^{\times}/_{+}$ 1.6	129.1 $^{\times}/_{+}$ 1.7	p < 0.001
Total cholesterol (mg/dl)	203.8 $^{\times}/_{+}$ 1.2	204.1 $^{\times}/_{+}$ 1.2	204.5 $^{\times}/_{+}$ 1.2	199.2 $^{\times}/_{+}$ 1.2	p = 0.165	203.9 $^{\times}/_{+}$ 1.2	205.8 $^{\times}/_{+}$ 1.2	198.7 $^{\times}/_{+}$ 1.2	p = 0.193
HDL-cholesterol (mg/dl)	53.8 $^{\times}/_{+}$ 1.3	54.4 $^{\times}/_{+}$ 1.3	53.7 $^{\times}/_{+}$ 1.3	50.4 $^{\times}/_{+}$ 1.3	p < 0.001	55.4 $^{\times}/_{+}$ 1.3	51.9 $^{\times}/_{+}$ 1.3	50.4 $^{\times}/_{+}$ 1.3	p < 0.001
LDL-cholesterol (mg/dl)	119.0 $^{\times}/_{+}$ 1.3	118.4 $^{\times}/_{+}$ 1.3	120.7 $^{\times}/_{+}$ 1.3	117.4 $^{\times}/_{+}$ 1.3	p = 0.694	117.5 $^{\times}/_{+}$ 1.3	122.6 $^{\times}/_{+}$ 1.3	117.8 $^{\times}/_{+}$ 1.3	p = 0.135
Creatinine (mg/dl)	0.87 $^{\times}/_{+}$ 1.2	0.88 $^{\times}/_{+}$ 1.2	0.87 $^{\times}/_{+}$ 1.2	0.88 $^{\times}/_{+}$ 1.3	p = 0.876	0.87 $^{\times}/_{+}$ 1.2	0.89 $^{\times}/_{+}$ 1.2	0.87 $^{\times}/_{+}$ 1.2	p = 0.072
eGFR (ml/min/1.73 m^2)	65.6 $^{\times}/_{+}$ 1.2	65.5 $^{\times}/_{+}$ 1.2	66.1 $^{\times}/_{+}$ 1.2	65.1 $^{\times}/_{+}$ 1.3	p = 0.933	66.4 $^{\times}/_{+}$ 1.2	64.0 $^{\times}/_{+}$ 1.2	65.9 $^{\times}/_{+}$ 1.3	p = 0.071
History or comorbidity, n (%)									
Type 2 diabetes mellitus	200 (10.3)	32 (2.7)	46 (8.3)	122 (63.5)	p < 0.001	10 (0.9)	54 (10.1)	136 (57.4)	p < 0.001
Insulin use	17 (0.9)	1 (0.1)	4 (0.7)	12 (6.3)	p < 0.001	0 (0)	4 (0.8)	13 (5.5)	p < 0.001
Other anti-diabetic drug use	169 (8.7)	28 (2.3)	39 (7.0)	102 (53.1)	p < 0.001	9 (0.8)	43 (8.0)	117 (49.4)	p < 0.001
Prostate cancer with hormone therapy	30 (1.5)	17 (1.4)	9 (1.6)	4 (2.1)	p = 0.483	17 (1.4)	9 (1.7)	4 (1.7)	p = 0.700
Glucocorticoid therapy	44 (2.3)	33 (2.7)	8 (1.4)	3 (1.6)	p = 0.100	30 (2.6)	12 (2.2)	2 (0.8)	p = 0.141
Gastrectomy	133 (6.8)	88 (7.3)	32 (5.8)	13 (6.8)	p = 0.414	58 (4.9)	55 (10.3)	20 (8.4)	p < 0.001
Stroke	128 (6.6)	77 (6.4)	40 (7.2)	11 (5.7)	p = 0.964	82 (7.0)	30 (5.6)	16 (6.8)	p = 0.579
eGFR < 60	559 (28.7)	363 (30.2)	139 (25.0)	57 (29.7)	p = 0.221	310 (26.3)	183 (34.1)	66 (27.9)	p = 0.068
Osteoporotic fracture	58 (3.0)	30 (2.5)	23 (4.1)	5 (2.6)	p = 0.313	37 (3.1)	15 (2.8)	6 (2.5)	p = 0.566
Major osteoporotic fracture	23 (1.2)	11 (0.9)	10 (1.8)	2 (1.0)	p = 0.360	13 (1.1)	7 (1.3)	3 (1.3)	p = 0.744
Incidence, N (rate/1000 PY)									
Osteoporotic fracture	44 (5.2)	21 (4.0)	15 (6.2)	8 (9.5)	p = 0.025	22 (4.2)	14 (6.1)	8 (7.9)	p = 0.117
Major osteoporotic fracture	34 (4.0)	18 (3.4)	10 (4.2)	6 (7.2)	p = 0.146	14 (12.7)	13 (5.7)	7 (6.9)	p = 0.021
Follow-up time (month)	52.2 ± 12.5	52.2 ± 12.5	51.9 ± 12.3	52.4 ± 13.7	p = 0.887	52.8 ± 12.1	51.2 ± 13.0	51.4 ± 13.6	p = 0.025

