Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration

UK Hypoglycaemia Study Group

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Abstract

Aims/hypothesis We explored the epidemiology of hypoglycaemia in individuals with insulin-treated diabetes by testing the hypothesis that diabetes type and duration of insulin treatment influence the risk of hypoglycaemia.

Materials and methods This was an observational study over 9–12 months in six UK secondary care diabetes centres. Altogether 383 patients were involved. Patients were divided into the following three treatment groups for type 2 diabetes: (1) sulfonylureas, (2) insulin for <2 years and (3) insulin for >5 years, and into two treatment groups for type 1 diabetes, namely <5 years disease duration and >15 years disease duration. Self-reported (mild and severe) and biochemical episodes (interstitial glucose <2.2 mmol/l using continuous glucose monitoring) were recorded.

Results Mild hypoglycaemia in type 2 diabetic patients on insulin for <2 years was less frequent than in type 1 patients with <5 years disease duration (mean rate: 4 vs 36 episodes per subject-year, $p<0.001$). In type 2 diabetic patients treated with sulfonylureas or insulin for <2 years, no differences were observed in the proportion experiencing severe hypoglycaemia (7 vs 7%, difference 0 [95% CI: -7

to 9%]), mild symptomatic (39 vs 51%, difference 12 [-3 to 25%]) or interstitial glucose <2.2 mmol/l (22 vs 20%, difference 2 [-13 to 10%]). Severe hypoglycaemia rates were comparable in patients with type 2 diabetes on sulfonylureas or insulin < 2 years (0.1 and 0.2 episodes per subject-year) and far less frequent than in type 1 diabetes (<5 years group, 1.1; >15 years group, 3.2 episodes per subject-year).

Conclusions/interpretation During early insulin use in type 2 diabetes, the frequency of hypoglycaemia is generally equivalent to that observed in patients treated with sulfonylureas and considerably lower than during the first 5 years of treatment in type 1 diabetes.

Keywords Continuous glucose monitoring · Epidemiology · Hypoglycaemia · Type 1 diabetes · Type 2 diabetes

Abbreviations

CGMS continuous glucose monitoring system
DCCT Diabetes Control and Complications Trial
LIG low interstitial glucose
LIG_{2.2} low interstitial glucose periods of <2.2 mmol/l
LIG_{3.0} low interstitial glucose periods of <3 mmol/l

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UK Hypoglycaemia Study Group: For a list of the members of this group and their affiliations, see the [Appendix](#).

UK Hypoglycaemia Study Group: For a list of each author's contribution to this study, see the Electronic supplementary material (ESM) which is available to authorised users at [doi:10.1007/s00125-007-0599-y](https://doi.org/10.1007/s00125-007-0599-y).

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Introduction

Hypoglycaemia is a common, unpredictable and potentially dangerous side effect of insulin therapy for diabetes. The greatest clinical risk results from a failure of cerebral glucose supply causing progressive cognitive impairment, confusion and coma. However, there may be important differences in hypoglycaemic risk, depending upon the type and duration of diabetes.

In type 1 diabetes, self-reported severe episodes have a reported incidence of ~1.3 per patient-year and affect one-third of individuals [1]. The use of insulin in patients with type 2 diabetes is steadily rising, but relatively little is known about the frequency of hypoglycaemia in type 2 diabetic patients, treated either with sulfonylureas or insulin. It has been presumed that hypoglycaemia is rare in people with insulin-treated type 2 diabetes [2, 3], but retrospective and small short-term prospective studies suggest that severe hypoglycaemia may be relatively common [4–7]. In type 2 diabetes, where insulin secretion deficiency is incomplete and progressive, the duration of insulin therapy may further influence hypoglycaemia risk.

We hypothesised that patients with type 2 diabetes, recently started on insulin, would have a lower hypoglycaemia risk than people with type 1 diabetes, and comparable with those taking sulfonylureas. We therefore measured hypoglycaemia experience in type 1 or type 2 diabetic patients, who were categorised on the basis of recent or prolonged duration of insulin therapy, plus use of sulfonylureas without insulin in type 2 patients.

Subject and methods

Study design and methodology

Hypoglycaemia frequency was recorded using two complementary methods: (1) self-reported; (2) biochemical hypoglycaemia by continuous glucose monitoring (which measures interstitial glucose concentrations).

