The Association between Hyperglycemia and Fracture Risk in Middle Age. A Prospective, Population-Based Study of 22,444 Men and 10,902 Women

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Aims: Type 1 diabetes mellitus is associated with increased fracture risk, whereas the risk associated with type 2 diabetes is less obvious. Elevated fasting blood glucose and high 2-h glucose during an oral glucose tolerance test indicate impaired glucose tolerance or diabetes. The associations among fasting blood glucose, 2-h glucose, and the risk of fracture were investigated.

Methods: The Malmö Preventive Project consists of 22,444 men (44 ± 6.6 yr) and 10,902 women (50 ±7.4 yr), with a follow-up of 19 yr (±3.9) and 15 yr (±4.5) for incident fractures. Baseline assessment included multiple examinations and lifestyle information. A logistic regression model was used. Adjustments were made for age, body mass index (BMI), and smoking.

Results: Low-energy fractures were recorded in 1246 men and 1236 women. A 2-h glucose measurement between 4.3 and 6.2 mmol/liter in men (second and third quartile), and above 6.5 mmol/liter in women (third and fourth quartile), adjusted for age, BMI, and smoking, was significantly associated with a decreased risk of multiple fractures, in men [odds ratios (ORs) 0.57–0.71] and women (ORs 0.38–0.66). In women, a 2-h glucose measurement above 7.5 mmol/liter was associated with a decreased risk of osteoporotic fractures (OR 0.57, 95% confidence interval 0.44–0.74).

Conclusions: In middle-aged men and women, elevated 2-h glucose levels were associated with decreased risks of multiple and osteoporotic fractures, independent of age, BMI, and smoking. A high 2-h glucose level is characterized by peripheral insulin resistance with a high insulin level. Our findings indirectly suggest a positive effect on bone from hyperglycemia. **(*J Clin Endocrinol Metab* 93: 815–822, 2008)**

Diabetes and osteoporosis are conditions with considerable impacts on public health. Prevalence rates for both conditions steeply increase with advancing age. Both types 1 and 2 diabetes are strong risk factors for cardiovascular disease (1, 2), whereas the ultimate disease outcome of osteoporosis is fracture. Type 1 diabetes is diagnosed early in life, whereas type 2 diabetes usually occurs later in life (3) and may go untreated for a long time (4). The development of type 2 diabetes and of osteoporosis is associated with changes in lifestyle, nutrition, and smoking, but the knowledge regarding risk interaction between glucose tolerance and fracture susceptibility in middle age is still limited.

Type 2 diabetes develops from impaired insulin response to glucose stimulation, or insufficient secretion of insulin, whereas type 1 diabetes is caused by deficient pancreatic β-cell secretion of insulin. The current diagnosis of diabetes is based on elevated fasting glucose levels. A glucose tolerance test provides an additional tool by using a glucose load to unmask hyperglycemia based on insulin resistance and detect impaired glucose tolerance.

With advancing age, fracture incidence increases. Hip fractures have the most severe impact and may lead to up to 20% mortality the first year after fracture (5). Vertebral fractures also increase the risk of death but to a lesser extent (6). Osteoporosis contributes substantially to fracture risk in both middle-aged and elderly individuals (7).

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; MPP, Malmö Preventive Project; OGTT, oral glucose tolerance test; OR, odds ratio; RR, relative risk.

Individuals with type 1 diabetes are reported to have lower bone mineral density (BMD) compared with the nondiabetic population (8, 9), and studies on elderly patients with type 1 diabetes have shown increased fracture risks (10–13). The increased fracture risk depends on many factors, including the development of diabetes complications (13). Peripheral neuropathy and poor vision due to retinopathy increase the risk of falling, whereas nephropathy and poorly regulated blood glucose levels may directly or indirectly affect bone strength and bone remodeling.

In contrast, individuals with type 2 diabetes have normal or increased BMD (14, 15). Many studies have shown an increased fracture risk for these individuals also, but to a much lesser extent compared with type 1 diabetics (10, 12, 16–18). Two studies have reported no risk or decreased fracture risk in these individuals (14, 19). Fracture risk in type 2 diabetes patients seems to be time dependent, with the risk increasing with disease duration (18, 20).

