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ARTICLE

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Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk

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Abstract *Aims/hypothesis:* We studied the association between fractures and type 1 and type 2 diabetes mellitus. *Methods:* In this case-control study, all subjects diagnosed with a fracture (n=124,655) in Denmark served as cases, and for each case three control subjects (n=373,962) matched for sex and age were retrieved from the general population. *Results:* Type 1 and type 2 diabetes were associated with an increased risk (1) of any fracture (odds ratio [OR]=1.3, 95% CI: 1.2–1.5 for type 1 diabetes and 1.2, 95% CI: 1.1–1.3 for type 2 diabetes after adjustment for confounders) and (2) of hip fractures (OR=1.7, 95% CI: 1.3–2.2 for type 1 diabetes, and 1.4, 95% CI: 1.2–1.6 for type 2 diabetes). Furthermore, type 2 diabetes was associated with a significant increase in forearm fractures (OR=1.2, 95% CI: 1.0–1.5), and type 1 diabetes was associated with an increased risk of spine fractures (OR=2.5, 95% CI: 1.3–4.6), whereas type 2 diabetes was not. Use of metformin and sulphonylureas was associated with a significantly decreased risk of any fracture, whereas a non-significant trend towards decreased risk of any fracture was associated with the use of insulin. Except for a decrease in hip fractures with use of sulphonylureas, no change in fracture risk in the hip, spine or forearm was associated with the use of insulin or oral antidiabetic drugs. *Conclusions/interpretation:* Type 1 and type 2 diabetes are associated with an increased risk of any fracture and hip fractures. The use of drugs to control diabetes may reduce the association between diabetes and fractures.

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Abbreviations ATC: Anatomical Therapeutical Chemical · BMD: bone mineral density · DDD: defined daily dose · GP: general practitioner · ICD: International Classification of Diseases · OR: odds ratio

Introduction

Calcium metabolism may be disturbed in patients with diabetes mellitus [1], depending on the type of diabetes [2]. The pathogenetic factors involve increased urinary calcium excretion [3, 4], and decreased intestinal calcium absorption [2]. This leads to a negative calcium balance with secondary hyperparathyroidism, increased bone turnover, and consequently a reduced bone mineral density (BMD). Furthermore, disturbances in vitamin D and parathyroid hormone metabolism are seen [1, 5], in particular in patients with renal disease [6]. Microvascular disease may compromise blood supply to the bones [7] leading to a decreased BMD. Diabetes influences endothelial function, and this may also contribute to a decreased BMD [8]. Finally, neuropathy may be accompanied by a decreased BMD [9]. Besides the alterations in calcium metabolism and BMD, an increased risk of falls due to impaired eyesight in diabetic eye disease [10] or because of episodes of hypoglycaemia [11] may contribute to fracture risk.

Studies of BMD in persons with diabetes have yielded conflicting results. In type 1 diabetes most studies have reported a moderately decreased BMD [2, 4, 12–18], whereas a normal to increased BMD has been reported in patients with type 2 diabetes [19–26], not entirely explained by overweight [2]. Insulin resistance may play a role in the changes in BMD [27].

From the BMD data one might expect an increased fracture risk in patients with type 1 diabetes and a normal to decreased fracture risk in patients with type 2 diabetes when all other factors for fracture are adjusted for. Previous studies have shown an increased risk of hip and humerus

fractures in patients with type 1 diabetes [28, 29], and no increase in forearm fractures. However, the study samples have been limited in size [28]. Among patients with type 2 diabetes, an increased risk of hip and humerus fractures has been reported [19, 28] after adjustment for BMI and BMD [19]. This increase may be related to other factors besides BMD, such as risk of falls. However, persons with type 2 diabetes may have an increased BMD, and one study reported a decreased risk of fractures in women with type 2 diabetes [23]. Two studies did not distinguish between type 1 and type 2 diabetes, one reporting a decreased fracture risk [30], and the other an increased fracture risk [31]. Ivers et al. [10] reported that insulin-treated diabetes but not tablet- or diet-treated diabetes was associated with an increased risk of fracture, although insulin treatment improves some of the disturbances in calcium metabolism [3, 32].