Data are expressed as mean ± standard deviation, geometric mean $^{\times}/_{+}$ standard deviation, or number (proportion in %).
BMI: body mass index.
LS: lumbar spine.
aBMD: areal bone mineral density.
FSI: fasting serum insulin.
HOMA-IR: homeostasis model assessment-insulin resistance.
HOMA-β: homeostasis model assessment-beta cell function.
HDL: high-density lipoprotein.
LDL: low-density lipoprotein.
GFR: estimated glomerular filtration rate.
PY: person years.
N: number of subjects.
A: for 1884 participants available for serum insulin measurement and not on current insulin treatment.
B: for 1774 participants with FPG < 140 mg/dl among those indicated by superscript A.

Table 2
Unadjusted hazard ratio (HR) for age and age-adjusted HR for other baseline characteristics on incident osteoporotic fractures during the 5-year follow-up period in participants of the FORMEN Cohort Study.

		Outcome			
		Osteoporotic fracture		Major osteoporotic fracture	
Variables for baseline characteristics	Unit/category	HR	95% CI	HR	95% CI
Age	5-year increase	1.35	(1.04, 1.74)	1.32	(0.99, 1.78)
Height	1 SD increase	0.97	(0.72, 1.31)	1.02	(0.73, 1.44)
Weight	1 SD increase	0.80	(0.58, 1.09)	0.72	(0.50, 1.03)
BMI	1 SD increase	0.83	(0.61, 1.12)	0.71	(0.50, 1.01)
LS-aBMD	1 SD increase	0.40	(0.28, 0.56)	0.31	(0.21, 0.46)
Hip-aBMD	1 SD increase	0.50	(0.37, 0.67)	0.42	(0.30, 0.59)
FPG	1 SD increase	1.39	(1.15, 1.69)	1.45	(1.18, 1.79)
HbA1c	1 SD increase	1.38	(1.10, 1.73)	1.48	(1.16, 1.88)
FSI[A]	1 SD increase	1.17	(0.87, 1.57)	1.19	(0.85, 1.67)
HOMA-IR[B]	1 SD increase	0.92	(0.66, 1.28)	0.80	(0.54, 1.18)
HOMA-β[B]	1 SD increase	0.76	(0.53, 1.08)	0.75	(0.50, 1.12)
Triglyceride	1 SD increase	0.74	(0.54, 1.02)	0.82	(0.58, 1.17)
Total cholesterol	1 SD increase	1.05	(0.78, 1.42)	1.07	(0.76, 1.50)
HDL-cholesterol	1 SD increase	1.07	(0.79, 1.44)	0.95	(0.68, 1.33)
LDL-cholesterol	1 SD increase	1.10	(0.81, 1.49)	1.18	(0.83, 1.68)
Creatinine	1 SD increase	0.82	(0.60, 1.13)	0.88	(0.62, 1.26)
eGFR	1 SD decrease	0.82	(0.59, 1.13)	0.88	(0.61, 1.26)
History or comorbidity					
Type 2 diabetes mellitus	Present/absent	1.94	(0.90, 4.18)	2.27	(0.99, 5.21)
Insulin use	Present/absent	2.75	(0.38, 20.0)	3.57	(0.49, 26.2)
Other anti-diabetic drug use	Present/absent	1.66	(0.70, 3.93)	1.82	(0.70, 4.69)
Prostate cancer with hormone therapy	Present/absent	2.78	(0.67, 11.6)	1.77	(0.24, 13.0)
Gastrectomy	Present/absent	2.77	(1.28, 5.99)	2.15	(0.83, 5.59)
Stroke	Present/absent	2.42	(1.07, 5.48)	1.70	(0.59, 4.87)
eGFR < 60	Present/absent	0.82	(0.42, 1.60)	0.92	(0.44, 1.95)
Osteoporotic fracture	Present/absent	4.41	(1.73, 11.2)	3.32	(1.01, 10.9)
Major osteoporotic fracture	Present/absent	1.83	(0.25, 13.3)	2.39	(0.32, 17.5)

