

Original Article

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The updated Pedersen-Bjergaard method for assessment of awareness of hypoglycaemia in type 1 diabetes

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ABSTRACT

INTRODUCTION. Loss of awareness of hypoglycaemia is the major risk factor for severe hypoglycaemia in type 1 diabetes. Three methods for assessment of self-reported awareness have been validated and used more widely: the Gold, the Clarke and the Pedersen-Bjergaard classification. Comparisons between the methods are hampered by the latter operating with three classes, whereas the other methods are bimodal. We have therefore updated the Pedersen-Bjergaard classification and here present a comparison of the three methods.

METHODS. Adult people with type 1 diabetes (n = 325) completed a validated questionnaire. Hypoglycaemia awareness was self-reported by the three methods: Gold, Clarke and Pedersen-Bjergaard scores. The latter was updated by renaming the previous “impaired” class to “intermediate”.

RESULTS. A total of 24%, 17% and 14% of patients were classified as having loss of awareness by the Gold, Clarke and updated Pedersen-Bjergaard methods, respectively, with reasonably good agreement and all with increased rates of severe hypoglycaemia. The latter classified 43% with normal and 43% with intermediate awareness and low and average rate of severe hypoglycaemia, respectively.

CONCLUSION. The three classifications identified people with loss of awareness with a reasonably high degree of concordance. In contrast to the others, the updated Pedersen-Bjergaard method identified groups with normal and intermediate awareness with clinically significant different risks of severe hypoglycaemia.

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Loss of awareness of hypoglycaemia is by far the most important known risk factor for severe hypoglycaemia in type 1 diabetes [1]. Identifying persons with loss of awareness is essential to instigating measures to reduce the consequences or restore awareness. Several clinical tools have been developed for assessment of awareness and in type 1 diabetes, three tools have been validated and used more widely in research and clinical practice [2-4].

The Gold score from 1994 was the first published method classifying people with type 1 diabetes by their answer to a single question (“Do you know when your hypos are commencing?”) as having a normal or an impaired awareness [2]. Patients with impaired awareness have an almost six-fold higher risk of severe hypoglycaemia than the group with normal awareness.

The Clarke method, published in 1995, uses an eight-item questionnaire (including previous experience of severe hypoglycaemia) that classifies patients as having a normal or a reduced awareness [3]. A gray-zone score leaves patients as unclassifiable, accounting for 10-20% in cohort studies. Patients with a reduced awareness have a three-fold higher risk of severe hypoglycaemia than those with a normal awareness.

The third method developed by our group (and referred to as the Pedersen-Bjergaard or the Hillerød method) was published in 2003 [4]. The rationale for developing an additional tool was the general clinical experience that awareness is not an all-or-none phenomenon, i.e., many patients seem to develop partial reduction of awareness, even if this does not result in an increased risk of severe hypoglycaemia as compared to the general population with type 1 diabetes. Our method is based on a single question “Can you feel when your blood sugar is low?” with the possible answers “always”, “usually”, “occasionally” or “never” (and “don’t know”). The method classifies people into three groups: normal awareness (“always”), impaired awareness (“usually”) and unawareness (“occasionally” or “never”). In our original paper, those with impaired awareness prospectively reported a more than five-fold and those with unawareness an almost ten-fold higher rate of severe hypoglycaemia than those in the group with normal awareness [4]. Our method has subsequently been used in many studies on people with type 1 diabetes in various countries and languages [5-8], basically confirming this result; and the Pedersen-Bjergaard method is recommended in the Danish National Guidelines on Treatment of Type 1 Diabetes [9].

During the years, confusion has surrounded the interpretation of our awareness classes [10, 11]. The reasons for this are that our classification operates with three classes in contrast to the others which are bimodal, and that we use of the term “impaired awareness” to describe the intermediate group. Thus, comparisons have, in some instances, been made between our pooled impaired and unawareness groups and the impaired/reduced groups of the Gold/Clarke methods [10]. The relevant comparison, however, is with our unaware class [8]. We have, therefore, updated the Pedersen-Bjergaard classification by renaming our intermediate group to “intermediate” instead of “impaired”.

