DELAYED RECOVERY OF COGNITIVE FUNCTION FOLLOWING HYPOGLYCEMIA IN ADULTS WITH TYPE 1 DIABETES: EFFECT OF IMPAIRED AWARENESS OF HYPOGLYCEMIA

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Running title: Cognitive recovery after hypoglycemia.

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ABSTRACT

Objective: Recovery times of cognitive functions were examined after exposure to hypoglycemia in people with diabetes with and without impaired hypoglycemia awareness.

Research Design and Methods: Thirty-six subjects with type 1 diabetes were studied (20 with normal hypoglycemia awareness {NHA}; 16 with impaired hypoglycemia awareness {IHA}). A hyperinsulinemic glucose clamp was used to lower blood glucose to 2.5 mmol/l (45 mg/dl) (hypoglycemia) for one hour, or to maintain blood glucose at 4.5 mmol/l (81 mg/dl) (euglycemia), on separate occasions. Cognitive tests were applied during each experimental condition and repeated at 10-15 minute intervals for 90 minutes after euglycemia had been restored.

Results: In the NHA group, performance was impaired on all cognitive tasks during hypoglycemia and remained impaired for up to 75 minutes on the choice reaction time (CRT) task (p=0.03, \(\eta^2=0.237\)). In the IHA group, performance did not deteriorate significantly during hypoglycemia. When all subjects were analyzed within the same general linear model, performance was impaired during hypoglycemia on all tasks. Significant impairment during recovery persisted for up to 40 minutes on the CRT task (p=0.04, \(\eta^2=0.125\)) with a significant glycemia-awareness interaction for CRT after one hour of hypoglycemia (p=0.045, \(\eta^2=0.124\)). Performance on the trail-making B task was impaired for up to 10 minutes after euglycemia was restored (p=0.024, \(\eta^2=0.158\)).

Conclusions: Following hypoglycemia, the recovery time for different cognitive tasks varied considerably. In the IHA group, performance was not significantly impaired during hypoglycemia. The state of awareness of hypoglycemia may influence cognitive function during, and after, hypoglycemia.

KEY WORDS. Type 1 diabetes; hypoglycaemia; hypoglycemia awareness; cognitive function; cognitive recovery.

ABBREVIATIONS. CRT – choice reaction time; DSST – digit symbol substitution test; IHA – impaired hypoglycemia awareness; NHA – normal hypoglycemia awareness; TMB – trail making B; T1DM – type 1 diabetes mellitus.
The recovery of cognitive function following hypoglycemia has not received rigorous evaluation. Previous studies examined non-diabetic volunteers (1-3) small numbers (3), did not include a euglycemia control arm (1, 4), measured neurophysiological parameters rather than cognitive function (1, 2, 5, 6) or restricted cognitive testing to one or two time points (3-5). The interval between restoration of euglycemia and cognitive testing was usually ill-defined (2, 4-6). Controversy exists as to whether impaired awareness of hypoglycemia is associated with relative preservation (7-13) or exacerbation of the cognitive impairment induced by hypoglycemia (14-16). The present study examined the time taken for recovery of cognitive function in adults with type 1 diabetes, and assessed the effect of their state of awareness on the response to, and recovery from, hypoglycemia.

**RESEARCH DESIGN AND METHODS**

The local medical research ethics committee approved the protocol. Subjects gave informed consent for participation.

**Subjects.** Inclusion criteria were a diagnosis of type 1 diabetes (T1DM) and age 18-45 years. Exclusion criteria included pregnancy or any significant concurrent medical condition, past history of head injury, epilepsy or hypoglycemia-induced seizure.

Thirty-six subjects with T1DM were recruited, 20 with NHA, 16 with IHA, confirmed by documenting their hypoglycemia history and using a validated hypoglycemia awareness scale (17). Microvascular complications were defined as any clinical diagnosis of diabetic retinopathy, neuropathy or nephropathy. The IHA group had a longer duration of diabetes (median [range] 33.5 [22-43] years) compared to the NHA group (29 [19-44] years; p<0.001) and a higher prevalence of microvascular complications (6 patients in NHA group, 1 patient in NHA group, $\chi^2$ =5.994, p=0.013). Other comparisons (sex, age, HbA1c, BMI) were non-significant.