We conducted a nationwide population-based case-control study on the relative risk of fractures in patients with type 1 diabetes and type 2 diabetes, adjusted for potential confounders, in order to assess the relative fracture risk associated with type 1 diabetes and type 2 diabetes and the effect of different treatment modalities (insulin and oral antidiabetic medication).

Subjects and methods

Study design The study was designed as a case-control study [33]. All subjects sustaining a fracture during the year 2000 in Denmark were included as cases (n=124,655), and for each case three control subjects of the same age (same birth year) and sex were randomly selected from the general population of Denmark (n=373,962). The exposure was presence of diabetes or not and use of antidiabetic medication or not. The odds ratios (ORs) were calculated for risk of fracture in patients with diabetes vs patients without diabetes and similarly for use of antidiabetic medication vs no use of antidiabetic medication. As this study is a case-control study the term 'case' denotes the presence of the outcome fracture and 'control' the absence of the outcome 'fracture', and the exposure is the presence or absence of diabetes in accordance with international standards [33]. Information on exposure variables was collected by the same methods in cases and control subjects. A ratio of three control subjects to one case was chosen based on power calculations showing that little would be gained from further increasing the number of control subjects per case. Furthermore, the more control subjects the higher the likelihood that a perfectly age- and sex-matched control could not be identified. This study was approved by the National Board of Health and the Danish Data Protection Agency.

End-points The case definition was any fracture between 1 January 2000 and 31 December 2000. All fractures were included at all ages, i.e. fractures in both children and adults, and fractures from high-energy traumas as well as low-energy and spontaneous fractures. Hip, spine and forearm fractures were analysed separately.

Exposure variables The prime exposure variable was presence of a diagnosis of: (1) type 1 diabetes; (2) type 2 diabetes; or (3) other non-specified types of diabetes from 1 January 1977 to 31 December 2000 or the date of fracture. The diabetes was diagnosed prior to the date of fracture, to avoid ascertainment bias at the time of fracture. The criteria for diagnosing type 1 diabetes, type 2 diabetes, and other types of diabetes followed the World Health Organization standards. All diagnoses, both main diagnoses and additional diagnoses (i.e. a patient mainly coming for treatment with a fracture, and having an additional diagnosis of arterial hypertension) were entered into the analysis. The secondary exposure was use of drugs to treat diabetes: (1) insulin, oral antidiabetic drugs; (2) sulphonylureas; (3) metformin; and (4) other oral antidiabetic drugs from 1 January to the date of censoring (date of fracture among cases or a similar dummy date among control subjects). Insulin was used in type 1 diabetics and type 2 diabetics.

The exposure was total number of defined daily doses (DDDs) consumed from 1996 to the date of censoring.

Other covariates included: (1) diseases or conditions known to affect fracture risk (e.g. prior stroke, acute myocardial infarction, and alcoholism); (2) use of medications reported to be associated with fracture risk (cholesterol-lowering drugs and antihypertensive drugs by diabetics); (3) number of contacts with the health service (hospitals, general practitioners [GPs] or specialists) as a proxy-variable for diabetes severity; and (4) social variables such as retirement, which may lead to social deprivation, which is linked to fracture risk [34].

The drugs associated with fracture risk were: (1) antiepileptic drugs [35]; (2) diuretics (thiazides, loop, potassium-sparing, and other types of diuretics) [36]; (3) sedatives, anxiolytics and hypnotics [37]; (4) neuroleptics [37]; (5) antidepressants [38]; (6) antihypertensive drugs; (7) statin and non-statin cholesterol-lowering drugs; and (8) glucocorticoids. The exposure was ever use of the drug in question from 1996 to the date of fracture among the cases and the date of censoring among the control subjects.

