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ORIGINAL ARTICLE

Diabetes mellitus and the risk of non-vertebral fractures: the Tromsø study

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Abstract We wanted to determine the risk of non-vertebral fracture associated with type and duration of diabetes mellitus, adjusting for other known risk factors. This is a population-based 6-year follow-up of 27,159 subjects from the municipality of Tromsø, followed from 1994 until 2001. The age range was 25–98 years. Self-reported diabetes cases were validated by review of the medical records. All non-vertebral fractures were registered by computerized search in radiographic archives. A total of 1,249 non-vertebral fractures was registered, and 455 validated cases of diabetes were identified. Men with type I diabetes had an increased risk of all non-vertebral [relative risk (RR) 3.1 (95% CI 1.3–7.4)] and hip fractures [RR 17.8 (95% CI 5.6–56.8)]. Diabetic women, regardless of type of diabetes, had significantly increased hip fracture risk [RR 8.9 (95% CI 1.2–64.4) and RR 2.0 (95% CI 1.2–3.6)] for type I and type II diabetes, respectively. Diabetic men and women using insulin had increased hip fracture risk. Duration of disease did not alter hip fracture risk. An increased risk of all non-vertebral fractures and, especially, hip fractures was associated with diabetes mellitus, especially type I. Type II diabetes was associated with increased hip fracture risk in women only.

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Introduction

Osteoporotic fractures are a major health problem in the western world. Bone mineral density, low body mass, sedentary lifestyle, type of fall and its risk factors, the presence of a previous fracture history, smoking, alcohol consumption, and a number of chronic medical disorders, are some of the risk factors reported to be associated with fracture incidence. Poor metabolic control and lifestyle constitute major risks for osteoporosis and fractures in diabetics [1]. Increased fracture risk in diabetic patients have been reported in some [2–6], but not all, follow-up studies [7, 8]. The risk associated with type I diabetes has been consistent in many earlier studies, but whether type II diabetes is a risk factor by itself, or whether its associated risk is mainly due to insulin use or its onset late in life is unclear. Most studies have focused on fracture risk in specific locations, mainly the hip.

We wanted to determine the risk of non-vertebral fracture associated with type and duration of diabetes mellitus in a large population-based follow-up of 27,159 people aged 25 years to 98 years at baseline, adjusting for other known risk factors.

Material and methods

Study population

The Tromsø study is a population-based cohort study with five repeated health surveys since 1974. In the fourth Tromsø survey (1994/1995), all residents of the Tromsø municipality born in 1969 or earlier were invited to the first phase of the survey. Among the 37,559 persons invited, 2,139 persons had died or had moved before their scheduled phase I examination. The eligible population was, therefore, 35,420 persons, and 27,159 (77%) participants

attended the phase I examination in the survey and answered the relevant questionnaires.

Registration of exposure variable and confounding factors

The first questionnaire was printed on the reverse side of a letter of invitation. At the health examination a trained nurse checked the questionnaire for inconsistency and handed out a second questionnaire to be returned by mail. The first questionnaire covered, among other topics, history of diabetes mellitus, age when diagnosed, history of stroke, physical activity, smoking habits and self-rated health status. In the second questionnaire there were questions about the use of insulin and anti-diabetes medication. The examination included, among others, standardized measurements of blood pressure, non-fasting serum lipids and height and weight determination. Height and weight were measured, with the subject wearing light clothing and without shoes, to the nearest centimeter/kilogram.

Validation of diabetes cases

Cases of diabetes were identified by review of the medical records of all participants who:

1. Reported diabetes mellitus or age when diagnosed in the fourth survey.
2. Reported use of anti-diabetes drugs in the fourth survey.
3. Reported diabetes mellitus in the second, third and fifth surveys.
4. Had elevated HbA1c (≥6.5) level in the fourth or fifth surveys.
5. Were registered with a diabetes-related diagnosis in the medical records.

In accordance with the International Classification of Diseases (ICD) coding, we validated any diabetes-related code by checking the medical records. Of 756 possible subjects with diabetes mellitus, 646 were confirmed to have diabetes, and, of them, 455 had had the disease before the start of follow-up and the other 191 subjects (pre-diabetics) developed the disease during the follow-up. Information regarding the type of diabetes and the use of insulin was collected from the medical records. Any patient using anti-diabetes tablets or diet to control diabetes was reported to be a type II diabetic. For those using insulin, the clinician's classification was used, in addition to WHO diagnostic criteria, usually based on clinical presentation in addition to level of C-peptide.