Participants were recruited from six secondary care diabetes centres and divided into the following three groups for subjects with type 2 diabetes: (1) treated with sulfonylureas; (2) treated with insulin for <2 years; (3) treated with insulin for >5 years. Subjects with type 1 diabetes were grouped as follows: (1) short disease duration (<5 years); (2) long disease duration (>15 years).

The groups were chosen on the basis of expected differences in the rates of hypoglycaemia as follows: type 2 with sulfonylurea or insulin treatment for <2 years, low; type 2 diabetes on insulin for >5 years, moderate; type 1 diabetes for <5 years, moderate; type 1 diabetes for >15 years, high. We aimed to recruit 120 participants in the three type 2 diabetic groups and 60 in the two type 1 groups (on the basis that events rates were likely to be higher). A pragmatic decision to select patients with type 1 diabetes for <5 years, rather than a shorter period, was made before the start of the study, based on the need to recruit sufficient numbers. Type 1 or type 2 diabetes had been diagnosed clinically at each centre, but this was corroborated by measurements of fasting and stimulated

C-peptide, measured by ELISA (reference range, 0.11–0.61 nmol/l; Dakocytomation, Ely, Cambs, UK).

Participants were aged between 17 and 75 years. Exclusion criteria were: (1) HbA_{1c} >9%, measured centrally by an HPLC, Diabetes Control and Complications Trial (DCCT)-aligned method [8] (Tosch Automated Glycohemoglobin Analyzer; Tosch Bioscience, Minato, Japan); (2) severe diabetic complications, e.g. binocular visual acuity <6/12, major amputation, severe peripheral sensory neuropathy; (3) treatment with metformin or acarbose alone; (4) seizures unrelated to hypoglycaemia; (5) concurrent malignant disease; (6) severe systemic diseases unrelated to diabetes; (7) pregnancy or inability to give informed consent. Insulin users had to be taking two or more injections daily.

All participants gave signed informed consent before participating in the study, which was approved by central and local research ethics committees.

Experimental procedures

Diabetic microvascular complications were documented. We trained subjects to perform home glucose monitoring (Medisense G glucose meters; Abbott Laboratories, Abbott Park, IL, USA). They recorded and classified any episode of perceived hypoglycaemia as severe (requiring help for recovery) or mild (self-treated) over 9 to 12 months of follow-up, noting time of episode and, if possible, the blood glucose measured before or immediately after treatment. Subjects were given hypoglycaemia reporting forms, on which they were asked to document the time, duration, symptoms, glucose level (if checked) and treatment required during any episode of hypoglycaemia. They were asked to report all episodes with glucose levels <3.0 mmol/l or when they experienced symptoms usually associated with hypoglycaemia. They were encouraged to record their glucose level during these episodes. It is known that recall for such events is poor after a few weeks, so they were asked to send in filled-in forms, or a blank sheet in the event of no hypoglycaemic incidents to report, every month. If no forms were received, the local centre made telephone enquiries to record the information.

The patients underwent continuous glucose monitoring with a continuous glucose monitoring system (CGMS) (Medtronic CGMS; Medtronic, Minneapolis, MN, USA) for at least 96 h (up to a maximum of 144 h) at the start (phase 1, within 1 month of recruitment) and end (phase 2, between 9 and 12 months later) of the study. This was undertaken to detect any changes in the frequency of low interstitial glucose (LIG) over the duration of the study and to ascertain reproducibility in a technique which has been criticised for lack of accuracy. Devices were calibrated five times per day. To avoid artefactual alterations in the glucose traces being

falsely identified as hypoglycaemia, each CGMS trace was analysed independently by two observers, using version 1.6a of the manufacturer's software and any discrepancies reconciled by a third. The total amount of valid CGMS data was determined for each recording and periods of LIG were classified into <3 mmol/l (LIG_{3,0}) and <2.2 mmol/l (LIG_{2,2}). A valid episode of LIG lasted ≥ 20 min and was considered complete once the glucose remained above the respective threshold for a further 20 min. We selected this duration and level of LIG on the basis of experimental observations that cognitive function deteriorates at around 3 mmol/l after such a duration of hypoglycaemia [9, 10] and because 2.2 mmol/l, at the limit of detection of a CGMS device, is most likely to represent true hypoglycaemia.