Here, we present a comparison of our updated classification with the Gold and the Clarke classifications in a type 1 diabetic cohort in terms of prevalence of loss of awareness and rates of severe hypoglycaemia.

METHODS

A total of 416 outpatients at Nordsjællands Hospital Hillerød, Denmark, were invited to participate in the study. Following written informed consent, 325 adult people with type 1 diabetes for more than one year were recruited. Type 1 diabetes was defined by insulin treatment from the time of diagnosis and a random C-peptide level below 300 pmol/l at a venous blood glucose concentration ≤ 12 mmol/l or a C-peptide level below 600 pmol/l at a venous blood glucose concentration >12 mmol/l. Pregnant women and individuals with significant comorbidities were excluded from participation. Data on history of diabetes, insulin therapy, concomitant medication and late diabetic complications were extracted from the medical records (Table 1). Baseline blood samples were drawn in the non-fasted condition for measurement of C-peptide, HbA_{1c} and routine biochemistry. Patients completed a questionnaire based on previously used and validated questions. Hypoglycaemia awareness was self-estimated using the three methods: Gold, Clarke and Pedersen-Bjergaard scores [2, 3, 4]. The Gold and Clarke methods were applied as described in the original publications [2, 3]. The Pedersen-Bjergaard classification was updated as described in the introduction. The rate of severe hypoglycaemia (defined by need for third party assistance to actively administer carbohydrate or glucagon) was based on one-year recall [12]. The study was approved by the Committee on Biomedical Ethics of the Capital Region of Denmark (H-4-2011-043) and the Danish Data Protection Agency (2012-58-0004).

TABLE 1 Demographics and clinical characteristics (N = 325).

Women, n (%)	129 (40)
Age, mean \pm SD, yrs	52.4 \pm 13.9
Duration of diabetes, mean \pm SD, yrs	23.1 \pm 14.2
Retinopathy, n (%)	153 (47)
Nephropathy, n (%)	41 (13)
BMI, mean \pm SD, kg/m ²	25.5 \pm 4.0
Hypertension, n (%)	80 (25)
HbA _{1c} , mean \pm SD, %	7.8 \pm 1.0
HbA _{1c} , mean \pm SD, mmol/mol	62 \pm 11
C-peptide negative, n (%)	245 (75)
Severe hypoglycaemia in preceding yr, n (%)	71 (22)
Rate of severe hypoglycaemia, episodes/patient-yr (range)	0.62 (0-15)

SD = standard deviation.

Laboratory tests

HbA_{1c} was measured by a Tosoh G8 HPLC Analyzer, Tosoh Bioscience Inc., San Francisco, CA, and C-peptide concentration by AutoDELFIA, Wallac Oy, Turku, Finland. Patients were classified as C-peptide-negative when the C-peptide concentration was below the detection limit of 10 pmol/l.

Statistics

Standard descriptive and comparative statistics were used. The term “loss of awareness” was used for the comparison between the unawareness group according to the Pedersen-Bjergaard classification, the impaired awareness group according to the Gold classification and the reduced awareness group according to the Clarke classification.

Trial registration: not relevant.

RESULTS

Prevalence of awareness classes

A total of 43%, 76% and 74% of patients were classified with normal awareness according to the Pedersen-Bjergaard method, the Gold method, and the Clarke method, respectively (**Table 2**), whereas 14%, 24% and 17% were classified as having loss of awareness with our method, the Gold method, and the Clarke method, respectively. A total of 43% were classified with intermediate awareness with our method and 9% were unclassifiable according to the Clarke method.

TABLE 2 Classification of hypoglycaemia awareness in a cohort of 325 type 1 diabetic patients using the updated Pedersen-Bjergaard classification and the Gold and Clarke classifications [10]. Prevalence of awareness classes and reporting of severe hypoglycaemia by class.

