CHAPTER 3

FREQUENCY OF SYMPTOMATIC AND ASYMPTOMATIC HYPOGLYCAEMIA IN TYPE 1 DIABETES: EFFECT OF IMPAIRED AWARENESS OF HYPOGLYCAEMIA

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ABSTRACT

**Aims**
To characterize the frequency and the nature (symptomatic vs. asymptomatic) of hypoglycaemia in people with type 1 diabetes with impaired awareness of hypoglycaemia.

**Methods**
A group of 19 patients with type 1 diabetes with normal hypoglycaemia awareness were matched for age, sex, duration of diabetes and glycaemic control with 19 patients with impaired awareness of hypoglycaemia. Frequency of severe hypoglycaemia in the preceding year was estimated retrospectively. Capillary blood glucose was monitored prospectively four times daily, over a 4-week period. All blood glucose values < 3 mmol/l were recorded and classified by symptom response.

**Results**
The patients with impaired awareness of hypoglycaemia exhibited twice the frequency of all episodes of hypoglycaemia over the four-week monitoring period than those with normal awareness (mean (SD) 7.9 ± 5.4 vs. 3.7 ± 3.6, *p* = 0.003). No differences between the two subgroups were observed in the total number of symptomatic hypoglycaemia episodes (4.2 ±3.3 vs. 3.2 ± 3.4, *p* = 0.25). The group with impaired awareness of hypoglycaemia had an seven-fold higher incidence of asymptomatic hypoglycaemia than those with normal awareness (3.7 ± 5.3 vs. 0.5 ± 1.2, *p* = 0.001); these episodes comprised 47% of all glucose values < 3.0mmol/L in this group, compared to 14% in the group with normal awareness of hypoglycaemia. The annual prevalence of severe hypoglycaemia for patients with impaired awareness of hypoglycaemia was 53% compared to 5% for patients with normal awareness, and they had a significantly higher incidence of severe events (1.6 ± 2.8 vs. 0.1 ± 0.3 *p* = 0.001).

**Conclusions**
Adults with type 1 diabetes who have impaired awareness of hypoglycaemia are exposed to a much higher incidence of asymptomatic hypoglycaemia than those with normal awareness, and are at higher risk of developing severe hypoglycaemia.
Hypoglycaemia remains the principal barrier to maintaining good glycaemic control in the management of diabetes, despite advances in insulin therapy and patient education. Hypoglycaemia can be categorised as symptomatic or asymptomatic hypoglycaemia (both of which self-treated when detected and classified as “mild”) or severe hypoglycaemia (where external assistance is required). In type 1 diabetes estimates have been made of the frequencies of mild and severe hypoglycaemia. Estimates of mild symptomatic hypoglycaemia have varied from 29 to 162 episodes per patient per year, but retrospectively is difficult to recall with accuracy beyond one week. Prospective studies have reported an average incidence of approximately 2 episodes per week. Retrospective recall of episodes of severe hypoglycaemia has been shown to be robust over a period of one year in people with type 1 diabetes. The incidence of severe hypoglycaemia has therefore been estimated with reasonable precision, ranging from 1.1 to 3.2 episodes per patient per year.

Recurrent exposure to hypoglycaemia (both symptomatic and asymptomatic) may underlie the development of the acquired syndrome of impaired awareness of hypoglycaemia, which affects one in five adults with type 1 diabetes. This diminished ability to perceive the onset of hypoglycaemia is associated with twice the usual frequency of mild hypoglycaemia and up to a sixfold greater incidence of severe hypoglycaemia. The present study was performed to characterise the nature (symptomatic vs. asymptomatic) and frequency of hypoglycaemia in people with type 1 diabetes, with and without impaired awareness of hypoglycaemia.