Thus, the association between type 2 diabetes and fracture risk seems to be complex and not completely understood. Even less is known about the possible associations between blood glucose levels and fracture risk.

We have in previous studies, based on the Malmö Preventive Project (MPP), reported established diabetes mellitus as a strong risk factor for incident fractures (21, 22). However, less is known regarding the influence on fracture risk from hyperglycemia and impaired glucose tolerance in nondiabetic middle-aged men and women. Subsequently, the aim of this population-based study was to evaluate prospectively possible effects on long-term fracture risk in relation to glucose tolerance in middle age.

Subjects and Methods

Subjects

The MPP, an observational, prospective, population-based screening study consisted of 22,444 men and 10,902 women, mean age 44 yr (±6.6) and 50 yr (±7.4), with an attendance rate of 72%. The study design has previously been described in detail (22). The study screened for cardiovascular risk factors and related conditions to improve the scientific basis for cardiovascular disease prevention.

The study also provides sufficient data for evaluation of other common public health conditions, such as fracture and diabetes. The participants were followed from their baseline visit (1974–1992) until either death or December 31, 1999, with a mean follow-up of 19 yr (±3.9) for men and 15 yr (±4.5) for women. During follow-up all clinical fractures were registered.

Physical examination

At baseline the participants underwent a physical examination, including measurements of body height (cm) and body weight (kg), allowing for calculation of body mass index (BMI) (kg/m^2).

Questionnaire

All subjects completed a comprehensive questionnaire regarding health-related and lifestyle issues. The questions used in this study had an overall response rate of 99%.

Laboratory analyses

Blood samples were collected after an overnight fast at baseline. In this study we focused on measurements of glycemia.

Fasting blood glucose (FBG)

FBG samples were available for 99% of the participants and analyzed by an automated hexokinase method. According to the questionnaire, 249 men (1.1%) and 132 women (1.2%) had previously diagnosed diabetes at study start. These individuals were excluded from further analyses.

Defining FBG levels

The participants were, based on their FBG levels, divided into quartiles. In men, the first quartile included FBG measurements up to 4.5 mmol/liter, the second quartile 4.6–4.9 mmol/liter, the third quartile 5.0–5.2 mmol/liter, and the fourth quartile measurements above 5.2 mmol/liter. In women the first quartile included FBG measurements up to 4.4 mmol/liter, the second quartile 4.5–4.7 mmol/liter, the third quartile 4.8–5.1 mmol/liter, and the fourth quartile measurements above 5.1 mmol/liter.

Oral glucose tolerance test (OGTT)

At baseline an OGTT was performed after an overnight fast in randomly selected age cohorts within the study population: 13,056 (58%) men and 5,904 (54%) women. Thirty grams of glucose per square meter body surface area were dissolved into a 10% aqueous solution, and ingested within 5 min. In the later part of the study, the method of the OGTT changed, and each individual, regardless of body size, was given a fixed dose of 75 g glucose dissolved in water, according to World Health Organization standards. Blood samples were drawn immediately before and 120 min after the glucose intake.

The 2-h post-OGTT blood glucose levels were divided into quartiles. In men, the first quartile included 2-h blood glucose measurements up to 4.2 mmol/liter, the second quartile 4.3–5.2 mmol/liter, the third quartile 5.3–6.2 mmol/liter, and the fourth quartile measurements above 6.2 mmol/liter. In women the first quartile included 2-h blood glucose measurements up to 5.4 mmol/liter, the second quartile 5.5–6.5 mmol/liter, the third quartile 6.6–7.5 mmol/liter, and the fourth quartile measurements above 7.5 mmol/liter.

Fasting plasma insulin

Plasma insulin levels were measured in a randomly selected subset of the individuals undergoing OGTTs. Sampling was performed simultaneously with the OGTT. In total, 6250 men and 1040 women, 22% of the study population, had their fasting plasma insulin levels measured. Plasma insulin was analyzed by a nonspecific RIA method (23).

