Concerns about hypoglycaemia and late complications in patients with insulin-treated diabetes

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Introduction

Managing insulin-treated diabetes is like sailing between Scylla and Charybdis: on one hand there is the risk of hyperglycaemia and late diabetic complications; on the other, the risk of mild or severe hypoglycaemia. Hypoglycaemia remains a major limitation in achieving optimal glycaemic control for many patients with insulin-treated diabetes.[1] The risk of severe hypoglycaemic episodes causes much anxiety among people with type 1 diabetes and may represent a significant psychological barrier to diabetic therapy adherence.[2] It has now become common to initiate early

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Abstract

Background: Diabetes-related anxiety influences the quality-of-life of people with diabetes.
Aim: To compare diabetes-related concerns in insulin-treated patients with type 1 and type 2 diabetes.
Method: A cross-sectional questionnaire survey was carried out in two cohorts of adult outpatients with type 1 diabetes (n=223) and insulin-treated type 2 diabetes (n=104). Assessment of concerns about mild and severe hypoglycaemia, blindness and kidney failure was carried out using the seven-point Likert scale.
Results: Insulin-treated patients with type 1 or 2 diabetes worry mostly about late diabetic complications, less about severe hypoglycaemia and little about mild hypoglycaemia. Patients with type 1 diabetes worry more about severe hypoglycaemia than those with type 2 diabetes; no differences in levels of anxiety about mild hypoglycaemia, blindness and kidney failure exist. Severe hypoglycaemia in the preceding year is associated with more worry about severe hypoglycaemia in patients with type 1 or 2 diabetes. Those with type 1 or 2 diabetes who have impaired awareness of hypoglycaemia tend to worry more about severe hypoglycaemia than those with normal awareness of hypoglycaemia. The presence of eye or kidney complications does not influence the level of anxiety in people with type 1 diabetes. Patients with type 2 diabetes without complications tend to worry more about mild and severe hypoglycaemia than those with complications.
Conclusion: Patients with insulin-treated diabetes worry considerably about microvascular complications and severe hypoglycaemia risk. Recent experience of severe hypoglycaemia and presence of impaired hypoglycaemia awareness are associated with increased worry scores for severe hypoglycaemia in patients with type 1 or 2 diabetes. Screening for diabetes-related concerns should be integrated into diabetes care.

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Key Words

Type 1 diabetes; type 2 diabetes; insulin therapy; hypoglycaemia; late diabetic complications; worries; fear; hypoglycaemia awareness

insulin treatment in type 2 diabetes to achieve recommended glycaemic targets.[3] The potential risk of severe hypoglycaemia is, however, a major concern when implementing this strategy.[4] Severe hypoglycaemia is associated with a decrement in patients' well-being, productivity and quality-of-life.[5,6] While worries about hypoglycaemia have been extensively studied in patients with type 1 diabetes,[2,5–13] research involving patients with insulin-treated type 2 diabetes is less prevalent.[5,6,9] In these studies, mild and severe

hypoglycaemia were combined,[9] or hypoglycaemia anxiety data in insulin-treated patients were not clearly separated from data involving non-insulin-treated patients.[5,6] Moreover, few studies have compared worries about hypoglycaemia and late complications in insulin-treated patients.[7,14]

We conducted a cross-sectional questionnaire survey that aimed to compare diabetes-related concerns in two cohorts of adult outpatients, with type 1 diabetes and insulin-treated type 2 diabetes, with

Mild hypoglycaemia	I am worried about suffering from mild hypos, which I am capable of managing by myself
Severe hypoglycaemia	I am worried about suffering from severe hypos, where I need assistance from other people
Blindness	I worry about blindness or decreased vision due to diabetes
Kidney failure	I worry about kidney failure due to diabetes

Table 1. Statements about patients' worries with numbers to ring on a seven-point Likert scale ranging from zero ('not at all') to six ('very often')

special emphasis on hypoglycaemia-related concerns.