The social variables were: (1) working or not; (2) income in the year of the fracture; and (3) living alone or together with another person.

Registers used The information on fracture occurrence and occurrence of other diseases, prior fractures, alcoholism etc. came from two registers: (1) The National Hospital Discharge Register [39]; and (2) The Psychiatric Central Register [40].

The National Hospital Discharge Register was founded in 1977 [39]. It covers all inpatient contacts from 1977 to 1994, and from 1995 also all outpatient visits to hospitals, outpatient clinics and emergency rooms. Upon discharge, the physician in charge of the patient codes the reason for the contact using the International Classification of Diseases (ICD) system (see Appendix). The coding includes one main diagnosis (the main reason for the contact), and up to 16 supplementary diagnoses (i.e. a patient with type 1 diabetes may be hospitalised with a pneumonia, then the

pneumonia is the main diagnosis, and the type 1 diabetes is the supplementary diagnosis). Any surgical procedures performed during the contact are also coded. The register has nationwide coverage and an almost 100% capture of contacts [39]. In general the validity of registrations is high [41], especially for fractures, where a precision of 97% has been reported [42].

The Psychiatric Central Register was founded in 1968 and covers all in- and outpatient contacts for Danish mental hospitals [40]. It has a nationwide coverage and a high validity of diagnoses has been reported [43]. This register also uses the ICD system for coding contacts.

Information on drug use among both patients and control subjects was obtained from The Danish Medicines Agency. This agency keeps a nationwide register of all drugs sold at pharmacies throughout the country from 1996 and onwards (The National Pharmacological Database run by the Danish Medicines Agency, http://www.dkma.dk). The drugs bought are registered by the person for whom the drugs were prescribed, the Anatomical Therapeutical Chemical (ATC) code of the drug sold (see Appendix), dosage sold and date of sale for the period 1 January 1996 to 31 December 2000.

Information on contacts with GPs and practising specialists came from the National Health Service. These contacts are registered by the date of the contact, and the type of contact. However, the contact is not coded with an ICD code.

Information on income was obtained from the Tax Authorities, and information on working status and marital status from the National Bureau of Statistics (Statistics Denmark).

It is possible to link these sources of information through the Central Person Number, which is a unique registration code given to every inhabitant—to some degree similar to the American Social Security Number—that allows registration on an individual basis.

The study was performed as a register-based study in accordance with the Declaration of Helsinki. It was approved by the Danish Board of Health and the Danish Data Protection Agency.

Statistical analyses Mean and SD were used as descriptive statistics. Crude ORs were calculated and 95% CIs. A conditional logistic regression analysis for matched case-control studies—the type which allows *m* to *n* matching where not all cases need to have exactly the same number of controls—was used to assess the association between any fracture and the exposure variable [44]. Analyses were also performed sex- and age-stratified (A:<15, 15–49, ≥50 years, B: above and below 75 years, and C:<59, 50–74 years, ≥75 years—data not shown).

From the observation that the risk estimates for a fracture between the different types of diabetes were similar (see Results), the analysis of fracture risk in patients with complications of diabetes was pooled across diabetes types.

Analyses were performed using STATA 8.1 (STATA, College Station, TX, USA) and SPSS 10.1.0 (SPSS., Chicago, IL, USA), both in the UNIX version.

Table 1 Characteristics of cases (all fractures in Denmark in the year 2000, *n*=124,655) and of control subjects (*n*=373,962, age- and sex-matched from the total population of Denmark in the year 2000, *n*=5,330,020)