**Glucose clamp procedure.** Each subject underwent one hypoglycemic and one euglycemic clamp, separated by at least two weeks. Subjects were blind to clamp order, which was randomised and counterbalanced. Six studies were postponed (2 NHA, 4 IHA) because of symptomatic hypoglycemia or blood glucose < 4.0mmol/l during the preceding 48h. Using a modified hyperinsulinemic glucose clamp technique (18), blood glucose was stabilised at 4.5mmol/l (81 mg/dl) (euglycemia) and maintained for 30 minutes while subjects practised the cognitive tests. In the euglycemic condition, glucose was maintained at this level. In the hypoglycemic condition blood glucose was lowered over 20 minutes to 2.5mmol/l (45mg/dl), where it was maintained for one hour (experimental phase). Euglycemia (>4.0mmol/l; >72 mg/dl) was then rapidly restored. The recovery phase start was defined by two consecutive arterialized glucose readings ≥ 4mmol/l (≥72 mg/dl), with cognitive testing commencing 10 minutes after the first of these readings.

**Symptom scores and cognitive function tests.** The cognitive tests were Trail Making B (TMB), Digit Symbol Substitution Test (DSST) and Four Choice Reaction Time (CRT), which are sensitive to hypoglycemia (20) and easy to administer repeatedly. The cognitive battery and the Edinburgh Hypoglycemia Scale (19) were applied at baseline, at the beginning and end of the experimental phase, and during the recovery period at 10, 20, 30, 40, 55, 70 and 85 minutes after euglycemia was restored.

**Statistical analysis.** Cognitive scores were compared using general linear modelling (repeated-measures analysis of variance [ANOVA]). In the full model, including all subjects, hypoglycemia awareness status was the between-subjects factors. The experimentally-induced state of hypoglycemia versus euglycemia was the within-subjects factor. Age, sex, duration of
diabetes and order of exposure to hypoglycemia had no significant effect on the results, so these fixed effects/covariables were excluded from the final model. Individuals’ test scores within a single clamp study were corrected for baseline performance by subtracting their baseline score from their scores at each time point. The model compared these adjusted scores between the euglycemic and hypoglycemic conditions (repeated measure). The effects of hypoglycemia in NHA and IHA groups separately are also reported. Statistical significance was accepted at p<0.05. Partial η² was used to indicate effect size. Analyses were performed using SPSS for Windows version 12.0.

RESULTS

Cognitive tasks. Table 1 shows mean (SD) test scores corrected for baseline performance. CRT and TMB scores are completion times; a lower score represents better performance. The DSST score is the number of items completed in two minutes; a higher score represents better performance. The effects of glycemic condition were first examined within NHA and IHA groups, and then for all subjects combined including interaction between glycemic condition and awareness status. A considerable practise effect was apparent on the DSST task but not on the CRT and TMB tasks. The randomised counterbalanced study design controls for practise effects.

NHA subjects. Performance on all cognitive tests was significantly impaired during hypoglycemia in NHA subjects (table 1 and figures 1a, 2a, 3a). Performance on DSST and TMB deteriorated significantly during hypoglycemia but reverted to baseline as soon as euglycemia was restored (table 1). CRT remained impaired after restoration of euglycemia, with significant differences between the hypoglycemic and euglycemic conditions at 20, 30, 40 and 75 minutes (table 1 and figure 1a).

IHA subjects. In IHA subjects, cognitive tests did not show significant impairment during hypoglycemia, with the exception of the DSST task after 60 minutes of hypoglycemia (p=0.041; table 1, figures 1b, 2b, 3b). There were no significant differences during the recovery phase. Compared with NHA subjects, trends towards a smaller deterioration in performance and more rapid recovery following hypoglycemia were observed.