Patients and methods

We enrolled adult ($\geq$ 18 years) outpatients with type 1 or insulin-treated type 2 diabetes. Patients who had had type 1 diabetes >2 years were recruited from a cohort included in a study of hypoglycaemia in 1999.[15] Type 1 diabetes was defined by insulin therapy from diagnosis and a random C-peptide concentration <300 pmol/l (<600 pmol/l if venous blood glucose concentration >12 mmol/l). Patients with insulin-treated type 2 diabetes were recruited from a cohort included in a study of hypoglycaemia in 2000.[16] Type 2 diabetes was defined by the 1999 WHO criteria and patients had had at least one year with diet and oral hypoglycaemic agents before commencing insulin therapy. For both patient groups, those with end-stage renal disease (on dialysis), concomitant malignant disease, pregnancy or an inability to complete the questionnaire for any reason were excluded. The study was approved by the regional medical ethics committee and written informed consent was obtained from all participants.

Patients were contacted by mail. Questionnaires, biochemical assessments and extraction of data on history of diabetes and late complications from medical records[15] were completed at each patient's first visit to the outpatient clinic, after obtaining informed consent.

The questionnaire included similar key questions to previous surveys.[7,17] It addressed diabetes-related issues such as experience of hypoglycaemia, hypoglycaemia awareness, demography and lifestyle. Patients' worries about mild and severe hypoglycaemia, blindness and kidney failure were rated on a seven-point Likert scale (Table 1). Retinopathy was classified as not present or present (background retinopathy and laser treated summed). Nephropathy included both microalbuminuria and macroalbuminuria (urinary albumin excretion rate 30–300 and >300 mg per 24 hours, respectively). Peripheral neuropathy included asymptomatic (raised vibration perception threshold) or symptomatic (any relevant symptom) neuropathy. Macrovascular complications comprised any previous cardiovascular event (stroke, myocardial infarction, lower limb amputation due to arterial insufficiency).

Mild hypoglycaemic episodes were reported for the previous week and were defined as subjective symptoms of hypoglycaemia, manageable by the patient. Severe hypoglycaemic episodes were defined as those in which assistance from other people was needed to recover, irrespective of whether or not consciousness was lost, as significant neuroglycopenia would evidently have occurred. These episodes were reported for the preceding year.

Hypoglycaemia awareness was classified according to four possible answers to the question: 'Do you recognise symptoms when you have a hypo?' The categories for answers were: always, usually, occasionally, and never. Patients answering 'always' were classified as having normal awareness, those answering 'usually' as having impaired awareness and those answering 'occasionally' or 'never' as having unawareness.[18] Due to a low number of type 2 diabetic subjects with unawareness, the groups with impaired awareness and unawareness were combined.

Glycosylated haemoglobin (HbA_{1c}) was measured using the DCA-2000 (Bayer, Leverkusen, Germany) with a normal range of 4.1 to 6.4%, standardised against the Diabetes Control and Complications Trial.[19] C-peptide was measured by radioimmunoassay (Autodelfia, Wallac Oy, Turku, Finland) with a detection limit of 10 pmol/l.

Standard descriptive statistics were used to characterise the study population and comparisons were made by parametric (t-test and linear regression analysis) and non-parametric methods (χ^2 test) when appropriate. As this is an explorative analysis the level of statistical significance was chosen as $p<0.05$ (two-sided).

Results

In total, 501 patients were contacted by mail. The complete response rates were 63% for people with type 1 diabetes (223 of 354 patients) and 71% for people with insulin-treated type 2 diabetes (104 of 147 patients). Patient characteristics appear in Table 2.