Variable	Cases	Control subjects	*p*
Age (years), mean±SD	43±27	43±27	–
Sex (%)			
Men	48.2	48.2	–
Women	51.8	51.8	–
Previous fracture (%)	33.1	15.0	<0.01
Prior acute myocardial infarction (%)	2.5	2.1	<0.01
Prior stroke (%)	3.5	2.2	<0.01
Ever use of other diuretics (%)	3.8	3.8	0.93
Ever use of potassium-sparing diuretics (%)	2.2	1.4	<0.01
Ever use of loop diuretics (%)	11.4	8.1	<0.01
Ever use of thiazide diuretics (%)	12.6	11.6	<0.01
Ever use of antihypertensive drugs (%)	16.0	15.2	<0.01
Ever use of statins (%)	1.5	1.6	0.02
Ever use of non-statins (%)	0.24	0.21	0.05
Ever use of any glucocorticoid (%)	54.3	50.7	<0.01

Results

Table 1 shows baseline characteristics of the cases and control subjects. Cases, more often than control subjects, were retired or living alone, and had a lower income. Cases also more often had concurrent diseases, and had been using medications. Only for prior fracture, prior use of loop diuretics, and prior use of any corticosteroid were major differences in terms of percent observed. Among the cases 26,220 were aged less than 15 years, and among the control subjects the number was 78,651.

Table 2 Prevalence of use of diabetic and antidiabetic drugs among cases (all fractures in Denmark in the year 2000, *n*=124,655), and control subjects (*n*=373,962, age- and sex-matched from the total population of Denmark in the year 2000, *n*=5,330,020)

Variable	Cases	Control subjects	*p*
Type 1 diabetes (%)	1.4	0.7	<0.01
Type 2 diabetes (%)	2.6	1.7	<0.01
Non-specified types of diabetes (%)	0.5	0.3	<0.01
Any prior episode of hypoglycaemia (%)	0.6	0.4	<0.01
Insulin (%)	1.5	0.9	<0.01
Metformin (%)	0.8	0.8	0.18
Sulphonylureas (%)	2.0	1.8	<0.01
Other oral antidiabetic drugs (%)	0.2	0.2	0.08
Cumulated DDD for insulin (mean±SD)	1,767±1,352	1,762±1,359	0.91

DDD Defined daily dosage

Table 3 Relative risk of any fracture here interpreted as odds ratio (OR) with 95% CI for several variables in the population of Denmark in the year 2000 estimated in a case-control study by conditional logistic regression (124,655 fractures and 373,962 age- and sex-matched control subjects)

Variable	Crude			Multiply-adjusted[a]		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Type 1 diabetes vs no diabetes	1.93	1.82	2.05	1.30	1.16	1.46
Type 2 diabetes vs no diabetes	1.55	1.48	1.61	1.19	1.11	1.27
Non-specified types of diabetes	2.14	1.95	2.36	1.20	1.07	1.34
Prior episode of hypoglycaemia vs no episode	1.69	1.55	1.84	1.13	1.00	1.26
Insulin						
<1,000 DDD	1.65	1.50	1.81	1.04	0.92	1.18
1,000–1,999 DDD	1.67	1.49	1.87	0.85	0.73	1.00
≥2,000 DDD	1.75	1.60	1.92	0.88	0.76	1.02
Metformin						
<150 DDD	1.07	0.95	1.22	0.87	0.76	1.01
150–499 DDD	1.06	0.93	1.20	0.81	0.71	0.94
≥500 DDD	1.02	0.91	1.15	0.81	0.70	0.93
Sulphonylureas						
<400 DDD	1.17	1.08	1.27	0.88	0.80	0.96
400–1,299 DDD	1.14	1.06	1.24	0.82	0.75	0.90
≥1,300 DDD	1.13	1.05	1.23	0.85	0.76	0.95
Other types of oral antidiabetics						
<45 DDD	1.16	0.90	1.50	1.03	0.79	1.36
45–199 DDD	1.00	0.77	1.28	0.89	0.68	1.17
≥200 DDD	1.26	0.99	1.60	1.17	0.90	1.52

DDD Defined daily dosages
[a]Adjusted for the variables in the table plus prior fracture, corticosteroid use, use of anti-epileptic drugs, use of diuretics (loop, thiazide, potassium-sparing, other types), use of anxiolytics and sedatives, use of neuroleptics, use of antidepressants, alcoholism, use of statins and non-statin cholesterol-lowering drugs, use of antihypertensives, myocardial infarction, stroke, number of bed days in 1999, number of contacts to GP or specialists in 1999, working or not, income, living with another person vs living alone

Table 2 shows the prevalence of diabetes by type and use of antidiabetic drugs. Type 1 and type 2 diabetes and use of insulin and sulphonylureas were more common in cases than in control subjects (all p values <0.01). The mean ingested dose (DDD) of insulin from 1996 to 2000 was similar in patients and control subjects.

