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Is autonomic neuropathy a risk factor for severe hypoglycaemia? The EURODIAB IDDM Complications Study

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Summary The hypothesis that diabetic patients with autonomic neuropathy are at increased risk of severe hypoglycaemia was examined in an epidemiological study of over 3000 IDDM patients in Europe (EURODIAB IDDM Complications Study). Autonomic function was assessed by two standard cardiovascular tests: change in heart rate and systolic blood pressure on standing. Severe hypoglycaemia was defined as an attack serious enough to require the help of another person. Compared to patients (68%) reporting no attacks in the last year, those reporting one or more attacks were older (34.0 ± 10.7 vs 32.1 ± 9.9 years, mean ± SD, $p < 0.0001$), had had diabetes for a longer period (16.6 ± 9.5 vs 13.8 ± 9.1 years, $p < 0.0001$), had better glycaemic control (HbA_{1c} 6.4 ± 1.8 vs 6.9 ± 1.9%, $p < 0.0001$) and were more likely ($p = 0.002$) to have abnormal responses to both autonomic tests (13.0 vs 7.7%). A single abnormal autonomic response was not associated with an increased risk of severe hypoglycaemia. The odds ratio for severe hypoglycaemia in people with abnormal responses to both autonomic tests, compared to those with normal responses, was 1.7 (95% confidence interval 1.3, 2.2) after controlling for age, duration of diabetes, glycaemic control and study centre. In conclusion, a combined autonomic deficit in heart rate and blood pressure responses to standing is associated with only a modest increase in the risk of severe spontaneous hypoglycaemia. Although the increase in risk is not large, severe hypoglycaemia was a frequently reported event in this study. IDDM patients with deficient autonomic responses who strive for tight glycaemic control may therefore be at particular risk of severe hypoglycaemia. [Diabetologia (1996) 39: 1372–1376]

Keywords Autonomic neuropathy, severe hypoglycaemia, glycaemic control, insulin-dependent diabetes mellitus.

Severe hypoglycaemia is one of the most feared complications of insulin-treated diabetes mellitus and lack of awareness of hypoglycaemia is a common antecedent. Lack of awareness of hypoglycaemia occurs when the autonomic response to a given degree of hypoglycaemia is reduced [1]. In people with diabetes, these events have plausibly and traditionally been attributed to autonomic neuropathy [2, 3]. However, this explanation has been questioned [4], mainly on the basis of small metabolic studies showing little association between lack of awareness and autonomic neuropathy [5, 6]. More recent attention has focused on the role of central nervous system (CNS) glucoregulatory mechanisms [7–9].

Few studies have examined the importance of autonomic neuropathy using severe hypoglycaemia as the major end-point. A report from the Diabetes Control and Complications Study (DCCT) on the epidemiology of severe hypoglycaemia [10], stated that "measures of peripheral or autonomic neuropathy were not consistently associated with the occurrence of severe hypoglycaemia," but details of the

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Abbreviations. IDDM, Insulin dependent diabetes; CI, confidence intervals; CNS, central nervous system.

analyses were not shown. We describe here the relation between autonomic neuropathy and severe hypoglycaemia in a large epidemiological study of over 3000 insulin-dependent diabetic (IDDM) patients in Europe (the EURODIAB IDDM Complications Study).

Subjects and methods

The EURODIAB IDDM Complications Study is a clinic-based study in 31 European centres designed to explore risk factors for diabetic complications. Patient selection and methods are described in detail elsewhere [11]. In brief, each centre selected a stratified random sample of clinic-attending patients, with IDDM defined as onset of diabetes before the age of 36 years with continuous insulin treatment initiated less than 1 year from diagnosis.

All patients were asked "over the past year, how many hypoglycaemic attacks have you had, serious enough to require the help of another person?" The response data was available for 3248 (99.9 %) of the total of 3250 patients in the study. Autonomic neuropathy was measured by testing two cardiovascular reflex responses: change in heart rate and change in systolic blood pressure on standing upright after resting horizontally for 5 min [12]. The choice of autonomic tests for this epidemiological study was influenced by the high reproducibility of the lying-to-standing heart rate response [13]. A single observer calculated the postural change in ECG-recorded heart rate as the ratio of the longest beat-to-beat (R-R interval between QRS complexes) interval between the 28th and 32nd beats, to the shortest beat-to-beat interval between the 13th and 17th beats (R-R ratio). Beats were counted from the time at which the patients started to stand up. Blood pressure was measured once in the horizontal position, and once again, 60 s after standing upright. Both measurements were made using a random zero sphygmomanometer. Responses to both autonomic tests were evaluable in 3007 (92.5 %) of the 3250 patients. (In most other cases, data was "missing" because the quality of the ECG recording was inadequate for measurement of the R-R ratio.) Mean baseline (sitting) blood pressure [14] was 121/75 mm Hg.