Fracture identification

Fracture data were obtained through linking the MPP data with the register at the Department of Diagnostic Radiology at Malmö University Hospital. Because Malmö University Hospital is the only local hospital, virtually all emergency radiographic examinations are performed there. At least 97% of all fractures that the Malmö population endures are recognized this way (24). Manual searches of the medical and radiological files confirmed and classified the type of fracture into one of 20 different fracture categories, including forearm, vertebral, proximal humerus, ankle, and hip fractures (25). Pathological fractures caused by cancer or other bone diseases were excluded from the analyses.

Based on data from the radiographic reports, the fractures were categorized into high or low-energy fractures. Fractures caused by falling from standing or less, or due to a low amount of trauma were classified as low-energy fractures, all others as high-energy fractures. All fractures caused by high-energy trauma were excluded from further analyses.

Data on the degree of trauma were found for 4098 fractures (97.7%). The remaining fractures were classified as low-energy fractures based on the experience that it is highly unlikely to omit information from high-energy accidents.

In the analysis of fractures related to low-energy trauma, other fractures caused by high-energy trauma in these individuals were excluded. Individuals with only high-energy trauma events were included in the nonfracture population.

Statistics

Study data were extracted from the MPP main database. Men and women were analyzed separately. Due to large differences in group size when using clinical cutoff values, the subjects were assessed using quartiles. Due to lack of precision in the blood glucose measurements (only one decimal), the individuals were unevenly distributed in the quartiles. A shift of the quartile cutoffs resulted in more even quartile numbers, but the results of the analyses changed only marginally. Therefore, the original quartiles were used in the analyses.

Descriptive data of the glucose quartiles were presented as means and SDs for the continuous variables, and as percentages for the categorical variables.

Individuals suffering low-energy fractures were subdivided into two groups: individuals with only one fracture or with multiple fractures, the latter presumably containing individuals with increased fracture risks. These groups were separately compared with the nonfracture population. To get a more specific evaluation of the effect of hyperglycemia on fracture types commonly associated with osteoporosis, an additional group was constructed: osteoporotic fractures. This group consisted of all individuals suffering at least one fracture of the forearm, hip, proximal humerus, vertebral, pelvis, or proximal tibia.

A logistic regression model was used, comparing the effects of FBG and 2-h glucose quartiles on the separate fracture groups.

A step-wise logistic regression was made, adding z scores for age, BMI, and smoking, evaluating their confounding effect. To evaluate our results even further, the same model was used with added variables representing the metabolic syndrome.

To detect a more continuous effect of glycemia on fracture risk, a logistic regression model was used with the z scores of FBG and 2-h glucose used as continuous variables.

To evaluate the effect of time of exposure on fracture risk, a multiple Cox regression model was used with time to first low-energy fracture, censoring, or death as endpoint.

P values less than 0.05 were considered significant. Nevertheless, due to multiple comparisons, borderline significant values may be spurious due to large numbers. The statistical program used was SPSS 12.0 for Windows (Statistical Package for the Social Sciences, Chicago, IL).

Results

Fractures were recorded in 1471 men, with 1246 of them suffering low-energy fractures. Of these, 808 men (65%) suffered only one fracture, whereas 438 had multiple fractures (mean: 2.8 fractures, range 2–10). In all, fractures were recorded in 1271 women, with 1236 of them suffering low-energy fractures. Of these, 880 (71%) women suffered only one fracture, whereas 356 had multiple fractures (mean: 2.5 fractures, range 2–20). At baseline these groups were similar, with the exception of smoking, which was more prevalent among those with multiple fractures.

Osteoporotic fractures were identified in 682 (55%) men and 939 (76%) women of the total fracture population.

FBG was measured in 22,100 men (98%) and 10,730 women (98%). At the time of our study, one measurement of FBG above 6.1 mmol/liter was considered indicative of diabetes, requiring two measurements for definitive diagnosis. FBG above 6.1 mmol/liter was found in 879 (3.9%) men and 365 (3.4%) women.