Table 3 shows the crude and adjusted ORs for any fracture in cases compared with control subjects. In the mul-

Table 4 Relative risk of fractures at typical osteoporotic fracture sites here interpreted as odds ratio (ORs) with 95% CIs for several variables in the population of Denmark in the year 2000 estimated in a case-control study by conditional logistic regression

Variable	Hip (*N*=10,530/31,535)			Forearm (*N*=20,035/60,030)			Spine (*N*=3,364/10,079)		
	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI	OR	Lower 95% CI	Upper 95% CI
Type 1 diabetes	1.70	1.31	2.21	1.04	0.76	1.44	2.48	1.33	4.62
Type 2 diabetes	1.38	1.18	1.60	1.21	1.01	1.45	1.34	0.97	1.86
Non-specified types of diabetes	1.52	1.18	1.96	1.23	0.88	1.70	1.23	0.64	2.37
Prior episode of hypoglycaemia	1.55	1.13	2.13	1.14	0.83	1.57	1.32	0.71	2.46
Insulin									
<1,000 DDD	1.18	0.88	1.57	0.99	0.70	1.39	0.53	0.26	1.09
1,000–1,999 DDD	0.70	0.69	1.01	1.13	0.74	1.72	0.21	0.09	0.52
≥2,000 DDD	0.80	0.54	1.20	0.94	0.62	1.41	0.49	0.22	1.11
Metformin									
<150 DDD	0.70	0.49	1.02	0.71	0.48	1.04	1.16	0.58	2.34
150–499 DDD	1.05	0.76	1.46	0.89	0.60	1.31	0.52	0.23	1.14
≥500 DDD	0.76	0.55	1.04	0.72	0.49	1.06	0.92	0.45	1.87
Sulphonylureas									
<400 DDD	0.86	0.70	1.05	0.91	0.71	1.15	0.89	0.57	1.38
400–1,299 DDD	0.77	0.63	0.95	0.81	0.63	1.03	1.03	0.65	1.62
≥1,300 DDD	0.74	0.58	0.93	0.82	0.60	1.11	0.88	0.51	1.53
Other types of oral antidiabetics									
<45 DDD	1.22	0.64	2.33	1.01	0.53	1.95	1.66	0.52	5.31
45–199 DDD	0.90	0.49	1.65	0.61	0.25	1.48	0.33	0.04	2.81
≥200 DDD	1.27	0.69	2.33	1.43	0.77	2.65	0.92	0.28	3.05

Adjusted for prior fracture, corticosteroid use, use of anti-epileptic drugs, use of diuretics (loop, thiazide, potassium-sparing, other types), use of anxiolytics and sedatives, use of neuroleptics, use of antidepressants, alcoholism, use of statins and non-statin cholesterol-lowering drugs, use of antihypertensives, myocardial infarction, stroke, number of bed days in 1999, number of contacts to GP or specialists in 1999, working or not, income, living with another person vs living alone
N Number of cases/control subjects, *DDD* defined daily dosage