HbA_{1c} was measured by an enzyme immunoassay [15] in a central laboratory (normal range 2.9 to 4.8 %).

Statistical analysis

Tests of significance for differences in proportions were based on the Cochran-Mantel-Haenszel chi-square statistic, and differences in means by Student's unpaired *t*-test. The relation of various risk factors (age, duration of diabetes, HbA_{1c}, change in heart rate and change in blood pressure) to severe hypoglycaemia was examined with the risk factors expressed as continuous variables and, separately, as categorical variables in univariate analyses and by multiple logistic regression. The response to each autonomic test was categorised as normal or abnormal, using Ewing's definitions of borderline/abnormal responses [12]. Thus, an R-R ratio of less than 1.04 was defined as abnormal, and a fall in blood pressure on standing of more than 10 mm Hg was defined as abnormal. Autonomic deficit was then described categorically as none, single (abnormal response to either test) or combined (abnormal response to both tests).

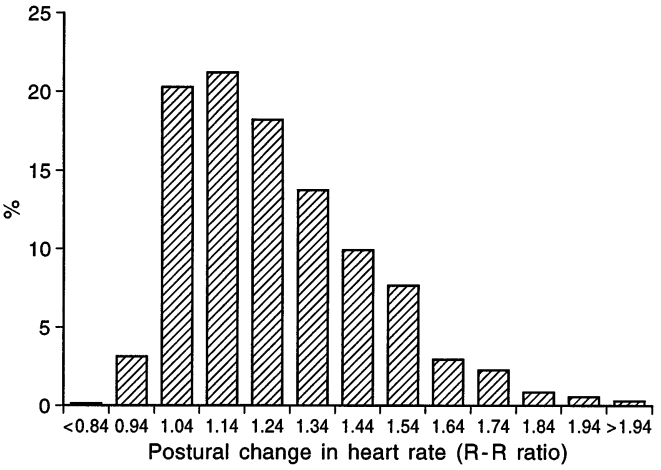

Fig. 1. Distribution of change in heart rate (R-R ratio) on standing

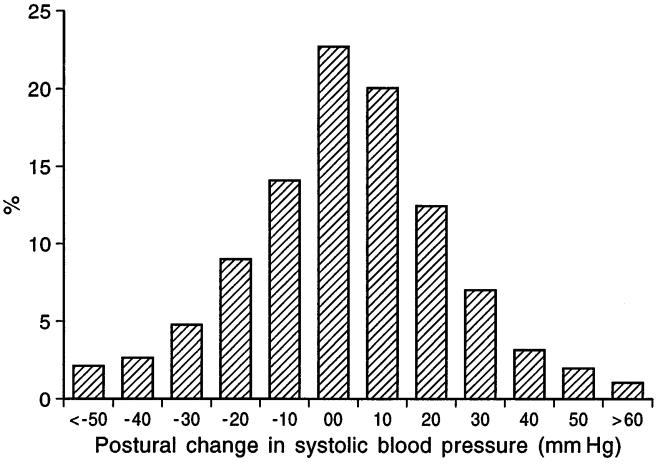

Fig. 2. Distribution of change in systolic blood pressure on standing

Results

As previously reported [11], almost one third (32 %) of patients reported one or more severe hypoglycaemic attacks over the past year.

The distribution of responses to the cardiovascular autonomic tests is shown in Figures 1 and 2. Nearly half (47 %) of all patients had an abnormal response to either one or both tests. Table 1 shows highly significant differences in age, duration of diabetes and glycaemic control by hypoglycaemia status. Mean R-R ratio was lower in patients reporting severe hypoglycaemia than those reporting none, and mean fall in blood pressure on standing was greater in those reporting hypoglycaemia, but neither of these associations alone was statistically significant. However, the frequency of combined autonomic deficit was nearly twice as high in those reporting severe hypoglycaemia.