The mean age and body height were similar between the quartiles of FBG in both genders, whereas body weight and BMI increased with each quartile. The difference in body weight between those in the first and fourth quartile was 5.3 kg in men and 6.6 kg in women (Table 1). Incident fractures were evenly distributed throughout the quartiles.

The OGTT was performed in 13,046 men (58%) and 5,888 women (54%), and included those of a slightly higher mean age than for the entire cohort (Table 2). Two-hour blood glucose levels above 10.0 mmol/liter, indicative of diabetes, were found in 223 men (1.7%) and 275 women (4.7%).

Across the 2-h glucose quartiles the same trends as for FBG were seen, with the highest mean body weight and BMI in the

TABLE 1. Baseline characteristics of subjects in quartiles of FBG for men and women

	First quartile	Second quartile	Third quartile	Fourth quartile
Men				
n	5414	4851	6164	5671
Age (yr)	45.7 ± 5.6	43.8 ± 6.8	42.8 ± 6.8	42.6 ± 6.6
Height (cm)	176 ± 6.7	177 ± 6.7	177 ± 6.8	177 ± 6.8
Weight (kg)	74.9 ± 10.8	76.2 ± 10.6	78.0 ± 11.2	80.2 ± 12.3
BMI (kg/m^2)	24.0 ± 3.1	24.3 ± 3.1	24.7 ± 3.2	25.5 ± 3.5
FBG (mmol/liter)	4.2 ± 0.3	4.7 ± 0.1	5.0 ± 0.1	5.8 ± 0.9
No. of fractures during follow-up	579	429	466	436
Individuals sustaining fracture(s) during follow-up (%)	6.4	5.7	5.1	5.4
Smoking (%)	51	50	48	48
Women				
n	2788	2413	2971	2558
Age (yr)	49.2 ± 7.5	49.0 ± 7.7	49.4 ± 7.7	51.2 ± 6.4
Height (cm)	164 ± 6.1	164 ± 6.0	164 ± 6.0	163 ± 6.1
Weight (kg)	62.6 ± 9.9	64.2 ± 10.3	65.2 ± 11.2	69.2 ± 13.3
BMI (kg/m^2)	23.3 ± 3.6	23.9 ± 3.7	24.3 ± 4.1	25.9 ± 4.8
FBG (mmol/liter)	4.1 ± 0.3	4.6 ± 0.1	4.9 ± 0.1	5.7 ± 0.9
No. of fractures during follow-up	424	427	476	431
Individuals sustaining fracture(s)during follow-up (%)	10.9	11.8	10.9	12.5
Smoking (%)	35	35	37	33

Values are means ± SD and proportions (%).

TABLE 2. Baseline characteristics of subjects in quartiles of the 2-h post-OGTT blood glucose for men and women

	First quartile	Second quartile	Third quartile	Fourth quartile
Men				
n	3215	3379	3171	3281
Age (yr)	47.3 ± 3.8	47.6 ± 4.1	47.8 ± 4.2	48.4 ± 4.6
Height (cm)	176 ± 6.6	177 ± 6.7	177 ± 6.6	176 ± 6.6
Weight (kg)	74.7 ± 10.5	77.0 ± 10.8	78.4 ± 11.1	81.4 ± 12.3
BMI (kg/m^2)	24.1 ± 2.9	24.7 ± 3.0	25.1 ± 3.1	26.2 ± 3.5
2-h blood glucose (mmol/liter)	3.6 ± 0.5	4.8 ± 0.3	5.7 ± 0.3	7.6 ± 1.5
No. of fractures during follow-up	406	352	236	302
Individuals sustaining fracture(s) (%)	7.2	6.3	5.1	5.8
Smoking (%)	67	52	40	38
Women				
n	1464	1526	1397	1501
Age (yr)	53.1 ± 4.5	53.3 ± 4.0	53.9 ± 3.7	54.5 ± 3.1
Height (cm)	164 ± 6.1	164 ± 5.6	163 ± 5.9	162 ± 6.1
Weight (kg)	65.6 ± 11.2	66.3 ± 11.3	66.8 ± 11.4	69.5 ± 13.5
BMI (kg/m^2)	24.5 ± 4.1	24.8 ± 4.2	25.0 ± 4.1	26.4 ± 4.8
2-h blood glucose (mmol/liter)	4.5 ± 0.7	6.0 ± 0.3	7.0 ± 0.3	9.1 ± 2.0
No. of fractures during follow-up	342	312	232	193
Individuals sustaining fracture(s) (%)	15.1	13.8	12.2	10.1
Smoking (%)	42	29	27	24