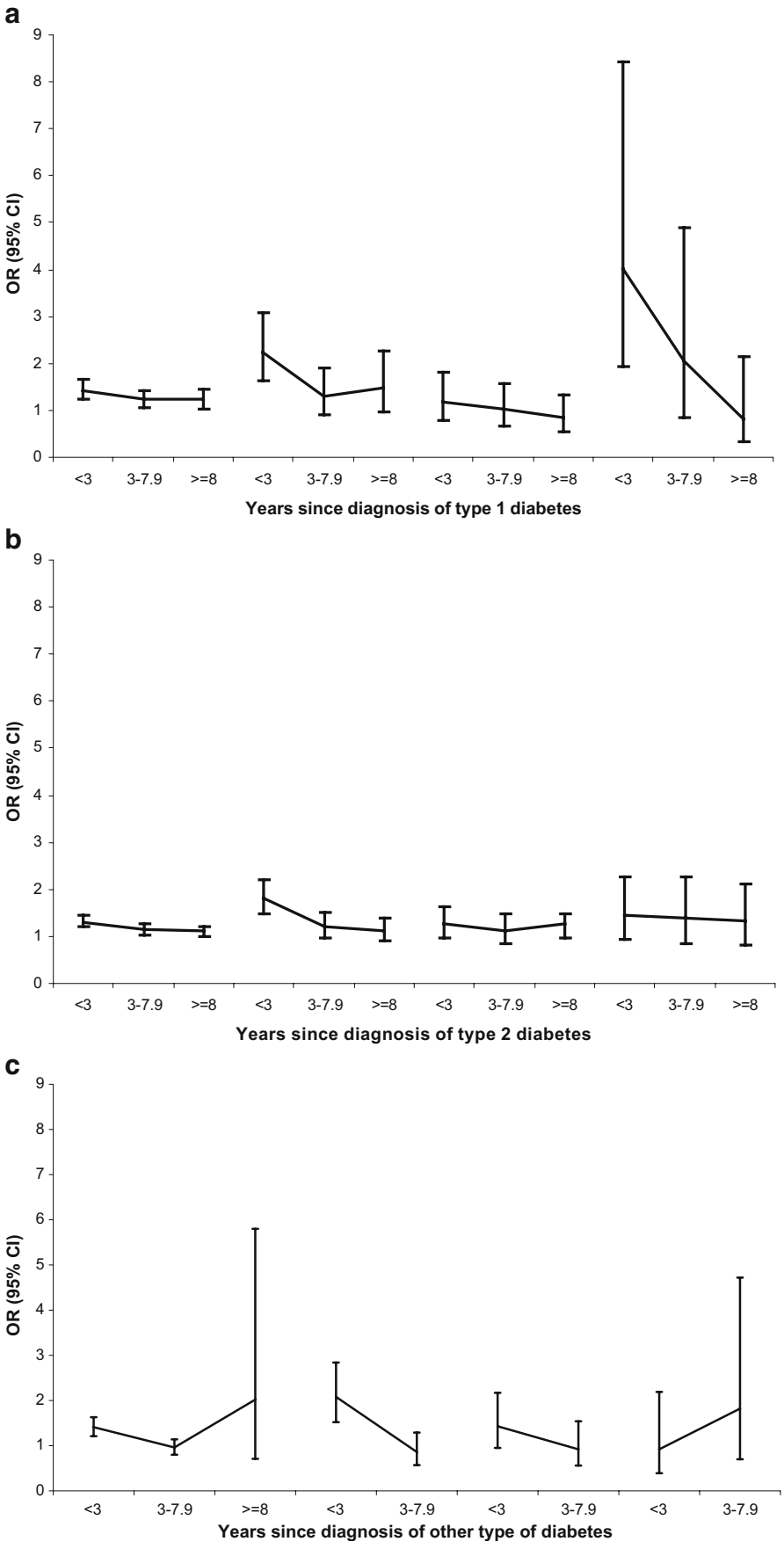

Fig. 1 Relative risk of fractures at typical osteoporotic fracture sites by inclusion of diabetes duration in the population of Denmark in the year 2000, estimated in a case-control study by conditional logistic regression. The relative risk is interpreted as odds ratios (OR) with 95% CIs. **a** Type 1 diabetes, **b** type 2 diabetes, **c** non-specified type of diabetes. All panels are adjusted for prior fracture, corticosteroid use, use of antiepileptic drugs, use of diuretics (loop, thiazide, potassium-sparing, other types), use of anxiolytics and sedatives, use of neuroleptics, use of antidepressants, alcoholism, use of statins and non-statin cholesterol-lowering drugs, use of antihypertensives, myocardial infarction, stroke, number of bed days in 1999, number of contacts to GP or specialists in 1999, working or not, income, living with another person vs living alone