Table 2 shows that mean HbA_{1c} and duration of diabetes increased considerably with extent of

Table 1. Comparison of autonomic responses and other risk factors for hypoglycaemia between patients reporting severe hypoglycaemia and patients reporting none

Characteristics *n*	No severe hypoglycaemia 2202	Severe hypoglycaemia 1046	*p*-value
Men Women	1124 (51%) 1078 (49%)	543 (52%) 503 (48%)	0.64
Mean age (years)	32.1 ± 9.9	34.0 ± 10.7	< 0.0001
Mean diabetes duration (years)	13.8 ± 9.1	16.6 ± 9.5	< 0.0001
Mean insulin dose (U/day)	45.7 ± 25.8	45.6 ± 15.6	0.89
Mean HbA_{1c} (%)	6.9 ± 1.9	6.4 ± 1.8	< 0.0001
Median min/max ratio	1.18	1.16	0.23
Mean fall in systolic BP on standing (mm Hg)	3.5 ± 21.0	4.9 ± 21.8	0.09
Frequency of autonomic dysfunction (%)			
– none	1105 (54.2%)	500 (51.7%)	
– single	777 (38.1%)	342 (35.3%)	
– combined	157 (7.7%)	126 (13.0%)	0.002

Values are mean ± SD

autonomic deficit. Any association between autonomic deficit and severe hypoglycaemia would therefore be influenced by the opposing effects of longer duration of diabetes, (which increases the risk of hypoglycaemia), and poorer glycaemic control (which reduces the risk of hypoglycaemia). These effects are examined simultaneously in Table 3 and expressed as adjusted odds ratios. The moderate association between combined autonomic deficit and severe hypoglycaemia remained significant after adjusting for the known confounding effect of duration of diabetes, age and level of glycaemic control. Neither univariate nor multivariate analyses showed a significant association between a single autonomic deficit and severe hypoglycaemia.

Discussion

This study shows that a combined deficit in both heart rate and blood pressure responses to standing is associated with a modest increase in risk of severe hypoglycaemia, independently of the major risk factors, duration of diabetes and glycaemic control. A single deficient response to either test was not associated with increased risk of severe hypoglycaemia.

Precise interpretation of abnormal cardiovascular autonomic responses is difficult. Postural hypotension is thought to be a sign of mainly sympathetic dysfunction, while postural changes in heart rate are mediated mainly by parasympathetic nerve function [12]. Patients in this study with combined deficit had considerably higher HbA_{1c} than those with a single deficit, and it is likely that they had more advanced autonomic dysfunction. An abnormal response to either test can arise from a defect at any part of the reflex arc, i.e. from the afferent receptor and afferent nerve through the reflex centre to the effector nerve and end organ. Thus, an abnormal reflex response does not necessarily imply functional, i.e. non-structural nerve damage.

This study has several limitations. We did not use a "full battery" of autonomic tests, and we relied on self-reports of spontaneous hypoglycaemia. Some patients were probably misclassified as having severe hypoglycaemia when in fact they had none (and vice versa) and some patients were probably misclassified as having autonomic deficit when they had none (and vice versa). However, patients answering the question about hypoglycaemia were not aware of the results of the autonomic tests and the observers measuring the test responses were not aware of the hypothesis being tested (and often unaware of the patient's hypoglycaemia history). Misclassification in this study is therefore likely to be non-differential and as such, would tend to underestimate the strength of the relation between autonomic deficit and severe hypoglycaemia [16].

In accordance with other large studies, such as the DCCT [10], the frequency of severe hypoglycaemia

Table 2. Age, sex, duration of diabetes, insulin dose, HbA_{1c} and frequency of severe hypoglycaemia by autonomic function status

Characteristics *n*	No autonomic dysfunction 1605	Either reflex test abnormal 1119	Both reflex tests abnormal 283	*p*-value[a]
Men Women	828 (52%) 777 (48%)	572 (51%) 547 (49%)	140 (50%) 143 (50%)	0.54
Mean age (years)	31.7 ± 9.4	33.2 ± 10.6	36.8 ± 11.2	< 0.0001
Mean duration (years)	13.6 ± 8.8	15.5 ± 9.4	18.3 ± 9.6	< 0.0001
Mean insulin (U/day)	45.2 ± 21	46.8 ± 25.2	44.7 ± 28.1	0.15
Mean HbA_{1c} (SD) (%)	6.5 ± 1.8	6.9 ± 1.9	7.2 ± 2.0	< 0.0001
Frequency of severe hypoglycaemia (%)	500 (31%)	342 (31%)	126 (45%)	0.002

