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ORIGINAL ARTICLE

Hypoglycaemia and type 1 diabetes are associated with an increased risk of fractures

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Abstract

Summary People with diabetes have an increased risk of fractures, and in this study, the effect of hypoglycaemia and insulin on this risk was investigated. Type 1 diabetes and hypoglycaemia did increase the fracture risk, and prevention of hypoglycaemia is thus an important focus area in the prevention of fractures.

Introduction Studies have shown that type 1 diabetes (T1D) and type 2 diabetes (T2D) are associated with increased risk of fractures. Especially, subjects with T1D have an increased risk of fractures. The purpose of this study was to investigate the association of T1D, hypoglycaemia and insulin on fracture risk.

Methods A cohort study with T1D subjects ($n = 19{,}896$) and T2D subjects ($n = 312{,}188$) matched with subjects from the general populated ($n = 996{,}252$) and a nested case-control study with T1D subjects with fracture ($n = 895$) as cases and T1D subjects without ($n = 2685$) as controls were conducted based on subjects from the Danish National Patient Registry (DNPR).

Results T1D (HR = 2.47, 95% CI 2.37 to 2.59), age (HR = 1.05, 95% CI 1.05 to 1.05), previous fracture (HR = 1.95, 95% CI 1.92 to 1.99) and being female (HR = 2.06, 95% CI 2.04 to 2.09) increased the risk of fractures. Also, T2D (HR = 1.14, 95% CI 1.11 to 1.18) increased the risk of proximal upper arm and shoulder fractures. T1D (HR = 2.41, 95% CI 2.20 to 2.65) increased the risk of hip and femoral region fractures. Hypoglycaemia (OR = 1.58, 95% CI 1.27 to 1.97) increased the risk of fractures, whereas insulin use did not change the risk.

Conclusions Hypoglycaemic episodes are associated with increased fracture risk, and the frequency of hypoglycaemic episodes leading to hospital admission was above 16% for T1D subjects. Prevention of hypoglycaemia is thus an important focus area in the prevention of fractures.

Keywords Diabetes · Fractures · Hypoglycaemia · Insulin · Type 1 diabetes

Introduction

An often overlooked complication to diabetes mellitus (DM) is the increased risk of fractures [1]. The deteriorated glucose metabolism affects bone mineral density (BMD) and increases the risk of fractures through falls and traumas [2, 3]. The underlying mechanisms of reduced BMD are among others increased urine calcium excretion [4], functional hypoparathyroidism [5] and alterations in vitamin D metabolism [6] as well as decreased bone biomechanical competence [7].

People with type 1 diabetes (T1D) are at a higher risk of fractures compared with people with type 2 diabetes (T2D) [2, 8]. Due to the autoimmune destruction of the pancreatic beta cells, people with T1D depend on exogenous insulin administration throughout life to avoid late-diabetic complications [9]. To delay onset and slow progression of the late-diabetic complications, intensive insulin treatment is necessary, but it comes at the cost of an increase in severe hypoglycaemia [10, 11]. Severe hypoglycaemia itself may lead to unconsciousness and subsequent falls and traumas increasing fracture risk [12, 13]. Furthermore, the glucose counter-regulation following onset of hypoglycaemia includes excretion of glucagon, adrenalin and cortisol [14], and the steroid hormones have

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also been associated with reduction of BMD leading to increased fracture risk [15]. Incidence of hypoglycaemia in people with DM is associated with use of insulin [16], but insulin may also contribute directly to the increased fracture risk [17, 18]. We hypothesised that T1D, hypoglycaemia and insulin use increase the fracture risk.

This study sought to investigate the association of T1D, hypoglycaemia and insulin on fracture risk.