tiply-adjusted analysis, diabetes irrespective of type was associated with an increased fracture risk, while use of metformin and sulphonylureas were associated with a decreased risk of fractures. The increased fracture risk associated with insulin was reversed after adjustment for total number of defined daily doses used and confounders.

Prior episodes of hypoglycaemia were weakly associated with fracture risk after adjustment for the presence of diabetes. Even after adjustment for episodes of hypoglycaemia, diabetes was still associated with an increased fracture risk. Most episodes of hypoglycaemia were seen in type 1 diabetes, but some episodes in persons with type 2 diabetes were associated with the use of insulin and sulphonylureas.

Table 4 shows the adjusted risk of fractures in specific skeletal sites. All types of diabetes were associated with an increased fracture risk in the hip, while only type 1 diabetes was associated with a significantly increased spine fracture risk, and only type 2 diabetes was associated with an increase in forearm fracture risk. Use of all but the lowest daily doses of sulphonylureas was associated with a decreased fracture risk in the hip, while insulin was associated with a non-significant trend towards a reduction in fracture risk. No consistent association with antidiabetic drugs and fracture risk at the spine or forearm was observed.

Figure 1 shows no significant association of the duration of type 1 diabetes or type 2 diabetes.

Discussion

We have demonstrated an independent increased risk of any fracture risk and hip fracture associated with any type of diabetes (type 1, type 2 and other non-specified diabetes). Only type 2 diabetes was associated with an increased risk of forearm fractures, and type 1 diabetes with an increased risk of spine fractures. Antidiabetic drugs—insulin, sulphonylureas and metformin—were each associated with a decrease in fracture risk that was not apparent before adjusting for multiple covariates.

Strengths and weaknesses of the study The advantages of the study is that it is population-based and nationwide, i.e. not from selected populations at specialised clinics, who may have a much different risk profile. Selection and information bias are thought to be limited as probably nearly all subjects with a fracture are included and the validity of a fracture diagnosis is high.

One major drawback is that we have no information on BMI [45] or metabolic control (HbA_1c) in the individual patient. In our study an increase in fracture risk is present in both type 1 and type 2 diabetes, and this was also reported in previous studies after adjustment for BMI [19, 28]. Another disadvantage is that nearly all patients diagnosed with type 1 diabetes are captured because these patients are managed in hospital, but not all patients diagnosed with type 2 diabetes may be registered with a diagnosis of type 2 diabetes. This is because in Denmark the GP manages many of these patients, and they do not necessarily have their diagnosis registered in the hospital-based discharge registry. Any bias from patients with type 2 diabetes not being registered in the system would tend to underestimate the actual OR associated with type 2 diabetes, as the patients with type 2 diabetes who are not registered are classified with the control group presumed to be without type 2 diabetes. Further, many people in the general population have undiagnosed type 2 diabetes, which may also underestimate the odds of fracture associated with type 2 diabetes.

Strengths and weaknesses in relation to other studies In this study a case-control design was chosen because a cohort study would have required a very large sample of patients with diabetes followed for a long period of time to yield a sufficient number of fractures. The registry-based case-control design also provides the opportunity to study multiple risk factors at the same time. On the other hand, the case-control design does not allow calculation of fracture incidence.