All subjects. Poorer performance during hypoglycemia versus euglycemia was seen for all cognitive tasks. This difference persisted for CRT at 20, 30 and 40 minutes after euglycemia was restored (p=0.04, η²=0.125), and for TMB at 10 minutes after euglycemia was restored (p=0.024, η²=0.158). There was no persistence of impairment of DSST performance.

Comparison of effect of hypoglycemia in NHA and IHA subjects (table 1). DSST: The interaction between glycemic condition and hypoglycemia awareness (hereafter termed the glycemia-awareness interaction) was significant only at the start of hypoglycemia (table 2) (p=0.009), suggesting that hypoglycemia caused significantly greater impairment in NHA subjects than in IHA subjects.

CRT: Performance was impaired during hypoglycemia and at 20, 30 and 40 minutes after euglycemia was restored (p=0.04, η²=0.125). The glycemia-awareness interaction was significant only at the end of hypoglycemia (p=0.045, η²=0.124). This infers that the NHA group were, relative to their baseline performance, more affected during hypoglycemia than the IHA group, but there were no significant between-group differences during recovery.

TMB: The glycemia-awareness interaction was not significant at any time point.

DISCUSSION

Results from the present study suggest three conclusions. Firstly, in all subjects combined, cognitive performance was significantly impaired during hypoglycemia by comparison with euglycemia, consistent with numerous previous studies (20). Secondly, cognitive performance was
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significantly impaired in NHA subjects alone, whereas only non-significant trends were seen in IHA subjects. This difference appears to suggest that individuals with IHA are less affected by hypoglycemia than those with NHA. A formal NHA-IHA difference requires a significant interaction between awareness status and glycemic condition; this was seen for CRT at the end of hypoglycemia, and for DSST at the start of hypoglycemia, without correction for multiple comparisons. This study therefore provides the first, but limited, evidence for a formally-tested difference in the cognitive effect of hypoglycemia depending on state of awareness. Thirdly, choice reaction time remained significantly prolonged up to 75 minutes after hypoglycemia in NHA subjects (and up to 40 minutes in all subjects combined), and TMB completion time remained significantly prolonged 10 minutes after hypoglycemia in all subjects combined. These data suggest that some aspects of cognitive function remain impaired for a clinically significant time after correction of hypoglycemia.

The absolute differences in CRT between the groups were small. There was a trend toward improvement in CRT during the euglycemic condition in the NHA group with a corresponding deterioration in the IHA group. This highlights the importance of the euglycemic control arm in that each group’s performance during hypoglycemia is compared to performance during euglycemia and not to that of a different group, thus controlling for between-group differences that may not be apparent.

The present study has a strong power for within-subjects comparisons but is less powerful at detecting between-subjects differences; high power for a medium effect size difference between groups requires over 50 subjects per group. It is impossible to exclude some overlap in hypoglycemia awareness between the two groups, because scoring methods require some degree of subjective self-assessment. The IHA subjects also had longer duration of diabetes and more microvascular disease, although as IHA appears to be strongly associated with diabetes duration, it may be impossible to match for these characteristics. Finally, asymptomatic hypoglycemia prior to the study cannot be excluded, particularly in IHA subjects, despite the frequent monitoring of blood glucose for the preceding 48h.

If the NHA-IHA differences are accepted, they suggest that IHA subjects develop cerebral adaptation to hypoglycemia. This interpretation may appear to be counterintuitive as these individuals have a higher risk of severe hypoglycemia than those with NHA (17, 21). However, this adaptation may increase their susceptibility to severe hypoglycemia by limiting the time to identify low blood glucose and allowing progression to debilitating neuroglycopenia. The degree of cognitive adaptation acquired by those with IHA is insufficient to compensate completely for the loss of physical symptoms. Cognitive dysfunction begins at lower blood glucose levels in people with T1DM and IHA compared to those with NHA (13) and antecedent hypoglycemia in individuals with T1DM and NHA can shift the thresholds for cognitive dysfunction to lower blood glucose levels (9, 10, 22, 23). Glucose clamp studies in non-diabetic individuals have shown that 90-150 minutes of hypoglycemia the day before cognitive testing attenuates the deterioration in short term memory, reaction time and auditory-evoked brain potentials (11, 24, 25) and avoidance of hypoglycemia can restore the glucose thresholds for cognitive dysfunction to higher levels (7, 8, 12).