Patients with type 1 diabetes and those with insulin-treated type 2 diabetes worried most about microvascular complications, with no differences in scoring of concerns about blindness and kidney

failure within or between the groups (p=0.25–0.66) (Table 3). Concerns about microvascular complications ranked higher than worries about severe hypoglycaemia (p<0.01), which in turn ranked higher than worries about mild hypoglycaemia for patients with both types of diabetes (p<0.01). Patients with type 1 diabetes worried more about severe hypoglycaemia than those with type 2 diabetes (p<0.005). Women with type 1 diabetes were significantly more worried about severe hypoglycaemia than men (p<0.05), while no significant differences existed for mild hypoglycaemia, blindness or kidney failure. No gender-related differences were seen in patients with type 2 diabetes. The percentages of patients most worried about severe hypoglycaemia, blindness and kidney failure – indicating six ('very often') on the Likert scale (Table 1) – were generally greater in people with type 1 diabetes (22%, 32%, and 30%, respectively) than in those with type 2 diabetes (13%, 27%, and 21%, respectively), but the difference was only significant for severe hypoglycaemia (p<0.05). Only 6% of the patients were 'very worried' about mild hypoglycaemia, with no difference between patients with either type of diabetes.

Severe hypoglycaemic episodes in the preceding year were associated with significantly more concerns about severe hypoglycaemia in both groups (p<0.05) (Table 4). Anxiety scores in patients with previous episodes of severe hypoglycaemia did not differ between diabetes types (p=0.48), while patients with type 1 diabetes without severe hypoglycaemia in the preceding year were more worried about severe hypoglycaemia than those with type 2 diabetes (p<0.005).

Patients with type 1 or 2 diabetes with impaired hypoglycaemia awareness tended to worry about severe

	Type 1 diabetes	Type 2 diabetes
Patients (no)	223	104
Females/males (%)	41/59	36/64
Age (years)	47 (13)	61 (11)
BMI (kg/m^2)	25.0 (3.4)	27.6 (4.4)
Duration of diabetes (years)	22 (12)	17 (8)
Duration of insulin therapy (years)	22 (12)	8 (5)
Insulin dose (IU/kg)	0.66 (0.19)	0.63 (0.26)
Number of injections per day (%) 1 2 3 $\geq$4	1 12 3 84	4 42 5 49
C-peptide (pmol/l)	16 (0–400)	307 (9–2918)
HbA$_{1c}$ (%)	8.5 (1.2)	8.6 (1.4)
Severe hypoglycaemia in the last year (%) $\geq$1 episode $\geq$2 episodes	34 20	20 10
Hypoglycaemia awareness (%) Normal Impaired Unaware	40 46 14	68 26 6
Diabetic complications (%) Retinopathy Nephropathy Peripheral neuropathy Macrovascular complications	55 25 36 8	50 37 54 20
BMI, body mass index; HbA$_{1c}$, glycosylated haemoglobin		

Table 2. Patient characteristics. Figures are percentages, mean (SD) or median (range) where indicated

hypoglycaemia (Table 5); those with type 1 diabetes were more worried about severe hypoglycaemia than patients with type 2 diabetes, independent of degree of hypoglycaemia awareness (both p<0.05).

There were no associations between worry about hypoglycaemia and age, duration of diabetes, HbA$_{1c}$ or C-peptide levels (data not shown). Presence of microvascular complications in eyes or kidneys was not associated with concerns about mild and severe hypoglycaemia in

patients with type 1 diabetes (Table 6). Patients with type 2 diabetes without complications tended to be more worried about both mild and severe hypoglycaemia than those with complications (p<0.05 and p=0.07, respectively). Patients with type 2 diabetes without late complications were more worried about mild hypoglycaemia risk than those with type 1 diabetes (p<0.01). In contrast, patients with type 1 diabetes and complications were more worried about severe

	Type 1 diabetes (n=223)	Type 2 diabetes (n=104)	p-value
Mild hypoglycaemia	1.7 (0.12)	2.0 (0.18)	NS
Severe hypoglycaemia	3.3 (0.13)**	2.5 (0.20)*	<0.005
Kidney failure	4.0 (0.12)**†	3.5 (0.18)**†	NS
Blindness	4.2 (0.11)**††	3.9 (0.17)**†††	NS

*p<0.01 versus mild hypoglycaemia
**p<0.00001 versus mild hypoglycaemia
†p<0.01 versus severe hypoglycaemia
††p<0.001 versus severe hypoglycaemia
†††p <0.0001 versus severe hypoglycaemia

Table 3. Concerns about mild and severe hypoglycaemia, blindness, and kidney failure in patients with type 1 diabetes and patients with type 2 diabetes, as rated on a seven-point Likert scale (Table 2). Mean (SEM)

hypoglycaemia risk than those with type 2 diabetes (p<0.001). Presence of microvascular complications was not associated with concerns about these complications in patients with either type 1 or type 2 diabetes on insulin therapy.