Implications The use of antidiabetic drugs seemed to counter the detrimental effects of diabetes. This is most likely not the result of a direct antifracture effect of the antidiabetic drugs identical to the effects of anti-osteoporotic drugs, such as for example bisphosphonates. The fracture-reducing potential was only present with oral antidiabetic drugs at skeletal sites where diabetes was associated with an increase in fracture risk, i.e. in the hip. At the forearm, no substantial increase in fracture risk was present for type 1 diabetes, and no fracture-reducing potential was observed for insulin.

This raises an interesting possibility that the increase in fracture risk may be linked to hyperglycaemia. The mechanism whereby hyperglycaemia exerts negative effects on fracture risk is not entirely clear. In an experimental study, glucose administration showed negative effects on both bone formation and bone resorption [46]. In a rat model of type 1 diabetes, improved metabolic control reversed the negative consequences of poor metabolic control on bone healing [47]. Among adolescents with type 1 diabetes, poor metabolic control was associated with a negative effect on bone mineral acquisition [48].

In our study, diabetes duration was not associated with fracture risk—in fact the relative risk of fracture tended to be higher in those with less than 3 years of diabetes than in those with diabetes of longer duration. This could be the result of initial poor control of diabetes with control improved over time. This could especially be of significance in patients with type 2 diabetes, who may have been asymptomatic for a long period before diagnosis.

In patients with type 2 diabetes, an increase in BMD [2] is often observed. However, in contrast to the expected decrease in fracture risk, the present study reveals an actual increase in the risk of hip and forearm fractures. In type 1 diabetes, weight loss, metabolic acidosis and hypoglycaemia may contribute to fracture risk, while vision loss, neuropathy and obesity may be of greater significance in type 2 diabetes.

In our study a trend towards an increase in fracture risk was present in patients with prior episodes of hypoglycaemia, and this trend was statistically significant for hip fractures. This is probably the result of a hypoglycaemia-induced risk of falls and thus fractures. Many episodes may be treated at home and thus not registered at the hospitals, with only the more severe episodes coming to hospital; many of these do not result in falls, as the subject is found unconscious. Thus the association between hypoglycaemia and fracture is probably underestimated in this study.

The overall number of fractures in the year 2000 (n=124,655) was small compared with the population size (n=5,330,020—rate 2.3%/year); therefore the calculated ORs could be interpreted as approximate relative risks. Caution is required for the interpretation of the p values in Table 1, because the large number of subjects means that small clinically insignificant differences may become statistically significant.

In conclusion, these data show that both type 1 and type 2 diabetes are associated with an increased risk of any fracture and hip fracture. Forearm fractures were associated with type 2 diabetes, and spine fractures with type 1. The use of drugs to control diabetes may reduce the diabetes–fracture associations. These results need confirmation from other studies.

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Appendix

List of all codes for drugs (ATC codes) and diseases (ICD8 and 10) referred to in the study as outcome (any fracture) or exposure (type of diabetes, types of antidiabetic drugs used).

Diabetes	ICD 8 codes	ICD 10 codes
Type 1 diabetes	24,900–24,909	E100–E109
Type 2 diabetes	25,000–25,009	E110–E119
Other non-specified types of diabetes	–	E120–E129, E130–E139, E140–E149

Drug	ATC code
Insulin	A10AB01, A10AB04, A10AB05, A10AC01, A10AD01, A10AD04, A10AD05
Sulphonylureas	A10BB01 (glibenclamide), A10BB03 (tolbutamide), A10BB07 (glipizide), A10BB09 (gliclazide), A10BB12 (glimepiride)
Metformin	A10BA02
Other types of oral antidiabetic drugs	A10BF01 (acarbose), A10BG02 (rosiglitazone), A10BG03 (pioglitazone), A10BX02 (repaglinide), A10BX03 (nateglinide)

Any fracture: ICD10 codes: S02.0–S02.9, S07.0–S07.9, S12.0–S12.9, S22.0–S22.9, S32.0–S32.8, S42.0–S42.9, S52.0–S52.9, S62.0–S62.9, S72.0–S72.9, S82.0–S82.9, S92.0–S92.9

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