Statistical analysis

Power calculations The two groups of main interest were patients with type 2 diabetes taking sulfonylureas and those on insulin for <2 years, the former being the reference group for sample size calculations. Using previous reports of the frequency of symptomatic hypoglycaemia in insulin-treated type 2 diabetes [2], we assumed that 60% of type 2 diabetic patients treated with sulfonylureas would experience at least one episode during CGMS monitoring. To show that the difference in the proportion of hypoglycaemic incidents experienced between the two groups of interest was within 15%, and assuming four ordered categories for the event data (0, 1, 2, and more than two events), the study required 120 patients for the two main groups of interest to achieve 80% power at a one-sided significance level of 5% [11].

Analysis Differences between the comparison groups with regard to the amount of valid time data collected were analysed using one-way ANOVA. Diagnostics on the assumptions underlying this test were undertaken. Where the assumptions were violated, the non-parametric Kruskal–Wallis test was used.

Data are presented by time and severity of episode. The distribution of LIG_{3,0} and LIG_{2,2} was similar so only the latter are presented. The proportion experiencing at least one episode was calculated, together with the unadjusted weekly hypoglycaemic episode rate. As the distributions of these rates were skewed, medians and ranges are presented in addition to means. Confidence limits for the proportions were produced using Wilson's method [12].

Many patients experienced no LIG episodes during monitoring and relatively few experienced multiple episodes, particularly in the two main groups of interest. Furthermore, no significant differences in follow-up time were identified between the different groups, so we compared the proportions of individuals having any episodes during the relevant monitoring period. Differences

in proportions between the groups were compared using the chi-squared test with continuity correction or Fisher's exact test when necessary. No adjustments were made for multiple comparisons [13].

Role of the funding source

The Department for Transport, who sponsored the study, had no role in study design, data collection, data analysis, data interpretation or writing of the paper. The corresponding author had full access to all the data in the study and has final responsibility for the decision to submit for publication.

Results

Study procedures and patient characteristics

Figure 1 shows patient flow through the study. Recruitment started in May 2002, with phase 1 completed in August 2003 and phase 2 in June 2004.

Recruitment achieved 80% of target, with $>74\%$ in all groups except the type 2 diabetic group treated with insulin for >5 years (64%). In phase 2, 86% of subjects participated and 84% successfully undertook a second period of CGMS.

Fig. 1 Flow of subjects through the study. WBGM, weekly blood glucose monitoring

Table 1 Demographic data

	Type 1 <5 years <i>n</i> =50	Type 1 >15 years <i>n</i> =57	Type 2 sulfonylurea <i>n</i> =108	Type 2 <2 years <i>n</i> =89	Type 2 >5 years <i>n</i> =77
Sex (% male) ^a	70.0	57.9	78.7	61.8	67.1
Age (years) ^a	41.3 (12.7)	53.2 (10.4)	60.8 (9.3)	59.7 (8.3)	62.4 (7.3)
BMI (kg/m ²) ^a	26.1 (4.3)	27.9 (4.9)	29.6 (4.6)	31.6 (4.4)	31.7 (6.5)
Duration of diabetes (years) ^b	3.0 (1.3–3.8)	29.8 (21.5–40.3)	6.0 (3.6–9.7)	7.0 (4.1–9.8)	14.2 (10.8–19.0)
Baseline HbA _{1c} (%) ^a	7.3 (1.02)	7.8 (0.73)	7.5 (0.84)	7.4 (0.89)	7.7 (0.90)
1 year HbA _{1c} (%) ^a	7.3 (1.16)	7.6 (0.85)	7.4 (0.90)	7.4 (1.13)	7.5 (0.97)
Fasting C pep (nmol/l) ^b	0.37 (0.17–0.58)	0.09 (0.05–0.27)	1.07 (0.93–1.56)	0.78 (0.52–1.07)	0.62 (0.36–1.00)
Post-glucagon C peptide (nmol/l) ^b	0.45 (0.25–0.69)	0.09 (0.05–0.26)	1.75 (1.28–2.60)	1.16 (0.82–1.87)	1.00 (0.58–1.47)
Hypo awareness score (1–7) ^a	1.85 (1.3)	2.97 (1.9)	1.30 (0.9)	1.45 (1.3)	1.52 (1.0)

Data are presented as either: ^a mean (SD) or as ^b median (interquartile range)

Self-reports of hypoglycaemia were returned for >1 month in 96% of recruited subjects, with 82% returning reports for over 6 months and 72% doing so for 9 to 12 months.