Values are means ± SD and proportions (%). The OGTT was performed in 13,046 men and 5,888 women.

fourth quartile in both genders (Table 2). A higher proportion of individuals with fracture was found in the first quartile of 2-h glucose, especially in women. The distribution of current smokers in the quartiles was also uneven, with the highest proportion in the first quartile in both genders.

FBG and fracture risk

The unadjusted fracture risks were significantly lower in the second to fourth quartile of FBG in men [odds ratios (ORs) 0.71–0.80], however, after adjusting for age, BMI, and smoking, the associations were no longer significant (data not shown). In women, the results were similar.

To evaluate further the fourth quartile of FBG, because it might contain the individuals with the most pronounced changes in their glucose metabolism, the quartile was divided into two and analyzed separately, with the first quartile as reference. No differences were found between the two groups (data not shown).

OGTT and fracture risk

In men, a post-OGTT 2-h glucose level above 4.2 mmol/liter (the second, third, and fourth quartile) was associated with a decreased risk of multiple fractures (ORs 0.49–0.66), with remaining risk reductions in the second and third quartile after adjustment for age, BMI, and smoking (ORs 0.57–0.71) (Table 3).

In women, 2-h glucose levels above 5.4 mmol/liter (the second, third, and fourth quartile) were associated with decreased risks of multiple fractures (ORs 0.34–0.65), the greatest risk reduction in the fourth quartile. Belonging to the third and fourth quartile was also associated with a decreased risk of osteoporotic fractures (ORs 0.53–0.77). After adjustments for age, BMI, and

TABLE 3. Fracture risk is reported as ORs based on the quartiles of 2-h glucose from the OGTTs in men and women

	Second quartile		Adjusted for age, BMI, and smoking		Third quartile		Adjusted for age, BMI, and smoking		Fourth quartile		Adjusted for age, BMI, and smoking	
Variables	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%
Men												
Single fracture	1.05	0.82, 1.34	1.05	0.82, 1.35	0.87	0.67, 1.14	0.87	0.67, 1.14	0.91	0.70, 1.18	0.91	0.67, 1.14
Multiple fractures	**0.66**	0.49, 0.89	**0.71**	0.53, 0.97	**0.49**	0.35, 0.69	**0.57**	0.41, 0.80	**0.65**	0.48, 0.88	0.76	0.55, 1.05
Osteoporotic fracture	**0.74**	0.57, 0.96	0.80	0.61, 1.04	**0.74**	0.56, 0.96	0.85	0.64, 1.10	0.87	0.68, 1.12	1.01	0.78, 1.32
Women												
Single fracture	0.95	0.74, 1.21	0.98	0.76, 1.26	0.84	0.65, 1.07	0.82	0.63, 1.06	**0.77**	0.60, 1.00	0.78	0.59, 1.02
Multiple fractures	**0.65**	0.46, 0.91	0.74	0.53, 1.05	**0.57**	0.40, 0.82	**0.66**	0.46, 0.96	**0.34**	0.22, 0.51	**0.38**	0.25, 0.59
Osteoporotic fracture	0.89	0.72, 1.12	0.95	0.76, 1.20	**0.77**	0.61, 0.98	0.84	0.66, 1.07	**0.53**	0.41, 0.68	**0.57**	0.44, 0.74

Individuals are grouped according to sustaining one or multiple fractures. Individuals with osteoporotic fractures are separately analyzed. The analyses are performed using logistic regression, adjusted for age, BMI, and smoking, with the lowest quartile used as reference. Significant results are shown in *bold*.

