



Hypoglycaemia Unawareness in Long-Standing Type 1 Diabetes: A Narrative Review of Restoring Awareness

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Abstract

Losing the warning symptoms of hypoglycaemia is among the more dangerous developments in long-standing type 1 diabetes, and it is identified in clinic by questionnaire. How many people have it depends heavily on which questionnaire is used: applied to the same cohort, the Gold, Clarke and Pedersen-Bjergaard instruments classified 33.3, 43.7 and 77.0 per cent respectively as having impaired awareness. All three identify a group at real risk, with reported increases in severe hypoglycaemia of six-fold, 4.63-fold and 5.83-fold. The difficulty is what they miss. In a contemporary cohort of 782 adults, 49 per cent of those who reported a severe episode had a Gold score below the impairment threshold, and the score achieved a sensitivity of 51 per cent for classifying risk. Impaired awareness is also associated with socioeconomic deprivation and with a positive depression screen, so it is not a purely physiological finding. This review sets out the physiology, the measurement problem, what technology has changed, and why a reassuring questionnaire should not end the conversation.

Keywords: Type 1 diabetes; Impaired awareness of hypoglycaemia; Gold score; Severe hypoglycaemia; Continuous glucose monitoring

Introduction

Hypoglycaemia is the limiting factor in the glycaemic management of type 1 diabetes [1,2]. Injected insulin cannot reproduce the profile of endogenous secretion, which produces relative insulin excess at inappropriate times, and repeated exposure to low glucose blunts the counter-regulatory hormone response [2,3].

The clinical consequence is impaired awareness of hypoglycaemia, in which the adrenergic warning symptoms that would normally prompt treatment are diminished, delayed or absent [4,5]. Because each episode further blunts the response to the next, the process is self-reinforcing (Figure 6) [3,6].

Impaired awareness is reported to affect 20 to 40 per cent of adults with type 1 diabetes and to increase the risk of severe hypoglycaemia, meaning an episode requiring assistance from another person, approximately six-fold [4,7,8,30]. Reporting conventions for both the glucose threshold and the episode itself

have needed formal agreement [28,34]. This review examines how that figure is arrived at, and how much confidence the underlying measurement supports.

Eligibility: Studies were included if they reported the prevalence of impaired awareness using a defined instrument, related awareness status to severe hypoglycaemia, or evaluated an intervention intended to restore awareness. Studies using non-standard thresholds are included and the deviation is stated.

Table 1: Instruments applied to the same cohort, with prevalence and associated risk as reported [15]

Material and Methods

Search strategy: PubMed and the archives of the major diabetes, endocrinology and diabetes technology journals were searched for studies of awareness of hypoglycaemia in type 1 diabetes. Search terms combined impaired awareness of hypoglycaemia and hypoglycaemia unawareness with Gold score, Clarke score, severe hypoglycaemia, continuous glucose monitoring, closed loop and restoration of awareness. Reference lists of systematic reviews [9,10] were screened by hand for primary sources.

Data extraction and handling: Design, cohort, the instrument used, its threshold and the reported estimate were extracted as published. The instrument is reported alongside every prevalence figure, because the instruments are not interchangeable and the choice changes the answer by a factor of more than two in the same population. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The physiology: Recurrent hypoglycaemia reduces the adrenaline and symptom response to subsequent episodes, a process described as hypoglycaemia-associated autonomic failure. Reduced symptoms permit deeper and more frequent hypoglycaemia, which further blunts the response (Figure 6) [3,6,11]. The cycle is at least partly reversible: scrupulous avoidance of hypoglycaemia can restore awareness [3,9,12].

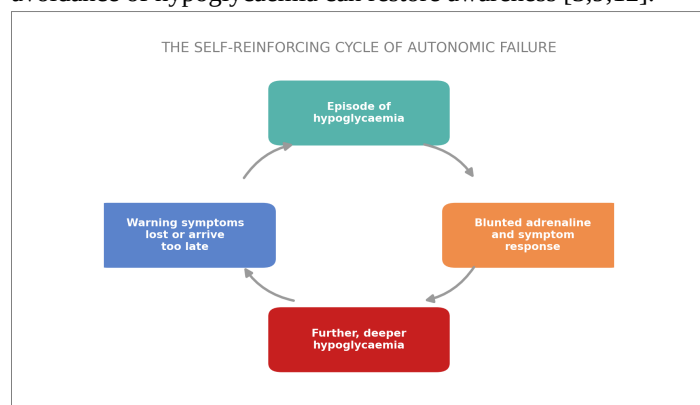


Figure 6: The self-reinforcing cycle of hypoglycaemia-associated autonomic failure [3,6,11]