Of the 53 who failed to return for the second phase of CGMS monitoring, three had died, two became pregnant, 16 lost contact and 32 declined for the following reasons: two too busy, 11 ill health, eight other reasons including dislike of CGMS, 11 unspecified.

Table 1 shows demographic data. Individuals with type 2 diabetes were, as expected, older than those with type 1 diabetes and had a higher BMI. All groups had a slight predominance of men. Glycaemic control was reasonably strict, reflected in an HbA_{1c} of ~7.5% in all groups and remaining unchanged during phase 2. Stimulated C-peptide concentrations, reflecting endogenous insulin secretory capacity, were highest among individuals taking sulfonylureas and lowest (at the limit of detection) in patients with type 1 diabetes of long duration, as anticipated. A hypoglycaemia awareness score was obtained by asking subjects to rate their awareness of the symptoms of

hypoglycaemia, where 1 stands for fully aware of the onset of symptoms, and 7 stands for totally unaware [14]. The mean scores showed that awareness was greatest among patients on sulfonylureas and patients with type 2 diabetes who had recently started on insulin. The highest scores reflecting less (low) hypoglycaemia awareness were found in patients with type 1 diabetes of long duration.

Self-reported episodes

The period over which subjects in the different groups recorded episodes of hypoglycaemia ranged from a mean of 8.8 (SD 2.6) months in sulfonylurea-treated subjects to 10.3 (SD 3) months in those with longstanding type 1, with no significant differences observed between groups. Table 2 shows self-reported episodes. Prevalence varied between 39% (sulfonylurea-treated) to 87% (short-duration type 1). No significant difference was observed in the frequency of mild hypoglycaemia between type 2 diabetic patients treated by sulfonylurea and those on insulin-treatment for

Table 2 Results for self-reported hypoglycaemic episodes

	<i>n</i>	Episodes per person-year		<i>p</i> value*	Proportion having at least one hypo (95% CI)	Difference in proportion compared with tablet-treated type 2	
		Median (range)	Mean (95% CI)			Difference (95% CI)	<i>p</i> value*
Mild self-reported hypoglycaemic episodes:							
Type 2 tablets	103	0 (0 to 25)	1.92 (1.2 to 2.6)		0.39 (0.30 to 0.49)		
Type 2 insulin <2 years	85	1 (0 to 44)	4.08 (2.4 to 5.8)	0.06	0.51 (0.40 to 0.61)	0.12 (−0.03 to 0.25)	0.14
Type 2 insulin >5 years	75	2.7 (0 to 144)	10.2 (5.4 to 15.0)	<0.001	0.64 (0.53 to 0.74)	0.25 (0.10 to 0.39)	0.002
Type 1 <5 years	46	22.3 (0 to 203)	35.5 (22.8 to 48.2)	<0.001	0.87 (0.74 to 0.94)	0.48 (0.32 to 0.59)	<0.001
Type 1 >15 years	54	13.7 (0 to 290)	29.0 (16.4 to 41.8)	<0.001	0.85 (0.73 to 0.92)	0.46 (0.31 to 0.58)	<0.001
Severe self-reported hypoglycaemic episodes:							
Type 2 tablets	103	0 (0 to 7.2)	0.1 (0.0 to 0.4)		0.07 (0.03 to 0.13)		
Type 2 insulin <2 years	85	0 (0 to 10.5)	0.1 (0.0 to 0.5)	0.95	0.07 (0.03 to 0.13)	0.00 (−0.07 to 0.09)	0.83
Type 2 Insulin >5 years	75	0 (0 to 10)	0.7 (0.4 to 1.1)	<0.001	0.25 (0.19 to 0.36)	0.19 (0.08 to 0.30)	0.001
Type 1 <5 years	46	0 (0 to 22.9)	1.1 (0.0 to 2.3)	0.008	0.22 (0.12 to 0.36)	0.15 (0.03 to 0.29)	0.02
Type 1 >15 years	54	0 (0 to 32)	3.2 (1.6 to 4.9)	<0.001	0.46 (0.34 to 0.59)	0.40 (0.25 to 0.53)	<0.001

