CHAPTER 2

PREVALENCE OF IMPAIRED AWARENESS OF HYPOGLYCAEMIA IN ADULTS WITH TYPE 1 DIABETES

Jacqueline Geddes
Josefine E Schopman
Nicola N Zammitt
Brian M Frier

ABSTRACT

Objective
Impaired awareness of hypoglycaemia (IAH) is thought to affect approximately 25% of people with type 1 diabetes. While this estimate was based on retrospective information from patients in several small studies performed several years ago, validated methods of assessment have not been applied to a large hospital clinic-based population to ascertain the prevalence in the present era.

Methods
Five hundred and eighteen people with type 1 diabetes were recruited by random selection over a 2-year period. Participants completed a questionnaire documenting baseline characteristics and assessment of their awareness status using the method described by Gold et al. The number of episodes of SH they had experienced in the preceding year was recorded retrospectively.

Results
IAH was present in 19.5% of the cohort. Compared to those with normal awareness of hypoglycaemia, those with IAH were significantly older (39.3 (12.9) vs. 45.9 (13.5) years, \( p < 0.001 \)), had a longer duration of diabetes (14 (8-22) vs. 23 (14-32) years, \( p < 0.001 \)), and had a six-fold higher incidence in rates of severe hypoglycaemia in the previous year (0.38 (1.04) vs. 2.36 (4.81), \( p < 0.001 \)).

Discussion
The present survey of a large hospital based clinic population has confirmed that a significant proportion of people with type 1 diabetes (19.5%) continue to have IAH. Despite improvements in insulin therapies, intensification of insulin regimens and innovative patient education, the prevalence of IAH remains high in type 1 diabetes.
INTRODUCTION

In unselected populations of people with type 1 diabetes the estimated incidence of severe hypoglycaemia (requiring external help) ranges from 1.0 to > 3.0 episodes/patient/year. Subjective recognition of the symptoms of hypoglycaemia is fundamental to effective self-management to prevent progression to severe hypoglycaemia. However, with increasing duration of treatment with insulin many people with type 1 diabetes experience a change in their symptoms of hypoglycaemia, manifested as either a reduction in intensity or number, or a change in symptom profile, so that neuroglycopenic symptoms predominate, while autonomic symptoms are less prominent or absent.

This diminished ability to perceive the onset of hypoglycaemia (impaired awareness of hypoglycaemia (IAH)), is alleged to affect approximately 25% of people with type 1 diabetes. This estimate was derived from small studies conducted in the 1980s and early 1990s, which utilised a retrospective review of clinical histories. However, validated methods of assessment, which have been developed subsequently, have not been applied to a large hospital clinic-based population. In addition, as IAH is thought to be induced by recurrent exposure to hypoglycaemia, the introduction of new insulins, the intensification of insulin regimens and improved methods of patient education may help to minimise exposure to hypoglycaemia and hence potentially decrease the prevalence of IAH. The present study was therefore performed to ascertain this prevalence in a randomly selected cohort of people with type 1 diabetes using the method described by Gold et al.

SUBJECTS AND METHODS

Patients

Adults with type 1 diabetes attending a diabetes outpatient clinic at the Royal Infirmary of Edinburgh (a large city teaching hospital), over a 3-year period, were recruited at random for the survey. Inclusion criteria consisted of type 1 diabetes of more than two years duration and being aged over 16 years. Exclusion criteria were pregnancy, advanced renal failure or inability to understand or complete the questionnaire. The local medical ethics committee approved the study, and informed consent was obtained from all participants.

The questionnaire was completed by 518 adults with type 1 diabetes (242 male; mean (SD) HbA1c 8.4 (1.4) %; median (inter quartile range, IQR) age, 39.0 (31-50) years; duration of diabetes, 16 (9-24) years. This group were using either insulin analogues (n=384; 74%), a mixture of analogue and human insulins (n = 93; 18%) or human insulins alone (n = 41; 8%).
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A basal-bolus insulin regimen was used by 82.3% (n=426), with 17.7% (n = 92) on a twice-daily regimen of fixed insulin mixtures, such as 30% soluble, 70% isophane.

Methods
Each participant completed a general questionnaire to document baseline demographic characteristics and quantified the frequency of exposure to self-treated hypoglycaemia and episodes of severe hypoglycaemia (defined as requiring external assistance) during the preceding 12 months. Retrospective recall of severe hypoglycaemia over a period of one year is a robust measure in people with type 1 diabetes. An investigator was present to assist with clarification of the content of the questionnaire if required.

HbA1c was measured by ion exchange high performance liquid chromatography via the Bio-Rad Variant II Haemoglobin testing system (Hercules, CA, USA). The results were DCCT-aligned; the local non-diabetic range for HbA1c is 5.0-6.5%.

Assessment of awareness of hypoglycaemia
Awareness of hypoglycaemia was assessed using the method described by Gold et al., which asks the question: “do you know when your hypos are commencing?” The respondent selects a number on a 7-point Likert scale with 1 representing “always aware” and 7 representing “never aware”. A score of 4 or more is designated as impaired awareness of hypoglycaemia. In addition to this subjects are asked if they have noticed a subjective alteration in their warning symptoms and their frequency of exposure to severe hypoglycaemia in the year preceding the study. Hypoglycaemia symptom scores were assessed using the Edinburgh Hypoglycaemia Scale.

Statistical analysis
All analyses were performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA) for Windows. Differences between groups were analyzed using either the two-sample t test or Mann-Whitney-U test. To assess the linear relationship between two variables a Spearman correlation coefficient was calculated. A p value < 0.05 was considered significant. All results are reported as mean (SD) unless otherwise stated.