Methods

Study design

The investigation was carried out using a cohort and a nested case-control design. The cohort consisted of subjects admitted to hospitals in Denmark from 1 January 1996 to 31 December 2017. The number of subjects enrolled can be seen in Fig. 1. Classification of subjects and identification of outcome and exposure was carried out via the International Classification of Diseases 10 (ICD-10) system and the Anatomical Therapeutical Chemical (ATC) classification system. T1D subjects ($n = 19{,}896$) were identified by at least one DE10 (type 1 diabetes mellitus) ICD-10 code and at least one A10A (insulins and analogues) and no A10B (blood glucose–lowering drugs, excl. insulins) ATC code. T2D subjects ($n = 312{,}188$) were identified by at least one A10B ATC code and no E10 ICD-10 code. The resultant subjects were then matched by sex and year of birth 1:3 with subjects from the general population ($n = 996{,}252$). The subjects from the general population received the diabetes diagnosis date from the matched diabetes subject as a 'dummy' diagnosis date.

In the nested case-control design, T1D subjects with fractures (cases, $n = 895$) were matched 1:3 with T1D subjects without fractures (controls, $n = 2685$). To balance the exposure periods, only controls that died or emigrated at least 10 years after diagnosis were included. The controls received the fracture date from the matched case subject as a 'dummy' fracture date.

Endpoints and exposure

The endpoint (outcome) in both the cohort and the nested case-control was first occurring fracture after baseline defined

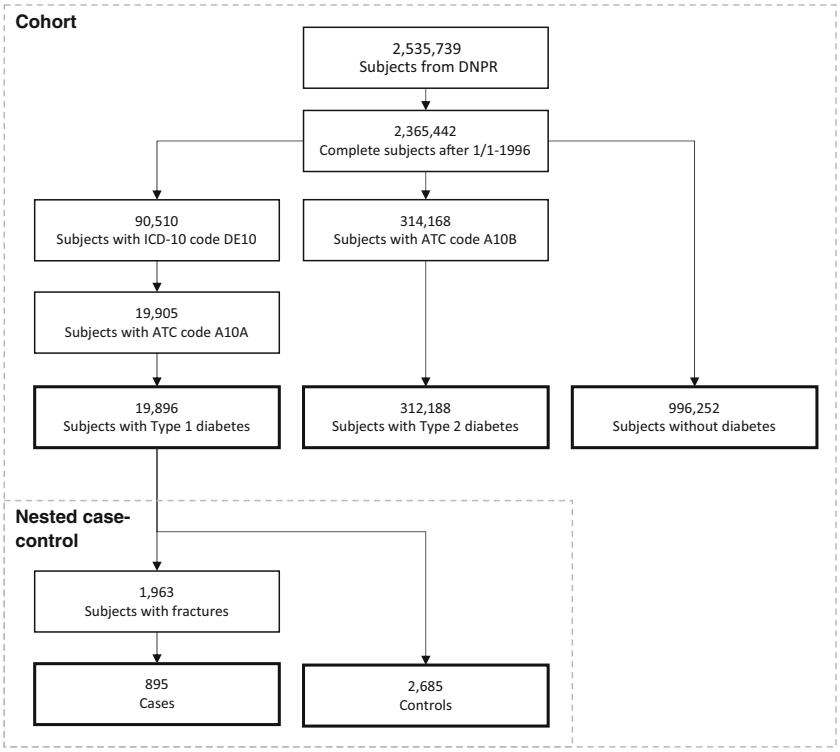

Fig. 1 Number of subjects in the cohort and nested case-control design. From the available subjects from the Danish National Patient Register (DNPR), 19,905 were identified as having T1D and 314,168 as T2D. Subjects from the general population were then extracted and matched by sex and date of birth 3:1 with the T1D and T2D subjects. If it was not possible to find three matches to the T1D and T2D subjects, they were excluded and the actual number of T1D and T2D subjects is thus slightly lower. Of the 19,896 T1D subjects, 1963 experienced fractures and these were matched 1:3 by sex and date of birth with T1D subject without fractures. However, only T1D subjects without fractures with at least 10 years to death or emigration from date of diagnosis were selected to obtain equal exposures in the two groups. Therefore, the number of cases and controls are lower