Fracture registration

Our fracture registry is based on the radiographic archives at the University Hospital in Tromsø. The nearest alternative radiographic service or fracture treatment facility is located 250 km from Tromsø. The only fractures that would have been missed were those that had occurred while inhabitants were traveling and had undergone no control radiographic examination when they returned home, in addition to fractures not radiographically examined. An earlier registration for participants in the second and third Tromsø surveys was performed, validated and described by Joakimsen et al. [9]. The computerized records in the radiographic archives of the University Hospital contain codes for different information about fractures in addition to the national personal identification number and time of investigation. Any fracture-coded radiographic examinations of participants in the fourth survey were reviewed to ascertain the fracture code, identify the exact anatomical location of the fracture and to distinguish consecutive fracture cases from one another. In addition, the discharge records were checked with respect to hip fractures.

For our target population, the fracture registry covered the period from the 1st of January 1994 to the 31st of December 2000 with respect to all non-vertebral fractures. Follow-up time was assigned from the date of phase I examination for each participant to date of first fracture, date of death or to the 31st of December 2000.

Statistics and analysis

The relative risk (RR) of fracture was calculated using the Cox proportional hazard model in the SAS statistical package [10]. Data are presented stratified by gender. Differences in means between groups were tested using age-adjusted general linear models. There was one diabetic woman with uncertain type who was excluded from the corresponding analyses. In a separate analysis the pre-diabetics were excluded from the non-diabetic population. To evaluate the effect of disease duration, we grouped type II diabetics into three groups, according to the duration of their disease (4-year intervals). In addition, the pre-diabetics were divided into two groups (those who would develop the disease within 4 years, and those who would develop the disease after more than 4 years, from the start of follow-up).

Interaction terms were introduced to the models to assess interaction between the disease and body mass index (BMI), self-reported health status and history of previous wrist or hip fracture. Physical activity and self-reported stroke/self-reported health status were left out of the final models as they did not contribute significantly to the models. The final gender-specific models were adjusted for age, BMI, smoking, and metabolic syndrome features (mean blood pressure, non-fasting serum high-density lipoprotein (HDL) and triglycerides).

Results

A total of 446 and 803 non-vertebral fractures was registered among 12,866 men and 14,293 women, respectively.

Table 1 Baseline characteristics of diabetic and non-diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study). Non-fasting values of high-density lipoprotein (HDL) and triglycerides are reported. Smoking, level of physical activity, previous stroke and health status are self-reported

Parameter	Number	No. of fractures	Mean age (years)	Mean BMI	Smokers (%)	Physically inactive (%)	Stroke (%)	Poor health (%)	Mean blood pressure (mmHg)	Mean HDL level (mmol/l)	Mean triglyceride level (mmol/l)
Men											
Non-diabetics	12,639	432	46.4	25.6	37.6	44.5	1.7	25.0	98.9	1.35	1.77
Pre-diabetics[a]	95	2	59.1[b]	29.6[c]	37.9	69.5[c]	3.2	51.6[c]	109.8[d]	1.22[d]	2.69[d]
Diabetics	227	14	59.7[b]	27.0[d]	23.3[c]	67.0[c]	6.6[c]	59.0[d]	104.1	1.27[d]	2.18[d]
Type I	52	5[c]	45.4	25.0	34.6	48.1	3.8	30.8	95.5	1.42	1.67
Type II	175	9	64.0[b]	28.0[d]	20.0[c]	72.6[c]	7.4[c]	67.4[d]	106.6	1.23[d]	2.33[d]
Insulin: yes	86	4	61.2[b]	28.6[d]	19.8[c]	70.9[c]	10.5[d]	62.8[d]	105.8	1.23[d]	2.38[d]
Insulin: no	89	5	66.7[b]	27.3[c]	20.2[c]	74.2	4.5	71.9[d]	107.4	1.23[d]	2.29[d]
Women											
Non-diabetics	14,065	777	46.9	24.7	36.5	57.3	1.2	32.4	94.7	1.64	1.33
Pre-diabetics[a]	96	8	61.1[b]	30.1[d]	21.9	79.2	3.2	59.4[c]	109.5[d]	1.42[d]	2.52[d]
Diabetics	228	26	65.8[b]	28.7[d]	22.4[c]	77.2	7.9[d]	68.9[d]	111.3[d]	1.45[d]	2.36[d]
Type I	29	3	43.5	24.3	41.4	48.3	0	20.7	95.9	1.81[c]	1.02
Type II	198	23	68.2[b]	29.3[d]	19.7[c]	81.3	9.1[d]	75.8[d]	113.5[d]	1.39[d]	2.56[d]
Insulin: yes	78	8	65.7[b]	30.5[d]	19.2	78.2	6.4[c]	74.4[d]	111.8[d]	1.41[d]	2.44[d]
Insulin: no	120	15	69.7[b]	28.6[d]	20.0	83.3	10.8[d]	76.7[d]	114.7[d]	1.38[d]	2.64[d]

