Hypoglycemia Unawareness Is Associated With Reduced Adherence to Therapeutic Decisions in Patients With Type 1 Diabetes

Evidence from a clinical audit

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OBJECTIVE — Hypoglycemia unawareness increases severe hypoglycemia risk. Hypoglycemia avoidance restores awareness, but it is difficult to sustain. We compared adherence to treatment changes by awareness status.

RESEARCH DESIGN AND METHODS — Case notes of 90 type 1 diabetic patients were analyzed retrospectively, identifying awareness status and insulin regimens over four visits. The proportion of patients adhering to advice and percent advice taken were calculated.

RESULTS — A total of 31 patients with hypoglycemia awareness and 19 patients with hypoglycemia unawareness were identified, with insulin regimens available in 23 and 13, respectively. Patients with hypoglycemia unawareness were older ($P = 0.001$) and had longer diabetes duration ($P = 0.002$) and lower A1C ($P = 0.007$). More patients with hypoglycemia unawareness reported severe hypoglycemia ($P = 0.002$) and fewer were adherent (53.8 vs. 87.0%, $P = 0.046$), with lower adherence scores (42.5 ± 24.7 vs. 75.3 ± 27.5%, $P = 0.001$).

CONCLUSIONS — Reduced adherence to changes in insulin regimen in hypoglycemia unawareness is compatible with habituation to hypoglycemic stress. Therapies aimed at reversing repetitive harmful behaviors may be useful to restore hypoglycemia awareness and protection from severe hypoglycemia.

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Hypoglycemia unawareness in type 1 diabetes increases risk of severe hypoglycemia more than fivefold (1). Hypoglycemia awareness can be restored by hypoglycemia avoidance (2–4), which can be difficult. We hypothesized that hypoglycemia unawareness may translate into resistance to changing insulin regimens targeting hypoglycemia avoidance.

RESEARCH DESIGN AND METHODS

— We conducted retrospective case-note analysis of 90 consecutive patients with type 1 diabetes, defined by history, attending an intensified insulin therapy clinic over 3 months. This was part of a routine clinic performance audit; therefore, patient consent was not required. Patients were excluded if they had attended fewer than four visits before the audit or had incomplete notes ($n = 19$) or had undertaken major regimen change by starting pump therapy (continuous subcutaneous insulin infusion) or attending the structured type 1 diabetes education program Dose Adjustment for Normal Eating (DAFNE) ($n = 11$) (5) within the audit duration.

Visit date, weight, A1C (high-performance liquid chromatography assay, inter- and intra-assay variation of 1.9 and 1.5, respectively), DAFNE training, hypoglycemia awareness status, severe hypoglycemia episodes (requiring assistance) since last visit, current insulin regimen, and changes made to it recorded by the clinician at each visit were collected for the last four visits. Hypoglycemia awareness was defined by the clinicians' documentation (6). Hypoglycemia-aware patients had symptomatic awareness <3.5 mmol/l as opposed to partially aware patients, who had inconsistent symptoms, and hypoglycemia-unaware patients, who had minimal or no symptoms <3.0 mmol/l. Adherence was defined using two methods. The proportion of agreed changes to insulin regimen adhered to across visits one to four was calculated for each set of consecutive visits (one to two, two to three, and three to four) and meaned to one value per patient. Patients scoring ≥50% were defined as adherent. Adherence scores (percent advice taken) were also measured. A total of 23 aware patients and 13 unaware patients had sufficient data for these assessments. Age, sex, height, psychiatric history, and exposure to cognitive behavioral therapy were collected from visit 4.

Data were analyzed using χ^2 or Mann-Whitney *U* test for categorical or non–normally distributed data; continuous data were tested for normality (Kolmogorov-Smirnov) and analyzed with Student's independent two-tailed *t* test.

RESULTS

— Of the 60 patients who met the inclusion criteria, 10 were excluded for partial awareness, leaving 31 with hypoglycemia awareness and 19 with hypoglycemia unawareness (Table 1).

The mean study period for patients with hypoglycemia unawareness was shorter than for patients with hypoglycemia awareness, reflecting shorter intervals between scheduled visits. Patients with hypoglycemia unawareness were older, with longer diabetes duration. There were no significant differences between groups in sex, weight or BMI, proportion previously attending DAFNE before audit, and proportion with psychiatric morbidity or history of previous coincidental cognitive behavioral therapy.