TABLE 4. Fracture risk is reported as ORs based on FBG and 2-h glucose (OGTT) in men and women

	FBG		Adjusted for age and BMI		OGTT		Adjusted for age, BMI, and smoking	
	OR	CI 95%	OR	CI 95%	OR	CI 95%	OR	CI 95%
Men								
Single fracture	0.99	0.93, 1.07	1.01	0.95, 1.08	0.96	0.87, 1.05	0.96	0.87, 1.06
Multiple fractures	1.06	0.98, 1.14	**1.07**	1.00, 1.15	0.95	0.84, 1.07	1.02	0.90, 1.15
Osteoporotic fracture	1.05	0.99, 1.12	**1.08**	1.02, 1.14	1.03	0.94, 1.13	**1.10**	1.00, 1.20
Women								
Single fracture	**1.07**	1.01, 1.14	**1.06**	1.00, 1.12	**0.91**	0.82, 1.00	0.91	0.82, 1.01
Multiple fractures	**1.10**	1.01, 1.18	**1.09**	1.01, 1.18	**0.66**	0.56, 0.77	**0.72**	0.61, 0.85
Osteoporotic fracture	**1.06**	1.00, 1.12	**1.06**	1.00, 1.12	**0.78**	0.71, 0.87	**0.81**	0.73, 0.90

The z scores of FBG and 2-h glucose were used as continuous variables, with 1 SD change as unit. Individuals are grouped according to sustaining one or multiple fractures. Individuals with osteoporotic fractures are separately analyzed. The analyses are performed using logistic regression, adjusted for age and BMI, for the OGTT also for smoking. Significant results are shown in *bold*.

smoking, the risk reduction remained for multiple fractures in the third and fourth quartile (ORs 0.38–0.66), and for osteoporotic fractures in the fourth quartile (OR 0.57) (Table 3).

As for FBG, dividing the fourth quartile into two and comparing with the first quartile did not change the results (data not shown).

Fasting plasma insulin was measured in 6250 men and 1040 women as part of the glucose tolerance test. No significant associations were found between serum insulin and fracture risk.

Continuous effects of glycemia on fracture risk

The analyses were repeated with 2-h glucose as a continuous variable. Significant risk reductions were found in the multiple and osteoporotic fracture groups in women, also after adjustment for age, BMI, and smoking. In men a small but significantly increased fracture risk was seen in the osteoporotic fracture group (Table 4).

In contrast, when FBG was used as a continuous variable, adjusted for age, BMI, and smoking, slight risk increases were seen for multiple and osteoporotic fractures in men, and for women in all fracture groups (Table 4).

The cause of fractures is multifactorial, and to address this, a multiple logistic regression model was constructed, with emphasis on symptoms included in the metabolic syndrome.

The results showed a protective effect of high 2-h glucose in the third and fourth quartile in women (ORs 0.36–0.66), and in the second, third, and fourth quartile in men (ORs 0.56–0.71) (Table 5).

A Cox multiple regression model was created using the long follow-up period, with time to first low-energy fracture, censoring, or death as endpoint. In this model, an increased 2-h glucose level decreased the risk of a low-energy fracture in women [relative risk (RR) 0.90, 95% confidence interval (CI) 0.83–0.98], but not in men (Table 6).

Discussion

The aim of this study has been to examine the effect of blood glucose levels and glucose tolerance on fracture risk. We found that a 2-h post-OGTT glucose level above 4.2 mmol/liter in men and above 5.4 mmol/liter in women decreased the risk of low-energy fractures, in comparison with the first quartile. In men, the individuals with 2-h glucose between 4.3 and 6.2 mmol/liter and in women those with 2-h glucose above 6.6 mmol/liter had significantly lowered risks of osteoporotic fractures, with a risk reduction of up to 65%. Adjustments for age and BMI altered the results only slightly, but after adding smoking status to the analyses, the risk reduction effect on osteoporotic fractures was no longer significant in men and remained significant only in the

TABLE 5. Multiple logistic regressions with multiple low-energy fractures as outcome for men and women