* Compared with the type 2 tablets group, Mann–Whitney *U* test

Table 3 Comparison between type 2 diabetic patients on insulin for <2 years and type 1 diabetic patients diagnosed within 5 years

	<i>n</i>	Rate ^a			Proportion having at least 1 hypo (95% CI)	Difference in proportion compared with tablet-treated type 2	
		Median (range)	Mean (95% CI)	<i>p</i> value ^b		Difference (95% CI)	<i>p</i> value ^c
Self-reported, mild:							
Type 2 insulin <2 years	85	1 (0–44)	4.08 (2.4–5.8)		0.51 (0.40–0.61)		
Type 1 <5 years	46	22.3 (0–203)	35.5 (22.8–48.2)	<0.001	0.87 (0.74–0.94)	0.36 (0.20–0.49)	<0.001
Self-reported, severe:							
Type 2 insulin <2 years	85	0 (0–10.5)	0.2 (0.0–0.5)		0.07 (0.03–0.13)		
Type 1 <5 years	46	0 (0–22.9)	1.1 (0.0–2.3)	0.013	0.22 (0.12–0.36)	0.15 (0.03–0.29)	0.03
LIG _{2,2} , phase 1:							
Type 2 insulin <2 years	89	0 (0–7.9)	0.63 (0.31–0.95)		0.20 (0.13–0.30)		
Type 1 <5 years	50	0 (0–15.9)	1.91 (1.04–2.78)	<0.001	0.46 (0.33–0.60)	0.26 (0.10–0.41)	0.003
LIG _{2,2} , phase 2:							
Type 2 insulin <2 years	76	0 (0–5.0)	0.29 (0.09–0.49)		0.13 (0.07–0.23)		
Type 1 <5 years	42	0 (0–7.1)	1.17 (0.55–1.79)	0.005	0.33 (0.21–0.49)	0.20 (0.05–0.36)	0.018

^a Weekly rate for LIG_{2,2}, yearly rate for self-reported episodes^b Mann–Whitney *U* test^c Chi-squared test

less than 2 years. Mild hypoglycaemia was 22 times higher in the group with short-duration type 1 diabetes than in patients with type 2 diabetes who had started on insulin within the previous 2 years (Table 3).

Of the type 2 diabetic patients treated with sulfonylurea or on short-duration insulin-treatment, 7% reported at least one episode of severe hypoglycaemia during the study, compared with 46% of those with longstanding type 1 diabetes (Fig. 2). The rate was low in patients with short-duration type 1 diabetes, although significantly greater than in the type 2 diabetes groups. Severe hypoglycaemia was most frequent in people with type 1 patients of long duration (>15 years).

CGMS recording: proportion and incidence of patients experiencing low interstitial glucose.

We calculated proportions and rates of LIG at both 3.0 and 2.2 mmol/l. However, since the pattern of differences

between groups was similar at both glucose levels, we only present the data for LIG_{2,2} (Fig. 3).

Phase 1 The duration of valid recording was 7,400–7,700 min in all groups, with no differences between groups in valid total data.

Table 4 shows the proportion of each group experiencing at least one episode of LIG_{2,2} and the weekly rates of LIG_{2,2} for the total periods of monitoring. About 20% of those with type 2 diabetes experienced at least one period of LIG_{2,2}, with no difference between those on sulfonylureas and those on insulin for <2 years. More individuals with type 1 diabetes experienced at least one LIG_{2,2} (Table 3).

Phase 2 The duration of valid recording for total monitoring was about 7,600–7,800 min in all groups, with no significant differences between groups.

Table 4 shows the proportion of those in each group experiencing at least one LIG_{2,2} episode and also weekly rates of LIG_{2,2} during monitoring. Around 15% of type 2 diabetic patients on sulfonylurea or short-duration insulin-treatment experienced at least one period of LIG_{2,2}. Proportionately more individuals with type 1 diabetes experienced at least one LIG_{2,2} compared with sulfonylurea-treated type 2 diabetic patients (Table 3).