as the date of diagnosis or dummy diagnosis date. The fractures were identified and classified according to the ICD-10 codes: Spinal fractures (M484, M485, M485A, M495, M809C, S32, S320, S320A, S320B, S320C, S320D, S320E, S327, S327A, S328, S328A, S220, S221 and T08), hip and femoral region fractures (M809B, S72, S720, S721, S721A, S721B, S722, S723, S724B, S724C, S727, S728A and S729), wrist and hand fractures (M809A, S52, S521A, S521B, S522, S523, S524, S525, S525A, S525B, S525C, S526, S527, S528, S528A, S528B, S528C, S529, S620 and S621), Proximal upper arm and shoulder (S422, S422A, S422B, S422C, S423, S423A, S424 and S427) and Multiple fractures (DT02, DT10, DT12).

The subjects without fractures were regarded as censored at the minimum date of death, emigration, or end of study (31 December 2017). If this date was less than the dummy diagnosis date for subjects from the general population, the dummy date was set to 1 January, the year of emigration or death.

In the nested case-control design, the fracture dummy date for controls was updated to date of death or emigration if such events occurred before the fracture dummy date. The exposure period in this design was defined from date of diagnosis to fracture/dummy date. Hospital admissions with the primary reason specified as hypoglycaemia was defined as a hypoglycaemic episode, and the date of admission was used as a surrogate for the date of the hypoglycaemic event. These hospital admissions were identified in the exposure period via the ICD-10 codes DE160 (drug-induced hypoglycaemia without coma), DE161 (other hypoglycaemia) and DE162 (hypoglycaemia, unspecified). Due to the limited number of hypoglycaemic episodes ($n = 1018$), the number was dichotomized to subjects with hypoglycaemia and subjects without.

Total daily insulin dose was calculated as the sum of the doses of all dispensed medicines with ATC code A10A in the exposure period divided by the number of days in the exposure period. The same calculation was performed for daily bolus insulin dose with ATC codes A10AB and A10AC and daily basal insulin dose with ATC codes A10AD and A10AE.

Source of data

The subject data with diagnoses of diabetes, fractures and hypoglycaemia came from the Danish National Patient Register (DNPR) [19]. DNPR was established in 1977 and initially covered information on inpatient in somatic wards. Since then, it has been expanded and now includes information on all patients in Danish hospitals [19]. The validity of registrations is high, especially for fractures [20, 21].

Information about drug use came from the National Pharmacological Database by the Danish Medicines Agency, which is a nationwide register of medicines sold after 1996.

Statistical analyses

Descriptive statistics will be presented with mean and standard deviation (SD) or percentage of subjects. Chi-square and Mann-Whitney *U* tests will be used to present statistical differences in subject characteristics. In the subject characteristics of the cohort, the differences between the group of diabetes subjects and the group of subjects from the general population were tested. Late-diabetic complications will be presented for the cohort in the following categories: Nephropathy (ICD-10: DE102, DE112), retinopathy (ICD-10: DE103, DE113), neuropathy (ICD-10: DE104-5, DE114-5), multiple (ICD-10: DE107, DE117 or > 1 of the mentioned complications) and other (ICD-10: DE106, DE108, DE116, DE118). A Cox proportional hazards model [22] was used with time on study as the time scale in order to estimate the hazard rate ratio (HR) and 95% confidence interval (CI) for the association between disease (T1D, T2D, controls) and the fracture rate in the cohort. The model included age, sex, previous fracture (at least one of the above-defined fractures before baseline) and anti-osteoporosis medication (ATC: M05BA, M05BB, G03XC01, H05AA, M05BX) as covariates. The model was adjusted for anti-osteoporosis medication to eliminate the effect of osteoporosis on fractures. Subgroup analyses were conducted on the five fracture groups individually using the exact same Cox model configuration. Logistic regression models were constructed to analyse the effect of hypoglycaemia and insulin use for T1D subjects on fractures. The models included previous fracture, history of alcohol abuse (ICD-10: DF10, DZ721), history of liver disease (ICD-10: DK70, DK71, DK74), use of glucocorticoids (ATC: H02AB), use of ACE inhibitors (ATC: C09A, C09B), use of beta blocking agents (ATC: C07), use of antiepileptics (ATC: N03AX12, N03AX16), use of antidepressants (ATC: N06AA) and anti-osteoporosis medication (ATC: M05BA, M05BB, G03XC01, H05AA, M05BX) as dichotomous covariates.