[a]Compared with non-diabetics (men n=12,544, women n=13,969)
[b]Mean difference between: (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, P<0.0001
[c]Age-adjusted mean difference between (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, P<0.05
[d]Age-adjusted mean difference between (all diabetics, type I, type II insulin yes and insulin no) and non-diabetics, P<0.0001

There were 227 men and 228 women with validated diabetes mellitus (22.9% and 12.7% type I diabetics, for men and women, respectively). Characteristics of the cohort are presented in Table 1. Type I diabetics were not significantly different from the non-diabetics except for higher HDL levels among type I diabetic women. On the other hand, type II diabetics, regardless insulin use, and those who developed type II diabetes after the start of follow-up were significantly different from the non-diabetics in most of the baseline characteristics. More than 62% of men and 72% of women using insulin were type II diabetics, and, of type II

Table 2 All non-vertebral fractures: adjusted relative risks and 95% CI among diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study)

Parameter	Number	No. of fractures	Age-adjusted RR	RR adjusted for age, BMI, and smoking	RR adjusted for age, BMI, smoking, and metabolic features[a]
Men					
Non-diabetics	12,639	432	1.0	1.0	1.0
Type I	52	5	3.06 (1.27–7.38)	3.08 (1.28–7.44)	3.05 (1.26–7.38)
Type II	175	9	1.19 (0.61–2.31)	1.31 (0.67–2.56)	1.21 (0.6–2.47)
Insulin: yes	86	4	1.1 (0.41–2.95)	1.24 (0.46–3.34)	0.95 (0.3–2.98)
Insulin: no	89	5	1.28 (0.53–3.11)	1.38 (0.57–3.35)	1.45 (0.59–3.52)
Insulin[b]					
Insulin, yes	138	9	1.71 (0.88–3.31)	1.87 (0.96–3.62)	1.68 (0.83–3.39)
Women					
Non–diabetics	14,065	777	1.0	1.0	1.0
Type I	29	3	3.03 (0.98–9.44)	2.97 (0.96–9.24)	2.85 (0.92–8.87)
Type II	198	23	0.89 (0.59–1.35)	0.97 (0.64–1.47)	1.08 (0.7–1.67)
Insulin: yes	78	8	0.87 (0.43–1.74)	0.99 (0.49–1.99)	1.09 (0.54–2.19)
Insulin: no	120	15	0.9 (0.54–1.5)	0.96 (0.57–1.6)	1.07 (0.63–1.83)
Insulin[b]					
Insulin, yes	107	11	1.08 (0.59–1.96)	1.21 (0.67–2.2)	1.31 (0.72–2.38)

[a]Mean blood pressure, HDL and triglycerides
[b]Regardless of type of diabetes

Table 3 Hip fractures: adjusted relative risks and 95% CI among diabetic men and women in the fourth survey, 1994–1995 (the Tromsø Study)

Parameter	Number	No. of fractures	Age-adjusted RR	RR adjusted for age, BMI, and smoking	RR adjusted for age, BMI, smoking, and metabolic features[a]
Men					
Non-diabetics	12,639	65	1.0	1.0	1.0
Type I	52	3	17.79 (5.57–56.75)	17.79 (5.57–56.79)	18.43 (5.72–59.34)
Type II	175	4	1.45 (0.53–3.99)	1.56 (0.57–4.3)	1.63 (0.59–4.5)
Insulin: yes	86	2	1.77 (0.43–7.22)	2.04 (0.49–8.41)	2.12 (0.51–8.76)
Insulin: no	89	2	1.23 (0.3–5.03)	1.25 (0.31–5.13)	1.28 (0.31–5.28)
Insulin[b]					
Insulin. yes	138	5	3.87 (1.56–9.6)	4.44 (1.77–11.15)	4.6 (1.83–11.56)
Women					
Non-diabetics	14,065	163	1.0	1.0	1.0
Type I	29	1	8.55 (1.19–61.49)	8.93 (1.24–64.36)	9.03 (1.25–65.07)
Type II	198	13	1.72 (0.97–3.02)	2.03 (1.15–3.58)	1.9 (1.04–3.49)
Insulin: yes	78	4	1.72 (0.64–4.64)	2.09 (0.77–5.67)	2.06 (0.76–5.62)
Insulin: no	120	9	1.71 (0.87–3.36)	1.99 (1.01–3.9)	1.78 (0.86–3.71)
Insulin[b]					
Insulin, yes	107	5	2.05 (0.84–4.98)	2.48 (1.02—6.06)	l2.43 (0.99–5.97)

