

## **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 (HU) increases severe hypoglycemia (SH) risk. Hypoglycemia avoidance restores awareness, but 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 4 visits. Proportion of patients adhering to advice and percent advice taken were calculated.

**Results:** 31 HA and 19 HU patients were identified with insulin regimens available in 23 and 13 respectively. HU patients were older ( $p=0.001$ ); had longer diabetes duration ( $p=0.002$ ) and lower HbA1c ( $p=0.007$ ). More HU reported SH ( $p=0.002$ ); fewer were adherent (53.8% vs 87.0%,  $p=0.046$ ), with lower adherence scores ( $42.5\pm 24.7$  vs  $75.3\pm 27.5\%$ ,  $p=0.001$ ).

**Conclusions:** Reduced adherence to changes in insulin regimen in HU is compatible with habituation to hypoglycemic stress. Therapies aimed at reversing repetitive harmful behaviors may be useful to restore HA and protection from SH.

**Abbreviations:** CSII continuous subcutaneous insulin infusion; DAFNE Dose Adjustment for Normal Eating, a 5-day structured education program for flexible insulin therapy in Type 1 diabetes patients; HA hypoglycemia aware, HU hypoglycemia unaware; SH severe hypoglycemia

Hypoglycemia unawareness (HU) in Type 1 diabetes (T1DM) increases risk of severe hypoglycemia (SH) over 5-fold [1]. Hypoglycemia awareness (HA) can be restored by hypoglycemia avoidance [e.g.2-4], which can be difficult. We hypothesized that HU 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 T1DM, defined by history, attending an intensified insulin therapy clinic over 3 months. As this was part of a routine clinic performance audit, patient consent was not required. Patients were excluded if they had attended <4 visits prior to the audit or incomplete notes (n=19); had undertaken major regimen change by starting pump therapy (CSII) or attending the structured T1DM education program Dose Adjustment for Normal Eating (DAFNE) (n=11)[5] within the audit duration.

Visit date, weight, HbA1c (HPLC assay, inter and intra-assay variation of 1.9 and 1.5), DAFNE training, hypoglycemia awareness status, SH 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 4 visits. Hypoglycemia awareness was defined by clinicians' documentation. HA had symptomatic awareness <3.5mmol/L as opposed to partially aware, who had inconsistent symptoms, and HU with minimal or no symptoms <3.0mmol/L. Adherence was defined using two methods. The proportion of agreed changes to insulin regimen adhered to across visit 1 to 4 was calculated for each set of consecutive visits (1 to 2; 2 to 3; 3

to 4) and meaned to one value per patient. Patients scoring  $\geq 50\%$  were defined as adherent. Adherence scores (% advice taken) were also measured. Twenty-three aware and 13 unaware had sufficient data for these assessments. Age, gender, height, psychiatric history and exposure to cognitive behavioral therapy (CBT) were collected from visit 4.

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

## **RESULTS**

Of the 60 patients that met the inclusion criteria, 10 were excluded for partial awareness, leaving 31 with HA and 19 with HU(table 1).

The mean study period for HU patients was shorter than for HA, reflecting shorter intervals between scheduled visits. HU patients were older, with longer diabetes duration. There were no significant differences between groups in gender; weight or body mass index; proportion previously attending DAFNE prior to audit; proportion with psychiatric morbidity or history of previous coincidental cognitive behavioural therapy (CBT).

At visit 1, HU patients had lower HbA1c, despite lower daily insulin doses. By visit 4, HbA1c in the HU group had risen to  $7.8 \pm 0.8\%$ ,  $p < 0.001$ ). Their insulin dose remained lower ( $0.54 \pm 0.19$  vs  $0.71 \pm 0.21$  units/kg/day,  $p = 0.01$ ). Nine of 17 HU patients (47.4%) vs 3 of 31 (9.6%) HA reported 1 or more SH during the study [RR 5.2 (95% CI 1.14-23.3);  $p = 0.002$ ]; median prevalence 71.4 (IQR 488.8) and 0.0 (IQR 0.0,  $p < 0.001$ ) per

100 patient years. No significant change occurred in awareness status over the audit ( $p=0.644$ ).

7 of 13 (53.8%) HU patients vs 20 of 23 (87.0%) HA were defined as adherent ( $p=0.046$ ). A smaller percentage of advice was followed by HU patients ( $44.7\pm 19.3\%$  vs  $70.4\pm 28.3\%$ ,  $p=0.009$ ).