Discussion

Our study findings indicate that people with insulin-treated diabetes worry considerably about the risk of being blind or losing kidney function and, to a lesser extent, about the risk of severe hypoglycaemia; the risk of mild hypoglycaemia does not cause much anxiety. Only the risk of severe hypoglycaemia is associated with significantly less anxiety in patients with insulin-treated type 2 diabetes than in patients with type 1 diabetes. In a study of 411 patients with type 1 diabetes – applying questions similar to ours – the risk of severe hypoglycaemic episodes generated as much anxiety as the threat of advanced late complications in eyes and kidneys.[7]

Anxiety scores for late complications were significantly higher in our study than scores for severe hypoglycaemia in patients with type 1 diabetes (approximately 25%), and even higher in patients with insulin-treated type 2 diabetes (35–56%). Due to methodological differences in measuring worries, data from the study by Pramming *et al*[7] and our own cannot be compared directly. However, it seems as if the patients with type 1 diabetes in our study were more worried about the risk of late complications – rather than less worried about the risk of severe hypoglycaemia – compared with patients in the Pramming *et al* study.[7] In research involving a mixed population of people with diabetes identified from insulin prescriptions, most of whom had type 1 diabetes, concerns about late complications were also more frequently described than anxiety about hypoglycaemic episodes.[10] No studies exist that enable direct comparison with our anxiety scores in patients with insulin-treated type 2 diabetes. Polonsky *et al* reported that patients with type 1 diabetes are significantly more fearful of hypoglycaemia than patients with insulin-treated type 2 diabetes,[9] but since the minor and major episodes of hypoglycaemia were summed in this study,[9] the relative contribution of mild and severe hypoglycaemia to fear of hypoglycaemia is unknown.

Recent exposure to severe hypoglycaemia is associated with increased anxiety scores for severe hypoglycaemia in both types of diabetes: this is in accordance with some studies in type 1 diabetes[7,9,13] and studies in mixtures of patients with type 1 and type 2 diabetes.[6,20] In contrast, in two studies in patients with type 1 diabetes, experience of severe hypoglycaemia in the preceding year did not influence the Hypoglycaemia Fear Survey (HFS) anxiety subscale.[8,11] No previous data exist solely for insulin-treated patients with type 2 diabetes.

Presence of impaired hypoglycaemia awareness, which is associated with a five to 20-fold increased risk of severe hypoglycaemia,[18,21] also tended to be associated with increased anxiety scores for severe hypoglycaemia in our study. This is in accordance with previous studies in type 1 diabetes,[11,22] whereas no data exist for insulin-treated type 2 diabetes.

Paradoxically, we found that patients with type 2 diabetes without late microvascular complications are more worried about the risk of mild hypoglycaemia than those with complications, in addition to patients with type 1 diabetes with complications. This finding cannot be readily explained, but it should be emphasised that these cross-sectional data are simply associations, not proving causality. However, in clinical practice, it is well known that the relationship between anxiety and hypoglycaemia occurrence is quite complex. In some people, fear of hypoglycaemia may be high but the risk is low; in others at high risk of hypoglycaemia, concerns may be only modest.