Fig. 2 Proportion of each group experiencing at least one severe self-reported hypoglycaemic episode during 9–12 months of follow-up. Vertical bars, 95% CI

Discussion

We examined the frequencies of mild (self-treated), severe (requiring help) and biochemical (CGMS) hypoglycaemia in people with diabetes with regard to treatment modality

Fig. 3 Proportion experiencing at least one LIG_{2.2} during CGMS monitoring period. Black, phase 1; red, phase 2. Vertical bars, 95% CI

(sulfonylurea or insulin) and in the event of the latter duration of insulin therapy, using the event rates of the sulfonylurea treated type 2 diabetes group as the comparator. Our main finding was that for people with type 2 diabetes within the first 2 years of insulin therapy, rates of hypoglycaemia were no higher than in those not on insulin and were much lower than in patients with type 1 diabetes of both short and long duration. This pattern continued over the 9–12 months of follow-up, suggesting that this relatively low risk persists for at least the first 3 years of insulin therapy. However, for type 2 diabetic patients on insulin for >5 years, the prevalence of mild and severe hypoglycaemia was similar to that for type 1 diabetic patients with short disease duration. This supports the contention that the risk of hypoglycaemia in insulin-treated

type 2 diabetes rises with increasing duration of insulin therapy [15], but is low in the first few years of treatment.

Given that the numbers recruited fell short of the target laid out in the power statement, it could be argued that the lack of an observed difference between the two main groups of interest was because the study was underpowered. However, the study was powered on the basis that a clinically important difference would be a difference between the sulfonylurea and insulin groups of no less than 15% in the proportions of subjects experiencing a low interstitial glucose. As the confidence interval for the difference in proportions between these two groups excluded this clinically relevant difference, we would argue that even with the smaller numbers recruited, the study demonstrated that the difference in rates of hypoglycaemia between type 2 diabetic patients taking sulfonylureas and those recently started on insulin is not clinically important.

Hypoglycaemia frequency in type 1 diabetes has been estimated in several Northern European studies. Mild hypoglycaemia occurs on average about twice weekly [1, 16] with an annual prevalence of severe hypoglycaemia between 30 and 40% [16–18]. In the present study, duration of type 1 diabetes did not influence either the prevalence or incidence of mild hypoglycaemia, consistent with previous observations [1]. However, the long-duration group experienced the highest frequency of severe episodes (prevalence 46%, mean rate 3.2 episodes per subject-year), confirming the increased risk of severe hypoglycaemia with increasing duration of type 1 diabetes [1, 16, 19]. The mean rate was substantially higher than that reported during the DCCT [19] and comparable with those observed in patients with hypoglycaemia unawareness [14]. This emphasises that rates of

Table 4 Results for total LIG_{2.2}, phase 1 and 2

	<i>n</i>	Episodes of LIG _{2.2} in persons per week			Proportion having at least 1 LIG _{2.2} (95% CI)	Difference in proportion compared with tablet-treated type 2	
		Median (range)	Mean (95% CI)	<i>p</i> value ^a		Difference (95% CI)	<i>p</i> value ^a
Phase 1							
Type 2 tablets	108	0 (0 to 13.2)	0.63 (0.30 to 0.95)		0.22 (0.15 to 0.31)		
Type 2 insulin <2 years	89	0 (0 to 7.9)	0.63 (0.31 to 0.95)	0.83	0.20 (0.13 to 0.30)	−0.02 (−0.13 to 0.10),	0.87
Type 2 insulin >5 years	77	0 (0 to 8.8)	0.76 (0.36 to 1.17)	0.89	0.22 (0.14 to 0.33)	0.00 (−0.12 to 0.12),	0.88
Type 1 <5 years	50	0 (0 to 15.9)	1.91 (1.04 to 2.78)	<0.001	0.46 (0.33 to 0.60)	0.24 (0.08 to 0.39),	0.004
Type 1 >15 years	57	1.44 (0 to 12.1)	2.96 (2.03 to 3.90)	<0.001	0.61 (0.48 to 0.73)	0.39 (0.24 to 0.53),	<0.001
Phase 2							
Type 2 tablets	90	0 (0 to 2.9)	0.25 (0.12 to 0.39)		0.14 (0.09 to 0.23)		
Type 2 insulin <2 years	76	0 (0 to 5.0)	0.29 (0.09 to 0.49)	0.84	0.13 (0.07 to 0.23)	−0.01 (−0.12 to 0.10),	0.99
Type 2 insulin >5 years	62	0 (0 to 8.4)	0.73 (0.27 to 1.18)	0.08	0.26 (0.17 to 0.38)	0.11 (−0.01 to 0.25),	0.12
Type 1 <5 years	42	0 (0 to 7.1)	1.17 (0.55 to 1.79)	0.004	0.33 (0.21 to 0.49)	0.19 (0.04 to 0.36),	0.02
Type 1 >15 years	49	1.21 (0 to 12.2)	2.06 (1.28 to 2.83)	<0.001	0.55 (0.41 to 0.68)	0.41 (0.24 to 0.55),	<0.001