[a]Mean blood pressure, HDL and triglycerides
[b]Regardless of type of diabetes

diabetics, 50.9% men and 60.6% women were not using insulin.

Tables 2 and 3 show, respectively, non-vertebral and hip fracture risks, adjusted for age, BMI, smoking and metabolic features. Further adjustment for physical activity and self-reported stroke or self-reported health status did not affect the risk estimates.

In Table 2, type I diabetes mellitus was a strong predictor for non-vertebral fractures among men unaffected by the adjustment factors. Among women, only those with type I diabetes had a consistent, increased—although not as strong statistically—risk of non-vertebral fractures.

In Table 3, type I diabetic men and women had a highly significant increased risk of hip fracture. On the other hand, type II diabetic women showed a significantly increased risk of hip fracture when adjustment was made for more factors than age, with the highest risk indicated when adjustment was made for age, BMI and smoking. Although hip fracture risk was consistently not significantly increased among type II diabetic women using insulin, type II diabetic women not using insulin had a significantly increased risk when adjustment was made for age, BMI and smoking. The use of insulin (regardless of type of diabetes) was associated with significantly increased risk of hip fracture in both men and women. The exclusion of subjects who developed diabetes mellitus after the start of follow-up from the non-diabetic population did not affect the results.

We found an increased risk of hip fractures independent of duration of diabetes in female type II diabetics (data not shown). This held true also when we included those who were diagnosed as type II diabetics within 4 years of the start of follow-up. When those who developed type II diabetes later than 4 years after the start of follow-up were included, there was a significant trend of increased risk of hip fractures (P=0.049) for increasing time as diabetics. This finding was mainly due to a lowered risk for those developing diabetes late in the follow-up. For men there was a similar but non-significant trend.

There was no significant interaction between the risk associated with diabetes mellitus and the other possibly confounding variables: BMI, history of previous fracture, smoking, physical activity, self-reported health status or self-reported stroke.

Discussion

We found an increased risk of non-vertebral and hip fractures in men with type I diabetes and those using insulin. Increased risk of hip fracture was found in diabetic women. The risk was consistent for both types of diabetes but higher in those with type I diabetes.

Bias considerations

This study included a large number of both men and women, with a wide age range at baseline. The external validity refers mainly to a Caucasian population. The potential for selection bias is limited with more than 77% of the eligible population included in the study. The lowest attendance rates were among those less than 45 years of age and those older than 75 years, with, respectively, rates of 66% and 74% of attendance among men and 73% and 67% among women. We had no possibility to explore differences between responders and non-responders; however, in

the second and third surveys, with an attendance rate of 73%, the age-adjusted mortality was higher among non-responders, and the incidence of fractures was almost similar in the two groups [11]. With the prospective design of this study, the risk factors included were measured and/or classified without knowledge of the future risk of fractures.

The limited power constitutes a major limitation in this study. Although the validation of diabetes cases was based on reviewing the medical records, there is a possibility of underestimation of diabetes in this cohort. This non-differential misclassification will render our results underestimated, as the diagnosed diabetic cases may constitute nearly 50% of the actual number of diabetics in the population, especially among those older than 30 years [12].

Implications

Earlier studies of fracture risk associated with diabetes mellitus have found conflicting results. Forsen et al. in the HUNT Study [2] found an increased risk of hip fracture in women younger than 75 years with type I diabetes and those with type II for more than 5 years, and in men older than 75 years with type II diabetes for less than 5 years. History of diabetes mellitus was associated with increased hip fracture risk in men and women aged 35 years to 49 years [13]. Increased risk of hip and proximal humerus fractures among women 65 years of age and older with type II diabetes was described by Schwartz et al. [3]. Diabetic Mexican–Americans aged over 65 years had an increased risk of hip fractures, especially those using insulin [4]. In the Rotterdam Study [6] men and women older than 55 years with already established and treated type II diabetes had an increased non-vertebral fracture risk. Insulin-treated diabetes was associated with proximal humerus fractures [14] and foot fractures [7] in women 65 years and older.