RESEARCH DESIGN AND METHODS

A group of 38 people with type 1 diabetes all of whom were receiving basal-bolus insulin regimens (rapid-acting insulin before meals and once daily long-acting insulin) were recruited, 19 of whom had normal awareness and 19 had a history of established impaired awareness of hypoglycaemia as confirmed by the method of Gold et al. The patients with impaired awareness of hypoglycaemia were recruited as they attended the diabetes outpatient clinic and were deliberately matched for age, sex, duration of diabetes and glycaemic control (estimated as HbA1c) with patients who attended subsequently who had normal awareness of hypoglycaemia. All patients completed an established scoring system to confirm their awareness status. Exposure to severe hypoglycaemia in the year preceding the study was estimated retrospectively by each patient. An investigator was present to clarify the content of the questionnaire if needed.

Participants were then asked to perform capillary blood glucose measurements (using their own blood glucose meters) four times daily, before each meal and at bedtime, over a
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4-week period. When a blood glucose value <3 mmol/L was recorded, subjects were required to document whether the hypoglycaemia had been detected subjectively or solely by the biochemical measurement of blood glucose. All patients completed and returned their diaries. Differences between subgroups (normal awareness vs. impaired awareness of hypoglycaemia) were analyzed using the two-sample t test/Mann-Whitney-U test or the χ²/Fisher's exact test. The analyses were performed using SPSS, version 12.0, for Microsoft Windows.

RESULTS

Frequency of hypoglycaemia (Table 1)
Patients with impaired awareness of hypoglycaemia exhibited a two-fold greater total frequency of episodes of hypoglycaemia (blood glucose < 3.0 mmol/L) over the four-week monitoring period than those with normal awareness. No significant differences between the two groups were observed with regard to the number of symptomatic episodes and no patients experienced any severe hypoglycaemia during the monitoring period. Participants with impaired awareness of hypoglycaemia demonstrated significantly more episodes of asymptomatic hypoglycaemia; these episodes comprised 47% of all hypoglycaemia in this group, compared to 14% in the normal awareness group.

Annual prevalence of severe hypoglycaemia (Table 1)
In the preceding year, 10 of 19 patients with impaired awareness of hypoglycaemia (53%) had experienced one or more episodes of severe hypoglycaemia compared to only 1 of 19 patients with normal awareness (5%). The participants with impaired awareness of hypoglycaemia had experienced significantly more episodes of severe hypoglycaemia per patient per year than those with normal awareness of hypoglycaemia.

CONCLUSIONS

The present study utilised home blood glucose monitoring to confirm (and quantitate) the greater frequency of hypoglycaemia that is believed to occur in people with type 1 diabetes who have impaired awareness of hypoglycaemia. During the period of monitoring, the patients with impaired awareness of hypoglycaemia recorded twice the frequency of hypoglycaemia than those with normal awareness. No difference was observed in the incidence of symptomatic hypoglycaemia (confirmed by blood glucose testing) but in those with impaired awareness of hypoglycaemia the incidence of asymptomatic hypoglycaemia was seven times greater than that recorded by people with normal awareness, which is consistent with earlier observations by Gold and colleagues. The present study confirms that patients with impaired awareness of hypoglycaemia have a much greater exposure to low blood glucose values.
Table 1 - The characteristics of participants with type 1 diabetes with and without impaired awareness of hypoglycaemia (IAH), the frequency of episodes of hypoglycaemia (symptomatic and asymptomatic) over the 4-week monitoring period and the number of episodes of severe hypoglycaemia (SH) during the preceding year.