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Table 1—*Subject characteristics*

	Hypoglycemia unaware	Hypoglycemia aware	*P*
n	19	31	—
Duration of observation (days)	419 ± 139	568 ± 255	0.024
Age (years)	47.5 ± 11.4	36.1 ± 10.2	0.001
Sex (% female)	52.6 (10)	71.0 (22)	0.190
Duration type 1 diabetes (years)	32.1 ± 12.9	20.5 ± 11.3	0.002
Weight (kg)	70.4 ± 16.2	73.7 ± 13.3	0.449
BMI	25.0 ± 5.0	26.1 ± 4.0	0.401
% Who did not attend	7.5 ± 11.4	12.3 ± 12.4	0.174
% Completed DAFNE	47.4 (9)	61.3 (19)	0.336
% Psychiatric history	10.5 (2)	29.2 (7)	0.282
% Cognitive behavioral therapy	10.5 (2)	24.0 (6)	0.409
% Retinopathy (any degree on retinal photography)*	55.6 (10)	61.3 (19)	0.694
% Nephropathy (microalbuminuria/ proteinuria)*	10.5 (2)	29.0 (9)	0.125
% Neuropathy (symptoms or sensory loss)*	21.1 (4)	9.7 (3)	0.261
A1C (%)	7.2 ± 0.7	8.3 ± 1.3	0.007
Insulin dose (units · kg^{-1} · day^{-1})	0.59 ± 0.16	0.77 ± 0.26	0.030

*Taken from annual review data during audit period. DAFNE, Dose Adjustment for Normal Eating, a 5-day structured education program in flexible insulin therapy for type 1 diabetic patients.

At visit 1, hypoglycemia-unaware patients had lower A1C, despite lower daily insulin doses. By visit 4, A1C in the hypoglycemia-unaware group had risen to 7.8 ± 0.8% ($P < 0.001$). Their insulin dose remained lower (0.54 ± 0.19 vs. 0.71 ± 0.21 units · kg^{-1} · day^{-1}, $P = 0.01$). Nine of 17 hypoglycemia-unaware patients (47.4%) versus three of 31 (9.6%) patients with hypoglycemia awareness reported one or more severe episode of hypoglycemia during the study (risk ratio 5.2 [95% CI 1.14–23.3], $P = 0.002$; median prevalence 71.4 [interquartile range 488.8] and 0.0 [0.0], $P < 0.001$, per 100 patient-years). No significant change occurred in awareness status over the audit ($P = 0.644$).

A total of 7 of 13 (53.8%) hypoglycemia-unaware patients versus 20 of 23 (87.0%) hypoglycemia-aware patients were defined as adherent ($P = 0.046$). A smaller percentage of advice was followed by patients with hypoglycemia unawareness (44.7 ± 19.3% vs. 70.4 ± 28.3%, $P = 0.009$).

More patients with previous contact with liaison psychiatry were adherent (80.7 ± 20.5% vs. 53.7 ± 28.1%, $P = 0.022$). Adherence was higher in patients who had experienced cognitive behavioral therapy (80.3 ± 16.5% advice taken vs. 54.6 ± 28.8%, $P = 0.042$).

CONCLUSIONS — Type 1 diabetic patients with hypoglycemia unawareness were older, with longer diabetes duration, more severe hypoglycemia, and lower A1C than patients with hypoglycemia awareness, consistent with published literature (7). The novel finding is that patients with hypoglycemia unawareness were significantly less adherent to agreed changes to insulin regimens than their hypoglycemia-aware counterparts, in spite of increased clinical contact. An apparent lack of benefit of this, with a rise in A1C and no change in awareness status, could relate to exclusion of 11 potentially eligible patients undertaking major changes to their diabetes management known to improve A1C and reduce hypoglycemia, group-structured education in flexible insulin therapy, or continuous subcutaneous insulin infusion (8,9).

Treatment targets in hypoglycemia unawareness focus on hypoglycemia avoidance (3,5), and the lower A1C of our hypoglycemia-unaware group at study start may have been in part related to greater exposure to hypoglycemia, a driver for unawareness. The explicit aim of treatment adjustments was impossible to assess from notes, but our data, with a rise in A1C in hypoglycemia-unaware patients, argue against benefit of relaxation of glycemic control alone (rather than hypoglycemia avoidance per se) to improve hypoglycemia awareness (10). Interestingly, patients who had attended coincidental cognitive behavioral therapy had a higher adherence than those who had not, although numbers were too small to analyze this by awareness status.

The audit was limited in that it was retrospective, not blinded, and did not use formal scoring to define awareness (2,11) or document discussion around insulin regimen change. Nevertheless, clinic notes were consistent in explicit documentation of the physician's assessment of awareness status. Where this was absent, the notes were excluded. Lack of clear documentation of insulin regimens across all four visits also reduced the number of records available for audit. However, these factors should not have operated differently between groups, and there were no differences in demographics between included and excluded patients. Importantly, the patients were not selected for research.

These data add a clinical dimension to neuroimaging data implicating cortical responses to hypoglycemia in generating awareness (12). Reduced adherence to changes in insulin regimens in hypoglycemia unawareness is compatible with habituation to hypoglycemic stress, with differences in central responses to it that makes further exposure to the same stimulus less stressful (13). Failure to perceive a situation as unpleasant or dangerous subjectively undermines motivation and ability to change behavior (14). About half of the patients with hypoglycemia unawareness in this audit had previously undertaken a structured education program proven both to reduce severe hypoglycemia rates (8) and restore hypoglycemia awareness in 48% of patients entering it with hypoglycemia unawareness (15). Therefore, they are likely to represent a population for whom educational strategies alone have failed. Behavioral strategies that address habituation may be useful adjuncts to educational approaches in restoring hypoglycemia awareness and protection against severe hypoglycemia.

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