HR: hazard ratio.
95% CI: 95% confidence interval.
SD: standard deviation.
BMI: body mass index.
LS: lumbar spine.
aBMD: areal bone mineral density.
FPG: fasting plasma glucose.
HbA1c: glycated hemoglobin A1c
FSI: fasting serum insulin.
HOMA-IR: homeostasis model assessment-insulin resistance
HOMA-β: homeostasis model assessment-beta cell function.
HDL: high-density lipoprotein
LDL: low-density lipoprotein.
eGFR: estimated glomerular filtration rate.
Model was not obtained for glucocorticoid therapy since no fracture occurred in participants with glucocorticoid therapy.
A: for 1884 participants available for serum insulin measurement and not on current insulin treatment.
B: for 1774 participants with FPG < 140 mg/dl among those indicated by superscript A.

diabetes showed an increased risk. Since subjects with IGT in that study did not undergo anti-diabetic treatment, the protective effect of higher aBMD and BMI on the bone may have been more evident. In the present study, the impaired fasting glucose/prediabetic category group, i.e., $100 \leq$ FPG < 125 mg/dl or $5.7\% \leq$ HbA1c $< 6.5\%$, had a somewhat increased risk of fracture compared to the normoglycemic category group, and the risk for MOP in the group with $5.7\% \leq$ HbA1c $< 6.5\%$ was higher (nearly significant) after adjusting for confounding factors including insulin use. Therefore, the higher risk previously reported for patients in the lowest glycemic category [18,19] was not observed. Rather, elderly men with HbA1c around 6% may have a higher risk of MOF compared to those in the normoglycemic category. This increase in MOF risk may have been masked in Caucasian studies due to the protective effect of obesity on the bone, while an elevated risk may have been more evident in the less obese Japanese population.

Some previous studies reported a significantly higher risk of fracture in patients on insulin therapy [20–22]. In the present study, insulin therapy showed an approximately two-fold elevated risk of fracture, but this increase in risk was not statistically significant. The present study may lack the power needed to deem this increase in risk of fracture associated with insulin use as significant, but it does support previously reported results.

The present study has several strengths. This is the first Japanese population-based study on this topic. The study had a relatively large sample size that likely reflects the health status of a community-dwelling elderly male population in Japan. The results expand our knowledge of T2DM in Japanese individuals; these differ from the characteristics of T2DM in Caucasians. The present study was conducted as part of an ongoing cohort study that anticipates 20-year follow-up with several waves of clinical surveys at a university hospital, where further follow-up is possible with our participants. As this is a single-center study, it also lacks inter-center variation.

However, there are also several limitations worth noting. Because participants of the present study were volunteers, patients with severe or symptomatic T2DM may have been less likely to participate in the study. In addition, we identified only 45 men with incident OPFs, which was approximately one-half of the expected number. This was not due to drop-outs from the cohort since the follow-up rate was extremely

Table 3
Adjusted hazard ratio (HR) for fasting plasma glucose (FPG) or glycated hemoglobin A1c (Hba1c) levels at baseline on incident osteoporotic fractures during the 5-year follow-up period in participants of the FORMEN Cohort Study.