Our study has limitations. A response rate averaging 65% is generally considered suboptimal, but is in fact typical of this type of survey and exceeds the percentages

found in many other large surveys (which report 30–50% response rates in this research area).[5,6,20] Furthermore, data on the occurrence of severe hypoglycaemic events are based on recall. However, we have previously demonstrated that recall of such events during a year is well preserved in people with type 1 and insulin-treated type 2 diabetes.[7,16,18] Finally, there is neither consensus on definitions of degrees of severity of hypoglycaemia and hypoglycaemia awareness, nor on the clinical assessment of the conditions. However, use of the present question about severe hypoglycaemia (Table 1) results in <3% of episodes fulfilling only one of the three criteria in Whipple's triad – i.e. symptoms of hypoglycaemia, blood glucose <3 mmol/l and adequate response to glucose/ glucagon treatment – in a prospective setting.[21] Moreover, our simple method for classifying hypoglycaemia awareness has previously been demonstrated to meet the important requirement of predicting those insulin-treated patients with type 1 or type 2 diabetes who are at risk of severe hypoglycaemia.[16,18]

Like people with type 1 diabetes, insulin-treated patients with type 2 diabetes are considerably worried about the risk of severe hypoglycaemia. This should, however, not preclude such patients from receiving insulin treatment when relevant. Thus, the risk of severe hypoglycaemia in patients with insulin-treated type 2 diabetes is only one third of that in type 1 diabetes.[23] Moreover, the distribution of episodes of severe hypoglycaemia is highly skewed. Fewer than 5% of patients with type 1 diabetes or insulin-treated type 2 diabetes account for over half of all episodes of severe hypoglycaemia.[17,23] Health care

Severe hypoglycaemia in the preceding year	Type 1 diabetes (n=223)	Type 2 diabetes (n=104)	p-value
No	3.2 (0.17)	2.3 (0.22)	<0.005
Yes	3.8 (0.22)	3.5 (0.4	NS
p-value	<0.05	<0.05	-

Table 4. Concerns about severe hypoglycaemia versus previous severe hypoglycaemic episodes, as rated on a seven-point Likert scale (Table 2). Mean (SEM)

professionals should, however, also be aware of the hypoglycaemic issue in patients with insulin-treated type 2 diabetes. They should aim to identify subjects at risk of hypoglycaemia to help them avoid these episodes by intervening against correctable risk factors[15,17,21] and, accordingly, instruct them to comply with guidelines for treating hypoglycaemia.[24,25] Equally important, patients who are very worried about severe hypoglycaemia who are at no particular risk of such events should also be identified: such individuals may be able to reduce their risk of late diabetic complications by improving glycaemic control, without increasing their risk of severe hypoglycaemia substantially. For this purpose, simple screening questions as used in our study are feasible in a busy clinical situation. Those who produce high anxiety scores may subsequently be assessed in greater detail by questionnaires such as the HFS. Knowledge of patients' worries about and strategies to avoid hypoglycaemia and late

complications should be an integrated part of diabetes care.

Conflict of interest statement:
None

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	Type 1 diabetes (n=221)	Type 2 diabetes (n=99)	p-value
Normal awareness	3.1 (0.22) (n=87)	2.3 (0.25) (n=67)	<0.05
Impaired awareness or unawareness	3.6 (0.17) (n=134)	3.1 (0.37) (n=32)	<0.05
p-value	0.093	0.062	-

Table 5. Concerns about severe hypoglycaemia versus degree of hypoglycaemia awareness, as rated on a seven-point Likert scale (Table 2). Mean ± SEM

	Type 1 diabetes n=210	Type 2 diabetes n=92	p-value
Mild hypoglycaemia - complications + complications p-value	1.6 (0.2) 1.8 (0.2) NS	2.5 (0.3) 1.6 (0.2) <0.05	<0.01 NS –
Severe hypoglycaemia - complications + complications p-value	3.3 (0.2) 3.4 (0.2) NS	3.1 (0.3) 2.3 (0.3) <0.07	NS <0.001 –
Blindness - complications + complications p-value	4.1 (0.2) 4.5 (0.2) NS	3.7 (0.3) 4.1 (0.2) NS	NS NS –
Kidney failure - complications + complications p-value	3.8 (0.2) 4.1 (0.2) NS	3.6 (0.3) 3.4 (0.3) NS	NS NS –

Table 6. Concerns about hypoglycaemia, blindness and kidney failure versus absence or presence of microvascular complications, as rated on a seven-point Likert scale (Table 2). Mean ± SEM

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