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

## CONCLUSIONS

Type 1 diabetic patients with HU were older, with longer diabetes duration, more severe hypoglycaemia and lower HbA1c than HA patients, consistent with published literature[7]. The novel finding is that patients with HU were significantly less adherent to agreed changes to insulin regimens than their HA counterparts, in spite of increased clinical contact. An apparent lack of benefit of this, with a rise in HbA1c 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 HbA1c and reduce hypoglycemia, group structured education in flexible insulin therapy or CSII[8,9].

Treatment targets in HU focus on hypoglycemia avoidance[3,5]) and the lower HbA1c of our HU 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 HbA1c in the HU, argue against benefit of relaxation of glycaemic control alone (rather than hypoglycemia

avoidance *per se*) to improve hypoglycemia awareness[10]. Interestingly, patients who had attended coincidental CBT had higher adherence than those who had not, although numbers were too small to analyse 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 4 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 HU 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 the HU patients 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 HU [15], so 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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## REFERENCES

1. Geddes J, Schoipman JE, Zammitt NN, Frier BM. . Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. *Diabetic Medicine* (25): 501-504, 2008
2. Cranston I, Lomas J, Maran A, Macdonald I, Amiel S. Restoration of hypoglycemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 344(8918):283-287, 1994
3. Dagago-Jack S, Rattarasan C, Cryer P. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 43(12):1426-1434, 1994
4. Fanelli C, Epifano L, Rambotti A, Pampanelli S, Vincenzo A, Modarelli F, Lepore M, Annibale B, Ciofetta M, Bottini P. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 42(11):1983-1989, 1993
5. DAFNE Study Group. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *Br Med J.* 325(7367):746, 2002
6. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care.*;28:1245-9. 2005
7. Mook M, Mitrakou A, Veneman T, Ryan C, Korytkowski M, Cryer P, Gerich J. Hypoglycemia unawareness in IDDM. *Diabetes Care* 17(12):1397-1403, 1994
8. Bott U, Bott S, Hemmann D, Berger M. Evaluation of a holistic treatment and teaching programme for patients with type 1 diabetes who failed to achieve their therapeutic goals under intensified insulin therapy. *Diabet Med* 17:635-643, 2000
9. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 25:765-774. 2008
10. Liu D, McManus R, Ryan E. Improved counter-regulatory hormonal and symptomatic responses to hypoglycemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycaemic control. *Clin Invest Med* 19:71-82, 1996
11. Clarke W, Cox D, Gonder-Frederick L, Julian D, Schlundt D, Polonsky W: Reduced awareness of hypoglycemia in IDDM adults: a prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 18:517-522, 1995
12. Dunn J, Cranston I, Marsden P, Amiel S, Reed L. Attenuation of amygdala and cortical responses to low blood glucose concentration in asymptomatic hypoglycemia in type 1 diabetes. *Diabetes* 56:2766-2773, 2007
13. Armario A, Valles A, Dal-Zotto S, Marquez C, Belda X: A single exposure to severe stressors causes long-term desensitisation of the physiological response to the homotypic stressor. *Stress* 7:157-172, 2004
14. Leventhal H, Diefenbach M, Leventhal EA. Illness cognition: using common sense to understand treatment adherence and affect cognition interactions. *Cognitive Therapy and Research.*; 16: 143-163. 1992
15. Hopkins D, Lawrence I, Mansell P, Thompson G, Heller S, Amiel SA. Routine structured education reduces HbA1c & hypoglycemia and improves psychological

health in patients with type 1 diabetes mellitus (Abstract). *Diabetes* 57 (Suppl 1): 122-OR, 2008

**TABLE 1**

	HU (19)	HA (31)	P
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 T1DM (years)	32.1±12.9	20.5±11.3	0.002
Weight	70.4±16.2	73.7±13.3	0.449
BMI	25.0±5.0	26.1±4.0	0.401
% DNAs	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
% CBT	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
HbA1c (%)	7.2±0.7	8.3±1.3	0.007
Insulin dose Units/kg.day	0.59±0.16	0.77±0.26	0.030

\* taken from annual review data during audit period.

BMI body mass index; CBT cognitive behavioural therapy; DNA did not attend; DAFNE Dose Adjustment for Normal Eating, a 5 day structured education program in flexible insulin therapy for T1 diabetes patients