RESULTS
IAH was present in 19.5% (n = 101), (Figure 1). Compared to people with normal awareness of hypoglycaemia, those with IAH were significantly older (p < 0.001) and had diabetes for longer (p < 0.001) (Table 1). The rate of severe hypoglycaemia in the preceding year was six-
fold higher in those with IAH compared to those with normal awareness (p < 0.001), (Figure 1). The prevalence of SH in the preceding year was 20.1% in the group with normal awareness and 50.5% in those with IAH (Figure 1). The reported intensity of autonomic symptoms was lower during episodes of self-treated hypoglycaemia in those with impaired awareness compared to those with normal awareness (p = 0.004). No statistical differences were observed between the groups (IAH vs. normal awareness) in the intensity of neuroglycopenic symptoms (p = 0.44). No differences were also observed with respect to glycaemic control (HbA1c 8.3 (1.4) % vs. 8.4 (1.4) %, p = 0.92). A moderate and highly significant association was observed between IAH and duration of diabetes (r_s = 0.21, p < 0.001) and between IAH and rate of SH (r_s = 0.34, p < 0.001).

DISCUSSION

The present survey, using a validated method of assessment, has demonstrated a prevalence of IAH of approximately 20% in an unselected adult population with type 1 diabetes. This is similar to previous estimates made 15-20 years ago that were derived on clinical history from hospital and community-based populations9, 10, 15, 16. Those with IAH were older, had a longer duration of diabetes, and had a six-fold higher frequency of episodes of severe hypoglycaemia and a lower intensity of autonomic symptoms during hypoglycaemia, all of which are consistent with recognised characteristics of this acquired syndrome9, 12, 16. Thus the method of Gold et al12 appears to be sufficiently discriminating in the identification of those with IAH.

A potential limitation in defining the prevalence of IAH with precision is that this is not an “all or nothing” phenomenon. Several studies of people with9, and without, type 1 diabetes20-22 have suggested that exposure to antecedent hypoglycaemia can shift the glycaemic thresholds for cognitive dysfunction, symptom generation and counterregulatory hormonal secretion to lower blood glucose levels, while strict avoidance of hypoglycaemia can restore normal responses93.

Views differ regarding the most appropriate methods and situations in which evaluation of the awareness of hypoglycaemia should be undertaken, ranging from the use of questionnaires, identification of symptom generation during experimental hypoglycaemia using glucose clamps and utilisation of continuous glucose monitoring (CGMS). In our opinion, IAH should be evaluated within the everyday experience of people treated with insulin, and not from observations carried out in the artificial setting of controlled hypoglycaemia in the laboratory. CGMS may have a useful contributory role in identifying asymptomatic biochemical hypoglycaemia, which is a feature of IAH. Kubiak et al24 used CGMS to examine the frequency of asymptomatic hypoglycaemia in 10 people with IAH (identified by the
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Figure 1 - Prevalence and incidence of severe hypoglycaemia (SH) in the year preceding the survey of 518 adults with type 1 diabetes, with, and without, impaired awareness of hypoglycaemia.

Table 1 - Clinical characteristics of participants with type 1 diabetes by awareness of hypoglycaemia.

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Normal</th>
<th>Impaired</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%)</td>
<td>417 (80.5%)</td>
<td>101 (19.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.3 (12.9)</td>
<td>45.9 (13.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration (years) (Median, IQR)</td>
<td>14 (8-22)</td>
<td>23 (14-32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 (1.4)</td>
<td>8.4 (1.4)</td>
<td>0.92</td>
</tr>
<tr>
<td>Incidence of SH in preceding year</td>
<td>0.38 (1.0)</td>
<td>2.36 (4.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>2.94 (1.1)</td>
<td>2.05 (1.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Neuroglycopenic symptoms</td>
<td>2.35 (1.0)</td>
<td>2.40 (1.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Malaise symptoms</td>
<td>1.95 (1.2)</td>
<td>2.2 (1.4)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

method of Gold et al\(^{(a)}\) and 10 people with normal awareness of hypoglycaemia. Those with IAH had a significantly more biochemical and asymptomatic hypoglycaemia than those with normal awareness, but these observations may be limited by having defined biochemical hypoglycaemia as an interstitial glucose level below 3.3 mmol/L, which is above the usual level for symptom generation.
The other questionnaire method for assessing awareness of hypoglycaemia is that of Clarke et al\textsuperscript{25}, which has been externally validated by a different group of investigators, who examined the relationship between the hypoglycaemia questionnaire, prospective blood glucose monitoring and glucose clamp studies to assess hypoglycaemia awareness\textsuperscript{18}. A recent study from our own centre has evaluated the Clarke\textsuperscript{25} and Gold\textsuperscript{12} methods for their sensitivity in identifying impaired awareness of hypoglycaemia and for their mutual concordance\textsuperscript{17}. A strong correlation was demonstrated between the two methods ($r = 0.868, p = 0.001$) in identifying people with IAH. Those identified by both methods as having IAH were older, had a longer duration of diabetes, recorded more frequent episodes of biochemical hypoglycaemia over a four-week monitoring period and experienced more episodes of severe hypoglycaemia in the year preceding the study. Although methods that utilise questionnaires are not perfect, the two currently available methods, which are easy and quick to administer in the clinical setting, have been externally validated, and demonstrate close internal concordance.

The present study, which has applied a specific method of assessing hypoglycaemia awareness in a large outpatient clinic population (using treatments with insulin analogues and MDI), has confirmed that the prevalence of IAH has not changed over the last 20 years, despite the introduction of novel therapies.

REFERENCES


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