	Women			Men		
Variable – z score (U)	OR	CI 95%	*P* value	OR	CI 95%	*P* value
Age (yr)	1.00	0.87–1.14	0.98	1.11	0.99–1.24	0.07
BMI (kg/m²)	0.89	0.76–1.04	0.14	0.87	0.77–0.99	**0.04**
Systolic blood pressure (mm Hg)	0.99	0.81–1.21	0.94	0.99	0.84–1.17	0.90
Diastolic blood pressure (mm Hg)	1.27	1.04–1.56	**0.02**	1.32	1.12–1.56	**0.001**
Serum-cholesterol (mmol/liter)	1.01	0.87–1.16	0.95	0.99	0.88–1.20	0.90
Serum-triglycerides (mmol/liter)	1.07	0.93–1.23	0.34	1.00	0.89–1.14	0.95
2-h glucose						
Quartile 2	0.74	0.52–1.04	0.08	0.70	0.52–0.95	**0.02**
Quartile 3	0.66	0.46–0.96	**0.03**	0.56	0.40–0.79	**0.001**
Quartile 4	0.36	0.23–0.56	**0.001**	0.71	0.51–0.98	**0.04**
Smoking	1.38	1.03–1.85	**0.03**	1.79	1.40–2.30	**0.001**

The variable 2-h glucose is divided into quartiles, with the lowest quartile used as reference. ORs calculated using z scores with 1 SD change as the unit for the continuous variables and yes *vs.* no for the categorical variables. Significant results are shown in *bold*.

TABLE 6. Cox multiple regression model for men and women, with first low-energy fracture as outcome

	Women			Men		
Variable – z score (U)	RR	CI 95%	*P* value	RR	CI 95%	*P* value
Age (yr)	1.16	1.07–1.27	**0.001**	1.20	1.12–1.28	**0.001**
BMI (kg/m²)	1.01	0.93–1.10	0.81	0.90	0.83–0.98	**0.01**
Systolic blood pressure (mm Hg)	0.93	0.83–1.04	0.23	1.05	0.94–1.16	0.52
Diastolic blood pressure (mm Hg)	1.06	0.95–1.19	0.27	1.11	1.00–1.23	**0.05**
Serum-cholesterol (mmol/liter)	0.99	0.91–1.08	0.84	0.98	0.91–1.05	0.56
Serum-triglycerides (mmol/liter)	1.01	0.93–1.10	0.79	0.96	0.88–1.05	0.34
2-h glucose	0.90	0.83–0.98	**0.02**	0.97	0.90–1.05	0.52
Smoking	1.04	0.88–1.23	0.60	1.37	1.18–1.58	**0.001**

The variables included represent the metabolic syndrome. Risk ratios are calculated using z scores with 1 SD change as the unit for the continuous variables and yes *vs.* no for the categorical variables. Significant results are shown in *bold*.

fourth quartile in women. A similar but smaller effect was seen on the risk of multiple fractures, where the risk reduction effect disappeared in the fourth quartile in men and in the second quartile in women. When further adjustments were added to the model, significantly decreased risks of multiple low-energy fractures in the third and fourth quartile in women, and in and in the second, third, and fourth quartile in men were found.

To address the influence of time on fracture risk, a Cox multiple regression model was created, and this showed a decreased risk of fracture in women, but not in men.

This study has shown that impaired glucose tolerance is associated with a decreased risk of low-energy fractures. Most fractures in women were found in the lowest quartile of 2-h glucose, the quartile with the lowest mean body weight and highest proportion of smokers. This may reflect the protective effect of high body weight against fracture, associated with higher BMD and a compensatory hyperinsulinemia caused by insulin resistance, but also the detrimental effect of smoking in leaner subjects. Our results confirm findings from the Rotterdam Study, showing that individuals with impaired glucose tolerance had significantly decreased risks of fracture (14, 26). Thus, data, including ours, associate hyperglycemia in nondiabetic subjects with a decreased risk of fracture. Individuals with impaired glucose tolerance, as well as type 2 diabetes mellitus subjects, are characterized by increased insulin resistance with, in the earlier stages of the disease, high levels of circulating insulin (27, 28). It has been proposed that insulin has an anabolic effect on bone cells and an indirect effect on bone formation through interaction with the IGF-I receptor and PTH (29), and our results indirectly support these theories.