The descriptive and inferential analyses were conducted in SAS 9.4. The significance level was set at a p value of less than 0.05 for two-sided testing.

Results

Table 1 shows the baseline characteristics of the subjects in the cohort.

The average age of subjects with T1D is approx. 24 years less than that of T2D and non-diabetes subjects. This difference should be kept in mind when looking at the percentage of fractures. Furthermore, the fractures in scope are only first occurring fracture after diabetes diagnosis, which means that if a person with T1D experiences a hand fracture and later a hip fracture, the subject will only count in the 'Wrist and hand

Table 1 Subject characteristics in cohort. All counts and percentages are on subject-level

Variable	Diabetes			Non-diabetes	*p*
	T1D	T2D	Both		
n	19,896	312,188	332,084	996,252	–
Age, mean ± SD	36 ± 24	60 ± 16	59 ± 17	59 ± 17	Matched
Sex (%)					
Female	39.9	47.5	47.1	47.1	Matched
Male	60.1	52.5	52.9	52.9	Matched
Late-diabetic complications					
Nephropathy (%)	1.4	1.5	1.5	0	–
Retinopathy (%)	3.2	0.5	0.7	0	–
Neuropathy (%)	3.0	3.1	3.1	0	–
Multiple (%)	12.8	5.3	5.7	0	–
Other (%)	14.9	8.2	8.6	0	–
Previous fracture (%)	7.4	7.0	7.0	7.3	< 0.001
All fractures[a] (%)	10.0	7.9	8.0	9.4	< 0.001
Spinal fractures[a,b] (%)	7.4	9.2	9.1	8.6	< 0.001
Hip and femoral region fractures[a,b] (%)	22.9	35.9	34.9	34.6	< 0.001
Wrist and hand fractures[a,b] (%)	50.5	33.4	34.7	39.5	< 0.001
Proximal upper arm and shoulder[a,b] (%)	19.2	21.5	21.3	17.1	< 0.001
Multiple fractures[a,b] (%)	0	0.01	0.01	0.01	–
Hypoglycaemia[c] (%)	16.8	1.9	2.8	0.1	< 0.001
Hypoglycaemia before fracture[b,d] (%)	3.2	1.1	1.2	0.1	< 0.001

[a] First occurring fracture after baseline

[b] Percentage of all fractures

[c] Subjects recorded with a hypoglycaemia from the Danish National Patient Register at any point in time

[d] Subjects with at least one hypoglycaemic episode within the week before the fracture

fractures' category. Late-diabetic complications were higher among T1D subjects, especially for multiple complications. Differences were statistically significant except for multiple fractures with too few events for analysis. As expected, T1D subjects suffered from more hypoglycaemic episodes than both T2D subjects and people from the general population. Three percent of all fractures for T1D subjects preceded with a hypoglycaemic episode.

Table 2 shows the results of the Cox proportional hazards model. All presented hazard ratios are statistically significant.

People with T1D have an increased fracture risk of 147% while people with T2D have a 7% decreased risk of fractures compared with subject from the general population. For each year of age, the fracture risk increases 5%. Being female or having a previous fracture doubles the risk of fractures. Table 3 shows the results of the subgroup analyses. The HRs are in line with the results from the model with all fractures. However, the HR for proximal upper arm and shoulder fractures turned from a decreased relative risk to an increased relative risk for T2D subjects.

Table 4 shows the characteristics of the case-control subjects. Exposure was equal among the two groups, whereas previous fracture and hypoglycaemia were statistically significantly different. Amount of insulin was not statistically significantly different between the two groups, but a slightly higher dose among controls can be observed. The incidence rate ratio (IRR) can, from the two incidence rates of hypoglycaemia specified in the table, be calculated to 1.62.

