Hypoglycaemia in diabetes
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CHAPTER 4

PREVALENCE OF IMPAIRED AWARENESS OF HYPOGLYCAEMIA AND FREQUENCY OF HYPOGLYCAEMIA IN INSULIN-TREATED TYPE 2 DIABETES

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ABSTRACT

Aims
The present study sought to ascertain the prevalence of impaired awareness of hypoglycaemia (IAH) in people with insulin-treated type 2 diabetes (T2DM) and its effect on risk of hypoglycaemia.

Methods
Data were obtained from 122 people with insulin-treated T2DM (63 male; mean (SD) HbA1c 8.4 % (1.5); median (IQR) age, 67 (58-72) years; duration of T2DM 15 (10-20) years; duration of insulin therapy, 6 (4-9) years). A questionnaire was used to evaluate hypoglycaemia awareness status and estimate the frequency of severe hypoglycaemia (SH) in the preceding year. Capillary blood glucose was monitored prospectively over a 4-week period to document biochemical hypoglycaemia.

Results
The prevalence of IAH was 9.8%. In the subgroup with IAH the incidence of SH in the preceding year was 17-fold higher than those with normal hypoglycaemia awareness (0.83 (1.12) vs. 0.05 (0.28) episodes per patient; p <0.001, (n=122)) and had a fivefold higher incidence of biochemical hypoglycaemia (2.43 (4.39) vs. 0.46 (1.21) episodes; p<0.001, (n=63)).

Conclusion
The prevalence of IAH in insulin-treated T2DM was associated with higher frequencies of SH and biochemical hypoglycaemia. Therefore the presence of IAH in those with insulin-treated T2DM should be evaluated at clinical review.
INTRODUCTION

Hypoglycaemia is a major limitation to achieving strict glycaemic control in type 1 diabetes and the acquired syndrome of impaired awareness of hypoglycaemia (IAH) is a major risk factor for severe events. IAH affects approximately 20-25% of people with type 1 diabetes and the incidence of severe hypoglycaemia (SH) in this group is three to six fold that of people with intact awareness. IAH is also thought to be associated with a higher frequency of asymptomatic biochemical hypoglycaemia. IAH in diabetes is a dynamic state; strict avoidance of hypoglycaemia may reverse impaired awareness of hypoglycaemia.

However, hypoglycaemia and IAH are not considered to present significant problems for the management of insulin-treated type 2 diabetes (T2DM), despite the increasing use of insulin to treat T2DM. It has been shown that the risk of hypoglycaemia in this group rises in direct relationship to the duration of insulin therapy.

T2DM is primarily associated with advancing age when symptoms of hypoglycaemia become less intense and the symptom profile is modified. In a recent study, hormonal, symptomatic and cognitive responses to hypoglycaemia were examined in 13 older people with T2DM (≥ 65 years), and compared with 13 matched middle-aged participants with T2DM (39-64 years). The older patients failed to perceive hypoglycaemic symptoms and had prolonged reaction times, which were unrelated to impaired counterregulation, but hypoglycaemia awareness status was not evaluated. Many previous studies of hypoglycaemia in T2DM have not considered the effects of age on responses to hypoglycaemia and few have included patients aged over 70 years. Older people with T2DM may be at higher risk of severe hypoglycaemia than is commonly believed.

Two prospective studies from the UK have examined hypoglycaemia in insulin-treated T2DM, reporting incidences ranging from 4 to 16 and from 0.1 to 0.7 episodes per patient per year of “biochemical” hypoglycaemia (defined by blood glucose level) and SH (defined by requiring help for recovery, or coma), respectively. The frequency of asymptomatic hypoglycaemia is determined principally by how often blood glucose is measured. In these previous studies the patients were not required to deviate from their normal routine of blood glucose monitoring, so only symptomatic hypoglycaemia was documented and no distinction was made in awareness of hypoglycaemia. Previous studies of clinical histories in our centre found a frequency of IAH of 8% in people with insulin-treated T2DM, and a nine-fold higher rate of SH. To our knowledge the influence of IAH on frequency of biochemical hypoglycaemia has not been assessed prospectively in insulin-treated T2DM.
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The present study was performed in a randomly selected cohort of individuals with insulin-treated T2DM, to ascertain the prevalence of IAH and to examine whether this is associated with a history of SH and a higher frequency of biochemically-determined hypoglycaemia.