[a] *p*-value tests for heterogeneity between groups

Table 3. Crude and adjusted odds ratios for severe hypoglycaemia by sex, autonomic dysfunction, duration of diabetes and HbA_{1c}

Characteristics	Crude odds ratio (95 % CI)	Adjusted odds ratio[a] (95 % CI)	Adjusted odds ratio[b] (95 % CI)
Sex			
– men	1	1	1
– women	1.0 (0.8–1.2)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Autonomic dysfunction			
– none	1	1	1
– single	1.0 (0.8–1.1)	1.0 (0.8–1.1)	1.0 (0.8–1.1)
– combined	1.8 (1.4–2.7)	1.7 (1.3–2.2)	1.7 (1.3–2.2)
Duration of diabetes			
– 1–7 years	1	1	1
– 8–14	1.6 (1.3–2.0)	1.7 (1.3–2.0)	1.7 (1.3–2.0)
– 15–24	1.8 (1.5–2.3)	1.8 (1.5–2.3)	1.8 (1.5–2.2)
– 25 +	2.4 (1.9–3.0)	2.2 (1.7–2.9)	2.2 (1.6–3.0)
HbA_{1c}			
– 4th quartile	1	1	
– 3rd quartile	1.4 (1.1–1.7)	1.3 (1.0–1.6)	1.3 (1.0–1.6)
– 2nd quartile	1.7 (1.3–2.0)	1.6 (1.3–2.0)	1.6 (1.3–2.0)
– 1st quartile	2.1 (1.7–2.6)	2.2 (1.8–2.8)	2.2 (1.8–2.8)

[a] Each odds ratio is adjusted for the effect of all other variables in the table

[b] Each odds ratio is adjusted for the effect of all other variables in the table and for centre

was clearly associated with longer duration of diabetes and better glycaemic control. It is therefore important to consider how much of the association between autonomic deficit and severe hypoglycaemia might be explained by confounding factors. The closeness of the crude and adjusted odds ratios indicates that there was little *net* confounding by known risk factors in this study. Although glycaemic control and duration of diabetes are both relatively strong risk factors for hypoglycaemia, they have opposing effects, with increasing duration increasing the risk, and increasing HbA_{1c} decreasing the risk of hypoglycaemia. In comparison with duration of IDDM, which is usually precisely known, a single HbA_{1c} result is a relatively imprecise measure of glycaemic control around hypoglycaemic attacks. This means that controlling for glycaemic control will have been less complete than controlling for duration, leading to further underestimation of the relation between autonomic deficit and hypoglycaemia [17].

The importance of peripheral autonomic neuropathy has been questioned by small studies [5, 18] of induced hypoglycaemia finding little or no association between autonomic neuropathy and hypoglycaemia unawareness or inadequate glucose counterregulation. Other evidence [19, 20] points to the powerful influence of CNS glucoregulatory mechanisms. For example, antecedent induced-hypoglycaemia results in substantially higher glycaemic thresholds (lower glucose levels) for symptomatic and autonomic responses to subsequent hypoglycaemia in people without diabetes [9]. More recently, Boyle et al. [7, 8] have measured increased rates of glucose uptake in the brain during hypoglycaemia in IDDM patients who have nearly normal plasma glucose concentrations and consequently frequent hypoglycaemia. Although the increased glucose uptake in the brain may be an important physiological response to impending neuroglycopaenia, it also reduces sympathoadrenal activation, so that patients are unaware of low blood glucose levels.

A causal association between autonomic dysfunction and severe hypoglycaemia is nonetheless biologically plausible. It may not be a strong association – an odds ratio of 1.7 is not large and only 13 % of those reporting severe hypoglycaemia had combined autonomic deficit – and it need not diminish the importance of central mechanisms in the response to hypoglycaemia. Given the vital importance, in evolutionary terms, of preventing and correcting hypoglycaemia, it would be surprising if multiple mechanisms were not involved.

The clinical implication of these findings is that IDDM patients with deficient autonomic responses who strive for tight glycaemic control may be at particular risk of severe hypoglycaemia.

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