Table 5 shows the logistic regression models. The first model includes hypoglycaemia Y/N as exposure, the second model total daily insulin dose as exposure, the third model hypoglycaemia as exposure and total daily insulin dose as covariate and finally the fourth model hypoglycaemia as exposure and daily bolus/basal insulin as covariates. Furthermore, all models were adjusted for previous fracture, history of alcohol abuse, history of liver disease, use of glucocorticoids, use of ACE inhibitors, use of beta blocking agents, use of antiepileptics, use of antidepressants and use of bisphosphonates. As can be observed, the fracture risk in case of previous fractures is higher than in the cohort with T2D subjects and subjects from the general population (Table 2). History of both alcohol abuse and liver disease increases the fracture risk significantly. Also, use of antiepileptics and bisphosphonates increases the risk significantly. Use of glucocorticoids, ACE inhibitors, beta blocking agents and antidepressants does not alter the risk. For subjects

Table 2 Results from Cox proportional hazards model for any fracture. Hazard ratio (HR) is shown followed by 95% confidence internal (CI). Finally, the *p* value is shown

Parameter	HR (95% CI)	*p* value
T1D	2.47 (2.37–2.59)	< 0.0001
T2D	0.93 (0.92–0.95)	< 0.0001
Controls	1	–
Age	1.05 (1.05–1.05)	< 0.0001
Sex		
Female	2.06 (2.04–2.09)	< 0.0001
Male	1	–
Previous fracture (Yes)	1.95 (1.92–1.99)	< 0.0001
Anti-osteoporosis medication (Yes)	1.31 (1.28–1.35)	< 0.0001

experiencing hypoglycaemia, the fracture risk is 58% increased (model 1) and this risk does not change much in models 3 and 4 where insulin use is included. Insulin use is not in any of the models 2–4 statistically significant.

Discussion

Findings from this study indicate a more than doubled risk of fractures for subjects with T1D compared to the general population. For subjects with T2D, the risk of proximal upper arm and shoulder fractures was increased, but no increase was observed for the other sites for T2D subjects. For subjects with T1D, an almost 2.5-fold increased risk of hip and femoral region fractures was observed. Furthermore, hypoglycaemic episodes increased the fracture risk by more than 50%, and these findings are consistent with the stated hypothesis. However, insulin did not change the fracture risk.

The increased fracture risk for T1D subjects are in line with results presented in a meta-analysis on fracture risk of T1D and T2D subjects conducted by Vestergaard [2] and a systematic review of the same topic by Janghorbani et al. [1]. The increase is slightly lower in this study, which may be explained by the fact that hip fracture was the typically investigated fracture in the other studies. In this study, spinal fracture risk was not increased for people with T2D. This is in line with a study by Napoli et al. [23] investigating vertebral fracture risk in elderly men. Furthermore, the hip and femoral region fracture risk was not increased in this study, which is not in line with the meta-analysis and systemic review of Vestergaard and Janghorbani et al. [1, 2]. Finally, the risk for T2D people of proximal upper arm and shoulder fractures was increased, whereas the risk of wrist and hand fractures was decreased driving the overall risk for fractures for people with T2D to be decreased. A protective effect of T2D has rarely been observed in other studies. In the Rotterdam Study [24], a protective effect *was* observed, but only for women with non-insulin-dependent DM. Later, they showed that the risk was related to the stage of T2D [25]. An explanation of the varying link of the T2D results of this study compared to current evidence might be related to the limitation that it was not possible to adjust the models for BMI and BMD due to the lack of these measurements in the registry. This omission may have biased the results, and the clinical recommendations by the Bone and Diabetes Working Group of IOF [26] should still be considered.