MATERIALS AND METHODS

Recruitment
Adults with T2DM who were attending a diabetes outpatient clinic at the Royal Infirmary of Edinburgh (a large urban teaching hospital), over a 6-month period, were approached at random for the survey. They had received treatment with two or more injections of insulin daily for at least one year. Patients on once daily insulin in combination with oral anti-diabetic medications were excluded. Very few patients declined to participate. The local ethics committee approved the study and written informed consent was obtained from the participants.

Methods
All participants completed a questionnaire to assess their awareness of hypoglycaemia using the method of Gold et al, which poses the question “do you know when your hypos are commencing?” The respondent scores on a 7-point Likert scale, where 1 represents “always aware” and 7 represents “never aware”. A score of ≥ 4 is considered to indicate IAH. This method has been shown to have good concordance with an alternative validated method of assessing IAH. Previous exposure to SH (events requiring external assistance) was estimated retrospectively for the year preceding the study. Recall of episodes of SH during a one-year period has been shown to be a robust measure in people with insulin-treated T2DM. An investigator was present to clarify the content of the questionnaire if required.

The participants were then asked to perform capillary blood glucose (CBG) measurements over a 4-week period (using their own blood glucose meters), four times daily, before each meal and at bedtime. When the measured value was recorded and biochemical hypoglycaemia was established (defined as any CBG value <3 mmol/L (54mg/dL), the subjects were requested to document the nature and the intensity of hypoglycaemic symptoms, using the Edinburgh Hypoglycaemia Scale.

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 reference range for HbA1c is 5.0–6.5%.
Differences between groups (IAH vs. normal awareness) were analyzed using two-sample t test/Mann-Whitney U test or the χ2/Fisher’s exact test. All analyses were performed using SPSS, version 12.0, for Microsoft Windows.

Subjects
A total of 122 people with insulin-treated T2DM (63 male; mean (SD) HbA1c 8.4 % (1.5); median (inter quartile range, IQR) age, 67 (58-72) years; duration of T2DM 15 (10-20) years; duration of insulin therapy, 6 (4-9) years were recruited. Ninety-nine were receiving a mixture of short-acting regular insulins or rapid-acting insulin analogues and intermediate-acting NPH (isophane) insulins, twice daily; 23 were taking three or more insulin injections daily, including a long-acting insulin analogue. Monitoring sheets that were not completed fully were discarded. Five patients reported that their blood glucose recording sheets had been lost in transit. Twenty-eight patients who completed the questionnaire said that they would be unable to undertake the entire monitoring period. Fully completed diaries and information sheets were returned at the conclusion of the monitoring period by 63 (51.6%) of the 122 participants. No significant differences in age (p = 0.56), duration of diabetes (p = 0.62), duration of insulin therapy (p = 0.76), insulin dosage (p = 0.18), glycemic control (p = 0.25) and hypoglycaemia awareness score (p = 0.33) were observed in those who participated in the entire study compared with those who did not provide CBG data.

RESULTS
Of the 122 participants 12 patients (overall prevalence 9.8%) showed evidence of IAH (Table 1). Hypoglycaemia had been experienced at some time since commencing treatment with insulin by 104 (85.2%) people. In the subgroup of 63 patients who returned CBG data, 7 had IAH (prevalence 11.1%), and they exhibited a fivefold higher incidence of recorded episodes of biochemical hypoglycaemia over the 4-week monitoring period compared with the patients with normal awareness of hypoglycaemia (Table 2; Figure 1).

No differences during this period were observed between the two groups in the reported intensity of symptoms that were experienced during episodes of biochemical hypoglycaemia (Table 2). The patients with IAH had better glycaemic control than the patients with normal awareness but this difference was not statistically significant (Table 1). No correlation was found between IAH and age, duration of diabetes or duration of treatment with insulin (Table 1).