^a Compared with the type 2 tablets group, Mann–Whitney *U* test

hypoglycaemia are often higher in unselected populations than in those in clinical trials [5], and also that even type 1 diabetic patients of long duration who do not report unawareness remain vulnerable to severe episodes due to failure of hypoglycaemic counter-regulation [20].

The present study shows that about 7% of people with type 2 diabetes who were followed for an average of 9 months had experienced at least one episode of severe hypoglycaemia in the first 2–3 years of insulin therapy, a proportion similar to those treated with sulfonylureas. The risk of severe hypoglycaemia associated with sulfonylureas is not negligible, with nearly one in ten individuals reporting this potentially serious side effect. One of our aims was to inform authorities who make decisions on restrictions imposed on insulin-treated patients in vulnerable professions. The rates of severe hypoglycaemia in sulfonylurea-treated individuals will need to be noted by such groups.

The low prevalence of severe hypoglycaemia in the UKPDS [2] and other trials [21] may not accurately represent the true frequency in insulin-treated type 2 diabetes. A population-based study found 7% of patients with type 1 and insulin-treated type 2 diabetes had required emergency treatment over 12 months compared with 0.8% of those taking oral agents [5]. It is likely that the people with insulin-treated type 2 diabetes were late in the evolution of their disease and may have been more akin to those in the present study who had been on insulin for >5 years. A retrospective study has reported an annual prevalence of severe hypoglycaemia in insulin-treated type 2 diabetes of 15%, directly related to the duration of insulin therapy [6]. With advancing beta cell failure, people with type 2 diabetes progressively resemble those with type 1 diabetes with regard to the increasing risk of hypoglycaemia, and our data support this.

Continuous glucose monitoring to corroborate self-reported hypoglycaemia has advantages and limitations. It should identify hypoglycaemia irrespective of subjective awareness, but its ability to detect clinically relevant hypoglycaemia has been questioned [22]. Potential problems are: (1) error in recording glucose values at the limit of the detection range; (2) artefact (a flat line might indicate a low glucose value or a technical problem); and (3) differences between blood and interstitial glucose. We developed strict rules for classifying traces as indicating LIG, with traces assessed by two independent observers and a third adjudicator where necessary to reduce errors due to (1) and (2) above.

The relationship between blood and interstitial glucose is poorly understood and there are physiological and pharmacological reasons why the two may differ. The relationship between blood and interstitial glucose concentrations is variable, according to whether they are falling or rising and circulating insulin concentrations may also be important [23]. However, studies that have compared blood and interstitial glucose indicate that an interstitial glucose value

of about 2.2 mmol/l represents true hypoglycaemia [24]. Although we cannot be certain which LIG level represents clinically important hypoglycaemia, this uncertainty applies equally across all groups.

In conclusion, our study shows a clinically relevant difference in hypoglycaemic risk between type 1 diabetic patients and type 2 diabetic patients who have recently started insulin treatment. The data indicate that within 2 years of commencing insulin treatment individuals with type 2 diabetes do not experience hypoglycaemia more frequently than patients taking sulfonylureas, an effect that appears to persist for at least a further year, but is lost by 5 years of insulin therapy. It therefore appears that within 2 years of starting insulin therapy, the hypoglycaemia risk in type 2 diabetes is no higher than in patients with similar glycated haemoglobin who are being treated with sulfonylureas. Although this risk rises with longer duration of insulin treatment, our observations might prompt a re-examination of the employment and driving restrictions currently imposed on type 2 diabetic patients who start insulin therapy.

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