Table 3 Results from the subgroup analyses of each fracture group. Hazard ratio (HR) is shown followed by 95% confidence internal (CI)

Fracture group	T1D	T2D
Spinal fractures[a]	2.18 (1.85–2.57)	0.98 (0.94–1.03)
Hip and femoral region fractures[a]	2.41 (2.20–2.65)	0.99 (0.97–1.02)
Wrist and hand fractures[a]	2.05 (1.92–2.19)	0.77 (0.75–0.79)
Proximal upper arm and shoulder[a]	2.67 (2.41–2.95)	1.14 (1.11–1.18)
Multiple fractures[b]	–	–

[a] Each model included age, sex, previous fracture, anti-osteoporosis medication as covariates

[b] Not enough observations to carry out analysis

The results from the logistic regression indicate that insulin does not play a major role in alteration of fracture risk, which is in line with an earlier study [8]. In another study by Schwartz et al. [27], insulin played a role, and risk of foot fractures was more than doubled for insulin-treated people with T2D. However, they were compared with people without diabetes, and causality would thus be difficult to establish from these results. In a study by Napoli et al. [28], elderly men with diabetes using insulin had an almost twofold increased risk of non-vertebral fractures compared to a group of men with normal fasting plasma glucose. In a study by Forsén et al. [3], insulin users had an almost sevenfold increased risk of hip fractures compared to people without diabetes. These results indicate that insulin may play a role, but further studies are needed to clarify causalities. A limitation related to the investigation of insulin in this study is that only dispenses of insulin was captured in data. Whether the subjects actually administered the insulin remains unknown.

On the other hand, hypoglycaemic episodes increased the fracture risk by 58%. This association is confirmed in a study by Hung et al. [13] and in a study by Ntouva et al. [29]. Hung et al. investigated the effect of severe hypoglycaemia on hip fracture risk in T2D subjects and found an adjusted increased fracture risk of 71% [13]. Ntouva et al. investigated the effect of documented hypoglycaemia on any fracture risk and found an adjusted increased fracture risk of 20% [29]. Interestingly, the increased fracture risk found in this study is similar to the increased fracture risk found by Hung et al. In this study, the

Table 4 Subject characteristics of people with T1D in the nested case-control

Variable	Cases	Controls	*p*
n	895	2685	–
Years of exposure per subject	6.05	6.02	0.935
Age, mean ± SD	30 ± 20	30 ± 20	Matched
Sex (%)			
Female	33.0	33.0	Matched
Male	67.0	67.0	Matched
Hypoglycaemia (%)	18.8	12.8	< 0.001
Hypoglycaemia rate per 1000 subject years	70.2	43.4	< 0.001
Total daily insulin dose, mean ± SD	37 ± 20	38 ± 21	0.052
Total daily bolus dose, mean ± SD	24 ± 18	24 ± 17	0.112
Total daily basal dose, mean ± SD	13 ± 14	14 ± 15	0.221
Previous fracture (%)	10.9	5.3	< 0.001
Alcohol abuse (%)	9.4	3.5	< 0.001
Liver disease (%)	3.5	1.0	< 0.001
Glucocorticoids (%)	7.3	5.4	0.045
ACE inhibitors (%)	14.1	14.4	0.825
Beta blocking agents (%)	7.9	7.8	0.886
Antiepileptics (%)	4.0	1.8	< 0.001
Antidepressants (%)	3.7	3.1	0.383
Anti-osteoporosis medicine (%)	2.3	0.7	< 0.001

hypoglycaemic episodes were registered in relation to a hospital admission, and the episodes could thus in many cases be categorized as level 3 (severe hypoglycaemia) [30]—thereby comparable episodes to the ones investigated in the study by Hung et al. This may explain the similar results even though the population and outcome were different.