The estimated incidence of SH recorded by the 12 patients with IAH in the year preceding the study was 17-fold higher than that recalled by those with normal awareness of hypoglycaemia (Table 2). However, the patients who completed the CBG monitoring period reported a lower
Table 1 - Clinical characteristics of insulin-treated T2DM participants with and without impaired 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>110 (90.2%)</td>
<td>12 (9.8%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Age (years) Median (IQR)</td>
<td>67 (58-72)</td>
<td>70 (59-77)</td>
<td>0.23</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>51.8 / 48.2 %</td>
<td>50 / 50 %</td>
<td>0.91</td>
</tr>
<tr>
<td>Diabetes duration (years) (Median, IQR)</td>
<td>15 (10-20)</td>
<td>17.5 (10-26)</td>
<td>0.64</td>
</tr>
<tr>
<td>Duration insulin therapy (years) (Median, IQR)</td>
<td>6.5 (4-9)</td>
<td>6 (4-8)</td>
<td>0.84</td>
</tr>
<tr>
<td>Daily insulin dose (SD)</td>
<td>70 (86)</td>
<td>54 (35)</td>
<td>0.09</td>
</tr>
<tr>
<td>Injections/ day</td>
<td>12.7 %</td>
<td>16.7 %</td>
<td>0.91</td>
</tr>
<tr>
<td>HbA1c (%) mean (SD)</td>
<td>8.4 (1.6)</td>
<td>7.9 (1.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Background Retinopathy (%)</td>
<td>60.0 %</td>
<td>50.0 %</td>
<td>0.27</td>
</tr>
<tr>
<td>Pre-proliferative Retinopathy (%)</td>
<td>1.8 %</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Laser-treated Retinopathy (%)</td>
<td>2.7 %</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Neuropathy (%)</td>
<td>55%</td>
<td>75%</td>
<td>0.18</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>23.6 %</td>
<td>16.7 %</td>
<td>0.60</td>
</tr>
<tr>
<td>Nephropathy (%)</td>
<td>5.5 %</td>
<td>8.3 %</td>
<td></td>
</tr>
<tr>
<td>Renal failure (%)</td>
<td>3.6 %</td>
<td>0 %</td>
<td></td>
</tr>
<tr>
<td>Autonomic neuropathy (%)</td>
<td>0.9 %</td>
<td>0%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 2 - The frequency of episodes of biochemical hypoglycaemia over the 4-week period and recollected total number of episodes of severe hypoglycaemia (SH) during the preceding year in insulin-treated T2DM participants with and without impaired awareness of hypoglycaemia (data are recorded as means (SD)).

<table>
<thead>
<tr>
<th>From record sheets (n = 63)</th>
<th>Normal</th>
<th>Impaired</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical glucose values 2.5-2.9 mmol/L</td>
<td>0.41 (1.08)</td>
<td>2.00 (4.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Biochemical glucose values &lt;2.5 mmol/L</td>
<td>0.09 (0.39)</td>
<td>0.43 (1.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>All biochemical hypoglycaemic reactions</td>
<td>0.46 (1.21)</td>
<td>2.43 (4.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe hypoglycaemic reactions</td>
<td>0.04 (0.27)</td>
<td>0 (0)</td>
<td>0.48</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>2.56 (1.19)</td>
<td>2.32 (0.95)</td>
<td>0.42</td>
</tr>
<tr>
<td>Neuroglycopenic symptoms</td>
<td>2.26 (1.03)</td>
<td>2.28 (1.13)</td>
<td>0.58</td>
</tr>
<tr>
<td>Malaise symptoms</td>
<td>2.09 (1.43)</td>
<td>1.72 (1.30)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From questionnaire (n = 122)</th>
<th>Normal</th>
<th>Impaired</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of SH (episodes per patient year)</td>
<td>0.05 (0.28)</td>
<td>0.83 (1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prevalence of SH</td>
<td>2.7%</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>
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Figure 1 - Incidence of biochemical hypoglycaemia (shown as episodes per patient per month) in people with insulin-treated type 2 diabetes, with and without impaired awareness of hypoglycaemia.

Figure 2 - Incidence of severe hypoglycaemia (SH) in patients with insulin-treated T2DM during the previous year related to the score for awareness of hypoglycaemia using the method of Gold et al [5].
incidence of SH in the preceding year compared to those who did not (mean (SD) 0.08 (0.33) vs. 0.17 (0.62); p =0.039). Figure 2 shows the incidence of SH in the preceding year in relation to the score for awareness of hypoglycaemia.