	Class of hypoglycaemia awareness		
	normal	intermediate ^a / unclassifiable ^b	unaware ^a / impaired ^c / reduced ^b
<i>Patients in class, n (%)^d</i>			
Updated Pedersen-Bjergaard	140 (43)	138 (43)	44 (14)
Gold	240 (76)	-	75 (24)
Clarke	227 (74)	30 (9)	52 (17)
<i>Reporting of severe hypoglycaemia</i>			
Prevalence, %:			
Updated Pedersen-Bjergaard	10	28	48
Gold	18	-	41
Clarke	15	38	52
Relative risk ^e :			
Updated Pedersen-Bjergaard	-	2.8	4.8
Gold	-	-	2.3
Clarke	-	2.5	3.5
Rate, mean (range) episodes/yr:			
Updated Pedersen-Bjergaard	0.30 (0-14)	0.57 (0-10)	1.71 (0-12)
Gold	0.42 (0-14)	-	1.21 (0-12)
Clarke	0.36 (0-14)	0.50 (0-3)	1.71 (0-12)
Relative rate ^e :			
Updated Pedersen-Bjergaard	-	1.9	5.7
Gold	-	-	2.9
Clarke	-	1.4	4.8

a) According to the updated Pedersen-Bjergaard method.

b) According to the Clarke method.

c) According to the Gold method.

d) Missing data: Pedersen-Bjergaard (n = 3), Gold (n = 10), Clarke (n = 16).

e) Compared with normal awareness.

Agreement between methods

35% of patients classified with loss of awareness by at least one method had loss of awareness according to all three methods, and a further 24% agreed between two of the methods, leaving 41% of the cases to be classified with loss of awareness only by one method (Figure 1). Good agreement was recorded between our and the other methods (Table 3 and Figure 1). Thus, 64% of patients classified with unawareness according to the Pedersen-Bjergaard method had loss of awareness according to both the Gold and the Clarke methods (Figure 1). In comparison, 38% and 50% of those classified with impaired/reduced awareness with the Gold and the Clarke methods, respectively, had loss of awareness by all methods.

FIGURE 1 Agreement in classification of 89 patients with loss of hypoglycaemia awareness according to at least one method.

A. The columns show for each method the number of patients with agreement between all methods, the number with agreement with one of the other methods and the number without agreement with any of the other methods. **B.** Venn diagram showing the detailed agreement between the three methods. Values are number of patients.

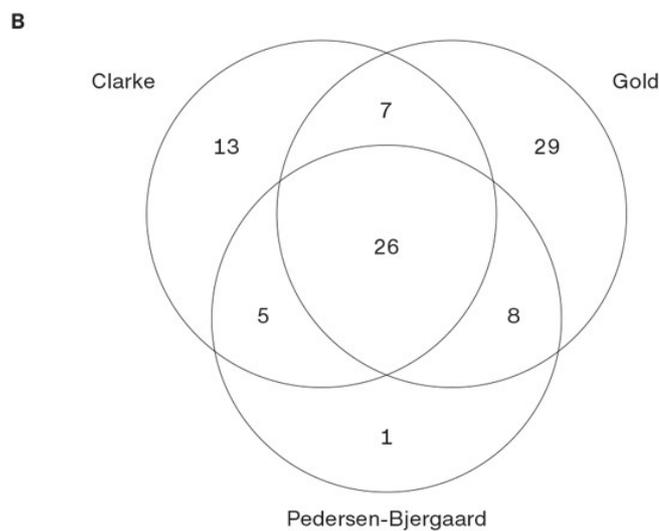
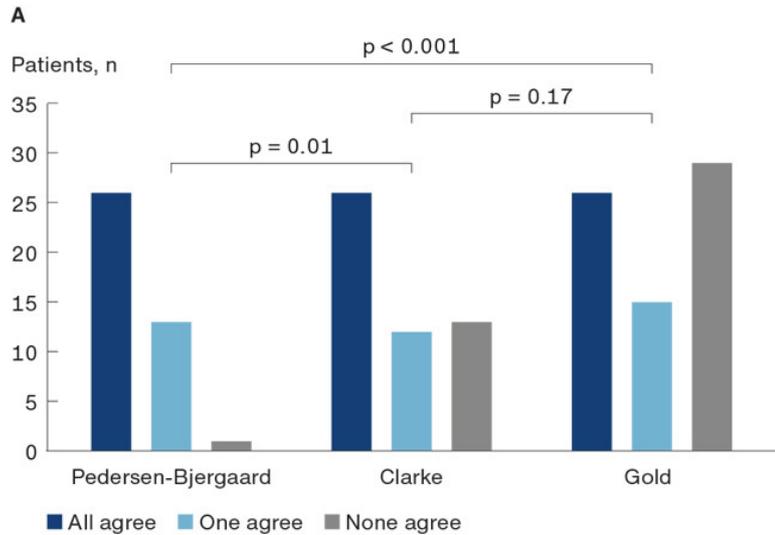