On the other hand, increased risk of ankle fractures was not associated with any type of diabetes in older women [7], hip fracture risk was not significantly increased in diabetics [8, 15], and hip and distal arm fracture rates were not increased in insulin-treated women [16]. The majority of these studies included only older women.

Generally, our findings support associations between types of diabetes mellitus and fracture risk, especially hip fractures. The increased fracture risk of the hip but not all non-vertebral fractures among women could suggest a different impact of diabetes on different skeletal locations.

Type I diabetes mellitus

Type I diabetes was associated with high risks of hip fracture in both men and women and a threefold increase in non-vertebral fracture risk, although it was borderline significant in women. Further adjustment for features of the metabolic syndrome increased the risk estimates of hip fracture associated with type I diabetes in both men and women.

The association between type I diabetes mellitus and fracture risk might act through changes in bone mass, which could be due to the co-morbidities, complications or poor control of type I diabetes [1, 17, 18]. Higher risk of falls due to episodes of hypoglycemia would be expected among type I diabetics, leading to increased fracture risk.

Type II diabetes mellitus

Our results showed an increased risk of hip fracture among type II diabetic women only. This risk was mainly affected by BMI in our models, as type II diabetics were generally obese and, therefore, expected to be protected against fracture; when adjusted for BMI and even for smoking habits, the risk increased significantly. The risk estimate did not change when the analysis was restricted to women older than 40 years or even older than 50 years, which supports earlier findings [19]. Despite the high bone mineral density usually found in type II diabetics [3, 6, 17, 20–22], the co-morbidities associated with diabetes, the visual or neuromuscular functions deficiencies, and the effect of medication, contribute to the increased fracture risk. In addition, increased risk of falling and its risk factors among diabetics [23, 24], or structurally altered bone in diabetes [25], could also play a major role in increasing fracture risk. Further adjustment for features of the metabolic syndrome, which is an important risk factor for diabetes [26], reduced the hip fracture risk estimate associated with type II diabetes in women.

Insulin use

We found that the use of insulin is associated with increasing hip fracture risk in both men and women. Among men using insulin who suffered hip fracture, 60% were type I diabetics and had had the disease for at least 32 years before suffering a hip fracture, whereas, among women, only 20% had type I diabetes, with a minimum duration of 13 years. Of type II diabetic women using insulin who had suffered hip fracture, 75% had had the disease for more than 12 years before the fracture.

These findings could indicate the possibility that the risk associated with insulin is not explained solely by type I diabetes, and the duration of the disease and, most probably, the duration of insulin use is the main predictor of fracture risk, especially in type II diabetic women. Moreover, insulin-treated diabetics are prone to suffer more episodes of hypoglycemia and falls than diabetics not using insulin. However, even though women with type II diabetes and women overall using insulin had significantly increased risks of hip fractures, type II diabetic women using insulin as an exposed group did not show a significantly increased risk of hip fracture compared with non-diabetics. Although a slightly higher risk estimate for those on insulin compared with those not using insulin could indicate an increased risk for type II diabetics using insulin,

a cautious interpretation of this finding is required, owing to the low power. Further investigations in populations with a higher prevalence of diabetes would clarify the effect of insulin on fracture risk among type II diabetics.

Disease duration

We found an increased risk of hip fractures, independent of duration of diabetes, among type II diabetic women. However, a significant trend of increasing hip fracture risk by increasing disease duration was shown when we included those who had developed type II diabetes late after the start of follow-up. Men and women who had developed type II diabetes after more than 4 years from the start of follow-up had the lowest mean age and the highest BMI at baseline, compared to the other type II duration categories, and, thus, the lowest hip fracture risk.

On the other hand, all type I diabetics who suffered fractures had had the disease for more than 13 years and were older than 41 years at the time of the fracture. The longer duration before type I diabetics suffered fractures, despite their low bone mass, indicated that other factors were needed, for instance, disease complications, or that certain threshold points of bone mass should be reached to cause a fracture.

Conclusion

In a follow-up of a large population aged 25 years to 99 years at baseline we found an increased risk for all non-vertebral fractures and, especially, hip fractures, in type I diabetic men and men using insulin. Regardless of the type, diabetic women had a high risk of hip fractures only. Further analyses are needed to clarify the associations between type II diabetes and insulin use and fracture risk.

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