		Outcome					
		Osteoporotic fracture			Major osteoporotic fracture		
Model	Category/unit	HR	95% CI	P for linear trend	HR	95% CI	P for linear trend
Model 1	FPG < 100 (reference)	1			1		
Unadjusted model	100 ≤ FPG < 126	1.56	(0.80, 3.02)		1.21	(0.56, 2.63)	
	FPG ≥ 126	2.42	(1.07, 5.46)	$p = 0.027$	2.12	(0.84, 5.34)	$p = 0.143$
Model 2	FPG < 100 (reference)	1			1		
Age-adjusted model	100 ≤ FPG < 126	1.52	(0.78, 2.95)		1.19	(0.55, 2.57)	
	FPG ≥ 126	2.41	(1.07, 5.45)	$p = 0.029$	2.12	(0.84, 5.34)	$p = 0.150$
Model 3	FPG < 100 (reference)	1			1		
Age- and aBMD-adjusted model	100 ≤ FPG < 126	1.67	(0.86, 3.25)		1.34	(0.62, 2.93)	
	FPG ≥ 126	2.91	(1.28, 6.58)	$p = 0.009$	2.70	(1.07, 6.83)	$p = 0.051$
Model 4	FPG < 100 (reference)	1			1		
Fully-adjusted model[A]	100 ≤ FPG < 126	1.52	(0.77, 3.01)		1.22	(0.55, 2.72)	
	FPG ≥ 126	2.76	(1.17, 6.50)	$p = 0.021$	2.44	(0.91, 6.54)	$p = 0.113$
Model 5	HbA1c < 5.7 (reference)	1			1		
Unadjusted model	5.7 ≤ HbA1c < 6.5	1.42	(0.73, 2.78)		2.08	(0.98, 4.42)	
	HbA1c ≥ 6.5	1.85	(0.82, 4.16)	$p = 0.108$	2.54	(1.03, 6.30)	p = 0.021
Model 6	HbA1c < 5.7 (reference)	1			1		
Age-adjusted model	5.7 ≤ HbA1c < 6.5	1.41	(0.72, 2.75)		2.06	(0.97, 4.39)	
	HbA1c ≥ 6.5	1.85	(0.82, 4.16)	$p = 0.111$	2.54	(1.03, 6.30)	p = 0.021
Model 7	HbA1c < 5.7 (reference)	1			1		
Age- and aBMD-adjusted model	5.7 ≤ HbA1c < 6.5	1.42	(0.73, 2.77)		2.04	(0.96, 4.35)	
	HbA1c ≥ 6.5	2.40	(1.07, 5.41)	$p = 0.036$	3.45	(1.39, 8.56)	$p = 0.005$
Model 8	HbA1c < 5.7 (reference)	1			1		
Fully-adjusted model[A]	5.7 ≤ HbA1c < 6.5	1.52	(0.77, 3.00)		2.15	(1.00, 4.62)	
	HbA1c ≥ 6.5	2.49	(1.07, 5.77)	$p = 0.030$	3.49	(1.35, 9.00)	p = 0.005

HR: hazard ratio.
95% CI: 95% confidence interval.
FPG: fasting plasma glucose.
HbA1c: glycated hemoglobin A1c
aBMD: areal bone mineral density at the spine.
A: adjusted for age, aBMD, triglyceride, and history of insulin use, gastrectomy, stroke and osteoporotic fracture.

high. This also suggests that participants of the present study were healthier than their counterparts in the general population. The so-called "healthy user bias" may have existed and led to an underestimation of the association of interest. Second, participants were restricted to elderly Japanese men; thus, caution should be exercised in generalizing the results. Third, the diagnosis of T2DM was based on self-reported data. FPG and HbA1c levels were determined only once, and the oral glucose tolerance test was not performed. Islet autoantibodies and c-peptide levels were not determined either. This could have led to a misclassification of patients. If T1DM patients were mixed with T2DM patients on insulin therapy, the association between hyperglycemia and elevated fracture risk may have been exaggerated by the elevated fracture risk due to T1DM. However, this may not have occurred in our study population because the results remained unchanged when patients undergoing insulin therapy were excluded from the analysis (Supplemental Table 2). Fourth, we informed participants of all laboratory test results and recommended that they consult an attending physician if there were any abnormal results. Therefore, antidiabetic therapy may have been initiated during the follow-up period, which in turn may have reduced the incidence of osteoporotic fractures. This may have underestimated the association between hyperglycemia and increased fracture risk. Fifth, sample size of the present study was determined separately for the present OPF and MOF analyses [29]. Therefore, the statistical power of the present study was 60% for the analysis using OPF as an outcome and 52% for MOF as an outcome. The lack of a significantly higher risk for MOF in the hyperglycemic group may have been due to insufficient statistical power. Sixth, the outcomes of the present study were based on self-reported data. This method of fracture detection has been repeatedly confirmed by medical charts or radiological chart reviews [37,38], but misclassification may have still occurred. Finally, we did not measure blood vitamin D levels. Vitamin D insufficiency may have increased the risk of T2DM [39] and fracture risk [40] simultaneously. This potential confounder remained unresolved in the present study.

5. Conclusions

Hyperglycemia was positively and linearly associated with an elevated risk of osteoporotic fractures in elderly Japanese men. MOF risk may be significantly elevated in Japanese elderly men in the prediabetic category of glycemic status.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2019.01.005.

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