The effect of hypoglycaemic episodes on fracture risk may be explained by falls at incidences of unconsciousness, especially, for the elderly [31]. In a study by Schwartz et al. [32], older people with T2D treated with insulin to achieve an HbA_{1c} level ≤ 6% (≈ 36 mmol/mol) experienced more frequent falls compared to those with HbA_{1c} level > 8% (≈

Table 5 Results from logistic regression models analysing the effect of hypoglycaemia and insulin on risk of fractures for people with T1D

Parameter	Model 1	Model 2	Model 3	Model 4
Hypoglycaemia (yes)	1.58 (1.27–1.97)		1.59 (1.28–1.98)	1.61 (1.29–2.00)
Total daily insulin dose	–			–
0–10 IU/day		1	1	
10–30 IU/day		1.16 (0.80–1.69	1.12 (0.77–1.63)	
30–50 IU/day		1.03 (0.71–1.49)	0.98 (0.67–1.42)	
> 50 IU/day		1.03 (0.70–1.52)	0.97 (0.66–1.44)	
Daily bolus insulin dose	–	–	–	
0–10 IU/day				1
10–30 IU/day				0.99 (0.80–1.23)
> 30 IU/day				0.89 (0.70–1.13)
Daily basal insulin dose	–	–	–	
0–10 IU/day				1
10–30 IU/day				0.89 (0.75–1.06)
> 30 IU/day				0.79 (0.62–1.00)

Models were adjusted for previous fracture, diabetes duration, history of alcohol abuse, history of liver disease, use of glucocorticoids, use of ACE inhibitors, use of beta blocking agents, use of antiepileptics, use of antidepressants and use of anti-osteoporosis medication

50 mmol/mol), and these results may explain the findings of our study. However, only 3% of the fractures for T1D subjects had a preceding hypoglycaemia within 1 week (a week was chosen because the dates are hospital admissions dates and therefore not the exact event dates). Many hypoglycaemic episodes are treated at home and these are not captured in the data material used in this study, which probably underestimates the association between hypoglycaemia and fractures.

During hypoglycaemia, counter-regulatory hormones are excreted to reverse the declining blood glucose [14]. Hormones, such as glucagon and epinephrine, result in an almost instantaneous increase in blood glucose, whereas cortisol, excreted at very low blood glucose levels, has a more long-term effect on blood glucose [14]. Both this hyperglycaemic effect of cortisol and the deteriorating effect of epinephrine and cortisol directly on BMD [15] may contribute to the explanation of the increased fracture risk of hypoglycaemia. Especially, because these subjects experiencing severe hypoglycaemia are more prone to experience subsequent severe hypoglycaemia [31].

The 'severe' hypoglycaemic episodes in this study occurred for more than 16% of subjects with T1D and 2% of subjects with T2D and even in the general population (see Table 1). It is thus of utmost importance to reduce these frequencies not only due to the hampering effect of the hypoglycaemia itself [33, 34], but also due to the increased fracture risk found in this study.

A major limitation of this study is the missing availability of BMI, HbA1c (or other metabolic measures) and BMD. These measures are important confounders to consider in epidemiological models of fractures, and the varying results of T2D as related to current evidence might be a consequence of this lack. Another limitation is that many subjects selected from the general population may have undiagnosed T2D resulting in less pronounced effect of T2D on fracture risk. Furthermore, the analysis of the effect of hypoglycaemia on fractures was only carried out on T1D subjects due to the insufficient number of T2D subjects with hypoglycaemia. A similar investigation is needed for T2D subjects where other confounders should be considered. For example, it is known that use of sulfonylureas increases the fracture risk significantly [28, 35], and it also increases the risk of hypoglycaemia, which is why especially this medication type should be investigated [35]. Finally, only a limited number of the hypoglycaemic episodes experienced by the subjects were included in the analyses, because only hospital-related episodes were available. The true effect of hypoglycaemia on fracture risk, therefore, remains unknown.

In conclusion, T1D and hypoglycaemia increase the risk of fractures, whereas insulin did not change the risk. Due to the hypoglycaemia-related increased fracture risk, and the occurrence of hypoglycaemic episodes in more than 16% of subjects with T1D and even in the general population, prevention of hypoglycaemia is an important focus area in the management of DM.

Compliance with ethical standards

Conflicts of interest PV has received unrestricted grants from MSD and Servier and travel grants from Amgen, Eli Lilly, Novartis, Sanofi-Aventis, and Servier.

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