Type 2 diabetes mellitus of long duration has increased hip fracture risk (12, 18, 20). This may be an effect of low levels of serum insulin due to exhausted pancreatic β-cells, as well as the development of diabetes complications. The medical treatment in itself may also contribute because one recent study showed associations between treatment with thiazolidinediones for diabetes and increased bone loss in elderly women (30). In addition, increased fracture rates have been observed in individuals treated with rosiglitazone (31).

Impaired glucose tolerance is a diagnosis included in the metabolic syndrome, and other factors included in the syndrome may affect fracture risk. However, when variables representing the metabolic syndrome were added into the logistic regression model, the associations remained.

Smoking affects the result of an OGTT through increasing gut motility and decreased gastric emptying time, thus decreasing the 2-h glucose level (32, 33). This is reflected in that the lowest quartile of 2-h glucose included the highest percentage of smokers. Smoking, both past and current, is associated with an increased risk of fractures in general and of osteoporotic fractures, the effect being more pronounced in men (34). Smoking has been associated with an increased risk of impaired fasting glucose and type 2 diabetes (35). The effect of smoking seems to be partly mediated by affecting BMD (36). However, also after adjustment for smoking status we found an increased risk of fracture in the lowest quartile of 2-h glucose.

To evaluate more continuous effects of glycemia on fracture risk, a further analysis was performed using z scores of FBG. This analysis revealed small but significantly increased risks of single, multiple, and osteoporotic fractures in women, and of multiple and osteoporotic fractures in men. These associations remained after adjustments for age, BMI, and smoking. These findings seem to be contradictory to our findings concerning 2-h glucose. However, impaired fasting glucose and 2-h glucose represent different aspects of the glucose metabolism. Impaired fasting glucose is characterized by increased hepatic glucose output and a defect early insulin secretion with low insulin levels. A high 2-h glucose level is characterized by peripheral insulin resistance with a high insulin level, common in early stages of type 2 diabetes (37). Prevalence studies have shown that only 20–30% of individuals with impaired glucose tolerance have impaired fasting glucose, and yet another difference is that the prevalence of impaired fasting glucose seems to plateau in middle age, whereas the prevalence of impaired glucose tolerance increases into old age. Thus, it seems that these two glucose measurement profiles mirror different parts of the glucose homeostasis, and this may explain their different impacts on fracture risk.

Our data indirectly indicate that high plasma insulin levels may be beneficiary for bone strength, and the direct effect of hyperinsulinemia on fracture risk would have been interesting to investigate. However, insufficient amounts of data prevented us from further exploring this.

This study has limitations; our findings are based on a single baseline measurement of FBG and only one OGTT, which may

be considered insufficient based on the known variability of the assessments (38, 39). However, this should mainly affect those with borderline values, and, furthermore, the purpose of this study was primarily to investigate the effect of FBG and 2-h glucose on fracture risk, and for this aim our data should be adequately suited. The OGTT was only performed in a subset of the study population, however, these subjects were randomly recruited, which should minimize any bias on the results. Another limitation of the study may be that participants with pathological FBG or 2-h glucose levels were referred to a specialist clinic for further evaluation and intervention, in total 5% of the study population (40). We have no information on follow-up.

The most important strength of the study is the prospective population-based design, evaluating a large cohort of men and women in middle age. It is one of the first studies addressing the issue of both fasting and post-challenge hyperglycemia and fracture risk in this important age group.

In conclusion, increased 2-h post-challenge blood glucose levels in middle-aged men and women were associated with decreased long-term risks of multiple low-energy fractures as well as of osteoporotic fractures, independent of age, BMI, and smoking habits. These findings indirectly suggest a positive effect on bone structure from insulin resistance, often associated with post-challenge hyperglycemia.

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