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>IAH</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>19 (50)</td>
<td>19 (50)</td>
<td>-</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>10 / 9</td>
<td>10 / 9</td>
<td>-</td>
</tr>
<tr>
<td>Age (years) (median, IQR)</td>
<td>50.3 (38.5-62.1)</td>
<td>53.7 (41.3-66.1)</td>
<td>0.4</td>
</tr>
<tr>
<td>Duration (years) (median, IQR)</td>
<td>22.5 (10.0-35.0)</td>
<td>24.5 (10.1-38.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>HbA1c (%) / HbA1c (mmol/mol)</td>
<td>8.3 (1.4) / 67</td>
<td>7.8 (1.3) / 62</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>From record sheets</strong></td>
<td></td>
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<tr>
<td>Total glucose values &lt; 3.0 mmol/L (mean, SD)</td>
<td>3.7 (3.6)</td>
<td>7.9 (5.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of episodes recognised by patients</td>
<td>3.2 (3.4)</td>
<td>4.2 (3.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Number of episodes recognised by routine testing with meter</td>
<td>0.5 (1.2)</td>
<td>3.7 (5.3)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>From questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of SH (mean, SD) (episodes per patient per year)</td>
<td>0.1 (0.3)</td>
<td>1.6 (2.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prevalence of SH</td>
<td>5%</td>
<td>53%</td>
<td>-</td>
</tr>
</tbody>
</table>

Currently available methods for determining the frequency of hypoglycaemia include estimates of capillary blood glucose at regular intervals, known as home blood glucose monitoring (HBGM), and continuous glucose monitoring systems, which measure interstitial glucose concentrations. The detection (and therefore the incidence) of hypoglycaemia using HBGM is limited by its dependency on the frequency and timing of testing. In the present study, blood glucose measurements were performed four times daily (pre-prandial and at bed-time, which predicts the potential risk of nocturnal hypoglycaemia). A 7-point glucose profile would have provided additional post-prandial and nocturnal values, but was less likely to have yielded comprehensive data over the time period of observation. The patients were asked to report if an episode of hypoglycaemia had been detected subjectively or solely by the biochemical measurement of blood glucose, which may conceivably have influenced the classification (symptomatic vs. asymptomatic) of hypoglycaemia. Although the use of continuous glucose monitoring systems is considered by some to provide the “gold standard” for estimating the frequency of hypoglycaemia, this method measures interstitial tissue glucose every three minutes for a period of up to 72 hours, and concerns have been raised about the accuracy of measurements, particularly within the hypoglycaemic range. The physiological delay that exists in the equilibration of blood with interstitial tissue glucose...
may be exaggerated when blood glucose falls rapidly \(^1\). During experimental hypoglycaemia in people with type 1 diabetes, while continuous glucose monitoring has been shown to underestimate interstitial tissue glucose concentrations it potentially overestimates the frequency and duration of hypoglycaemia \(^2\).

Kubiak et al \(^3\) used continuous glucose monitoring systems to examine the frequency of hypoglycaemia in 20 people with type 1 diabetes (10 with impaired awareness of hypoglycaemia vs. 10 who had normal awareness of hypoglycaemia). A two-fold increase in mild hypoglycaemia and a three-fold increase in asymptomatic hypoglycaemia were observed in those with impaired awareness of hypoglycaemia compared to the participants with normal awareness. However, in that small study the groups were not matched for glycaemic control: the impaired awareness of hypoglycaemia group had a significantly lower mean HbA1c (6.4% (46 mmol/mol) vs. 7.6% (60 mmol/mol)), thus introducing an important confounding variable. The observations reported by Kubiak et al \(^3\) were not confirmed by Choudhary et al \(^4\) in a study utilizing continuous glucose monitoring systems in 95 patients (21 of whom had impaired awareness of hypoglycaemia), where no differences were demonstrable either in frequency or duration of hypoglycaemia. The clinical utility and accuracy of continuous glucose monitoring systems in estimating the frequency of hypoglycaemia in people with impaired awareness of hypoglycaemia remain undetermined.

In conclusion, people with type 1 diabetes who have impaired awareness of hypoglycaemia, are exposed to a significantly higher incidence of asymptomatic hypoglycaemia than people who have normal awareness, which contributes to their greatly enhanced risk of developing severe hypoglycaemia, the high rate of which was demonstrated in the present study. However, because the estimates of severe hypoglycaemia were made retrospectively in small selected subgroups of patients, the absolute figures that were recorded can not be be compared to those derived prospectively over a period of a year in a larger cohort with type 1 diabetes \(^5\).

REFERENCES