TABLE 3 Agreement in classification of hypoglycaemia awareness in a cohort of 325 type 1 diabetic patients using the updated Pedersen-Bjergaard classification and the Gold and Clarke classifications. The values are number of patients^a.

	Updated Pedersen-Bjergaard classification of hypoglycaemia awareness		
	normal (N _n = 135)	intermediate (N _i = 129)	unawareness (N _u = 40)
Normal with Gold and Clarke	125	71	0
Impaired (Gold) and reduced (Clarke)	0	7	26
<i>Gold</i>			
Normal	127	101	6
Impaired	8	28	34
<i>Clarke</i>			
Normal	133	89	1
Unclassifiable	2	20	8
Reduced	0	20	31

a) Missing data: Pedersen-Bjergaard (n = 3), Gold (n = 10), Clarke (n = 16).

Only one patient classified as unaware by the Pedersen-Bjergaard method was not impaired/reduced by at least one of the other methods (Figure 1). For comparison, 29 patients classified with impaired awareness by the Gold method were not classified as unaware/reduced according to our method or the Clarke method, whereas 13 patients classified with reduced awareness by the Clarke method were not classified as unaware/impaired according to our method or the Gold method.

Risk of severe hypoglycaemia

Severe hypoglycaemia in the preceding year was reported by 23.7% of the patients with a mean rate of 0.62 episodes per patient year (Table 1). All three classifications identified groups of patients with a clinically significantly increased prevalence and rate of hypoglycaemia as compared with those with normal awareness (Table 2). No significant differences were found between the methods in prevalence of severe hypoglycaemia in the groups with loss of awareness. The relative rates of severe hypoglycaemia compared with normal awareness was 1.9 and 5.7 in the groups with intermediate and unawareness by the Pedersen-Bjergaard method, respectively. A relative rate of 2.9 was found in patients with impaired awareness according to the Gold method and of 4.8 in patients with reduced awareness according to the Clarke method, respectively, when compared with normal awareness.

The prevalence of severe hypoglycaemia was lower in the group with normal awareness according to the Pedersen-Bjergaard method than according to the Gold method ($\chi^2 = 5.0$; $p = 0.024$), but not according to the Clarke score ($\chi^2 = 1.9$; $p = 0.17$).

DISCUSSION

This study shows that the updated version of the Pedersen-Bjergaard classification of awareness of hypoglycaemia works in terms of agreement with the Clarke and Gold classifications in identification of patients with loss of awareness and of patients at increased risk of severe hypoglycaemia. Both regarding the fraction of

patients identified with loss of awareness and risk of severe hypoglycaemia, the Pedersen-Bjergaard classification was closer to the Clarke classification than to the Gold method. The Gold method identified more patients with loss of awareness, and the rate of severe hypoglycaemia in this group was numerically lower than with the Pedersen-Bjergaard and the Clarke classifications, suggesting a lower specificity of the Gold classification.