A previous, smaller study from our centre compared the effects of hypoglycemia on cognitive function in 20 people with T1DM with either IHA or NHA and reported a trend towards poorer performance during hypoglycemia in IHA subjects (14). Methodological differences exist between the two studies, with the earlier study applying a cognitive battery of 20 minutes duration at one time point only, 10 minutes after euglycemia was restored.
The effect of awareness was not significant for any of the tests employed except for the Rapid Visual Information Processing (RVIP), where the results are given for RVIP hits, misses and reaction time. The result was not significant for the hits (ie correct answers) or reaction time but there was a significant effect on RVIP misses (ie there were more false positive responses in the group with impaired awareness). However, on this latter measure, the effect of the study condition (ie euglycemia versus hypoglycemia) was not significant. The cognitive tests used differed from the current study and CRT (the test yielding the most interesting results in the present study) was not used.

There was inter-individual variability in the effects of hypoglycemia on cognition, consistent with anecdotal observations. The present study was not sufficiently large to study the determinants of these differences formally. Thus, advice to individuals should not be too dogmatic given the possibility of inter-individual differences. Furthermore, although an hour of asymptomatic hypoglycemia may occur frequently in individuals with IHA, hypoglycemia is probably perceived and corrected earlier in those with NHA. Exposure to a shorter period of hypoglycemia should be examined in a group of individuals with NHA to ascertain whether the duration of hypoglycemia affects the recovery of cognitive function.

The present study indicates that cognitive recovery is variable for different tasks but is prolonged for four-choice reaction time. It also provides evidence to support the concept of cognitive adaptation to hypoglycemia in people with IHA, possibly as a consequence of recurrent exposure to hypoglycemia. The delay in recovery has implications for the safety of undertaking tasks requiring cognitive performance immediately after hypoglycemia, such as driving.

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REFERENCES

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FIGURE LEGENDS

Figure 1
1a. Mean (SE) times on CRT test during hypoglycemia and euglycemia conditions in individuals with normal awareness of hypoglycemia.
Squares=EU Triangles=HYPO *= p<0.05 EU vs HYPO
1b. Mean (SE) times on CRT test during hypoglycemia and euglycemia conditions in individuals with impaired awareness of hypoglycemia.
Squares=EU Triangles=HYPO

Figure 2
2a. Mean (SE) times on TMB test during hypoglycemia and euglycemia conditions in individuals with normal awareness of hypoglycemia.
Squares=EU Triangles=HYPO *= p<0.05 EU vs HYPO
2b. Mean (SE) times on TMB test during hypoglycemia and euglycemia conditions in individuals with impaired awareness of hypoglycemia.
Data for one subject was omitted at this time point as it skewed the data markedly (required 212 seconds to complete the task during hypoglycemia). The difference between hypoglycemia and euglycemia was not significant regardless of whether these data were included in the analysis.
Squares=EU Triangles=HYPO

Figure 3
3a. Mean (SE) times on DSST test during hypoglycemia and euglycemia conditions in individuals with normal awareness of hypoglycemia.
Squares=EU Triangles=HYPO *= p<0.05 EU vs HYPO
3b. Mean (SE) times on DSST test during hypoglycemia and euglycemia conditions in individuals with impaired awareness of hypoglycemia.
Squares=EU Triangles=HYPO
FIGURE 1

1a

1b
FIGURE 2

2a.

2b.
FIGURE 3

3a.

3b.