DISCUSSION

The present study has characterized the prevalence of IAH in people with insulin-treated T2DM and has prospectively estimated the frequency of biochemical hypoglycaemia associated with this clinical syndrome. The method by Gold et al ⁵ was used to evaluate hypoglycaemia awareness status. Although this method was validated in people with type 1 diabetes ⁷, it is likely to be applicable in T2DM, as symptoms of hypoglycaemia are age-specific and unrelated to type of diabetes, and impaired awareness is not considered to differ with type of diabetes. We believe that the method of Gold et al ⁵ was appropriate for use in the present study and by applying this scoring method the prevalence of IAH was found to be less than 10%. This observation is consistent with two previous surveys of similar patients in our centre ¹⁰, ²¹. A retrospective Danish survey of 401 patients with insulin-treated T2DM recorded IAH in 46 patients (12.5%) ²⁴, but the method used by these authors for identifying IAH has been criticized as over-estimating the prevalence ⁷, ²⁵.

A lower intensity of autonomic symptoms, a higher intensity of neuroglycopenic symptoms and a longer duration of insulin therapy would be anticipated in the group with IAH. No differences were observed between those with normal awareness of hypoglycaemia and those with IAH in the reported intensity of symptoms when classified into three major groups (autonomic, neuroglycopenic (including neurological symptoms that are prominent in older people ¹⁴) and malaise symptoms). One possible explanation is that although the symptoms are generated, they are not perceived as early warning symptoms of hypoglycaemia by patients with IAH, who therefore report that they are unaware of hypoglycaemia.

A lower range for the duration of insulin therapy would be anticipated (Table 1), as T2DM patients who had been taking insulin for more than one year were included in the study. However many T2DM patients requiring insulin therapy often commence with once daily insulin in combination with oral anti-diabetic medications. The exclusion of patients who were receiving once daily insulin may explain the observed range of duration of insulin therapy.

Many participants in the present study failed to provide a complete set of CBG monitoring data. Although this failure to complete the period of monitoring was disappointing, this rate is not unusual in clinical studies of this nature. Specific reasons for the inability or unwillingness of participants to complete the study were not explored. It is possible that people with IAH,
who are more likely to encounter serious hypoglycaemia, would be more willing to perform CBG monitoring than those with normal awareness. However, no statistical difference was observed in the prevalence of IAH between those who completed the monitoring period and those who did not. The entire group of 122 patients included in the study was used to estimate the prevalence of IAH and frequency of SH in the previous year. Therefore it is unlikely that the prevalence of IAH in insulin-treated T2DM was overestimated despite the relatively small size of the study. A lower incidence of SH in the preceding year was reported by those who completed the entire study, which may indicate that their willingness to self-monitor blood glucose is effective in limiting the frequency of SH.

In urban centres in Scotland, most people with insulin-treated T2DM attend specialist clinics in secondary care, with the exception of those who are housebound or live in residential homes. The patients included in this study were relatively old, particularly when compared to large studies of T2DM such as the UKPDS 9. Therefore the present data are likely to be representative of the local diabetic community with insulin-treated T2DM.

The occurrence of biochemical hypoglycaemia in people with insulin-treated T2DM differed considerably depending on their state of hypoglycaemia awareness. These events are relatively uncommon in patients with normal awareness of hypoglycaemia which is consistent with the findings of a large multicentre prospective study in the UK 17. By extrapolating the results of the 4-week CBG data, those with normal awareness of hypoglycaemia would be expected to have only 6 episodes of biochemical hypoglycaemia annually, compared to 29 episodes for the patients with IAH (a fivefold difference).

In view of the greatly enhanced risk of hypoglycaemia associated with impaired awareness of hypoglycaemia, the possible development of IAH should not be ignored in patients with insulin-treated T2DM and enquiry as to its possible development should be made at routine clinical review. The method of Gold et al 5 to assess awareness of hypoglycaemia is quick and easy to administer in clinical practice and identifies most people with IAH.

REFERENCES


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