The important difference between the Pedersen-Bjergaard method and the Gold and Clarke method remains the three classes, reflecting that loss of awareness probably develops gradually and may become clinically important already at an earlier disease stage, just like many other diabetic complications, thereby enabling further differentiation in risk of severe hypoglycaemia. Thus, previous studies using our classification in unselected type 1 diabetic cohorts have consistently shown that 40-50% of patients are classified as having a normal awareness with a very low risk (0.1-0.4 episodes of severe hypoglycaemia per patient-year), 40-50% as having an intermediate (previously termed impaired) awareness with an intermediate (but already two- to eight-fold increased) risk and 10-15% as having unawareness with a high (seven- to 21-fold increased) risk of severe hypoglycaemia [5-7, 9]. Furthermore, the rate of severe hypoglycaemia in the intermediate group has consistently fallen close to the mean rate in the cohorts, which was also the case in the present study. The intermediate group in the Pedersen-Bjergaard classification also explains why the risk of hypoglycaemia in the group with normal awareness tended to be lower than in the other classifications.

The three different awareness classes in the Pedersen-Bjergaard classification provide benefit both in daily clinical practice and in research. Clinically, patients at an increased risk of severe hypoglycaemia who are in need of special attention can be identified and offered educational interventions [13, 14] aimed at restoring awareness or provision of artificial awareness in terms of continuous glucose monitoring (CGM) systems with alarm features [15]. Ultimately, hybrid closed-loop systems that can trigger an alarm and automatically reduce insulin infusion when hypoglycaemia is predicted may help these people [16]. Also, patients at a particularly low risk of severe hypoglycaemia who may be candidates for tighter glycaemic control if needed to avoid progression of microvascular complications can be identified. In a research context, studies exploring, e.g., the pathophysiology of loss of awareness may gain considerable additional power using a control group with the opposite phenotype – best possible awareness.

The Gold and the Pedersen-Bjergaard classifications are both based on the answer to a single question and as such they are easy to implement in clinical practice. This contrasts with the eight-item Clarke score. However, the Clarke score does not seem to provide more information than the other methods. Even the fact that one of the items in the Clarke score is occurrence of severe hypoglycaemia in the preceding year did not provide an advantage for the Clarke score in terms of association with severe hypoglycaemia in the preceding year.

All three methods have been validated in hyperinsulinaemic hypoglycaemic clamp studies showing that patients with loss of awareness have reduced sympathoadrenal counterregulatory responses and blunted warning symptoms compared with patients with normal awareness [17]. Patients with loss of awareness according to all three methods less frequently reported autonomic symptoms as their main warning symptoms [8] and a lower glucose level as the threshold for perception of warning symptoms [8]. Furthermore, studies using CGM have shown that patients with loss of awareness are more prone to asymptomatic hypoglycaemic events than patients who declare normal awareness [18].

The strengths of this study are the use of validated questionnaires and a high inclusion rate. The major weakness is the lack of an objective gold standard measurement of awareness. Except for the very cumbersome recording of warning symptoms generated during a hypoglycaemic clamp, such a method has still to be developed. Furthermore, the real value of an awareness classification is prediction of future risk of severe hypoglycaemia, which we cannot identify from this retrospective study. However, the general impression from the literature is

that retrospective associations with and prospective prediction of severe hypoglycaemia are rather consistent between the methods.

CONCLUSION

The revised version of the Pedersen-Bjergaard classification for hypoglycaemia awareness and the Gold and Clarke classifications – all based on a self-reported perception of the ability to feel hypoglycaemic warning symptoms – identified people with loss of awareness with reasonably high degree of concordance. The Pedersen-Bjergaard method, in contrast to the others, identified groups with a normal and an intermediate awareness with clinically significantly different risks of severe hypoglycaemia.

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