How prevalence depends on the instrument: Three validated instruments are in common use. The Gold score asks a single question answered on a seven-point scale, with 4 or more indicating impairment; the Clarke score comprises eight questions scored 0 to 8, again with 4 or more indicating impairment; the Pedersen-Bjergaard questionnaire classifies awareness separately [4,13,14]. Applied to the same cohort of adults using continuous glucose monitoring, they classified 33.3, 43.7 and 77.0 per cent respectively as having impaired or abnormal awareness (Figure 1) [15].

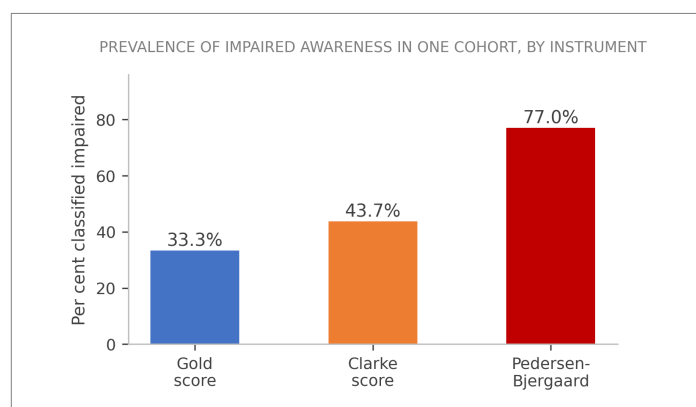


Figure 1: Prevalence of impaired awareness in one cohort measured by three instruments [15]

All three identify real risk: In that cohort, 24.5 per cent of participants using continuous glucose monitoring for more than six months reported at least one severe episode in the preceding six months. Impairment identified by the Gold, Clarke and Pedersen-Bjergaard instruments was associated with six-fold, 4.63-fold and 5.83-fold increases in the risk of severe hypoglycaemia respectively, with p values of 0.001, 0.004 and 0.013 (Figure 2) [15].

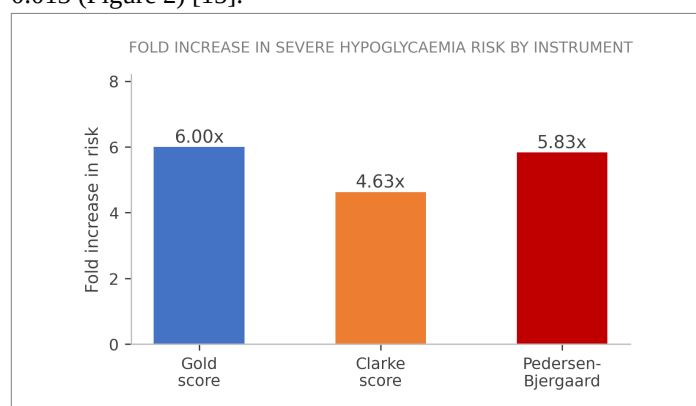


Figure 2: Reported fold increase in severe hypoglycaemia risk by instrument [15]

What the questionnaire misses: A cross-sectional survey of 782 adults, of whom 89 per cent used continuous glucose monitoring, found 21 per cent had impaired awareness by Gold score and 5.3 per cent reported a recent severe episode. Severe hypoglycaemia was reported by 3.0 per cent of those with a Gold score below 4 against 12 per cent of those scoring 4 or above, and by 4.0 per cent of those with a hypoglycaemia detection threshold of 3.0 mM or above against 16 per cent of those below it (Figure 4) [16]. The critical figure is the converse: 49 per cent of people who reported severe hypoglycaemia had a Gold score below 4, and the score had a sensitivity of 51 per cent and specificity of 80 per cent for classifying severe hypoglycaemia risk (Figure 3) [16].

Table 2: Factors independently associated with impaired awareness and severe hypoglycaemia [16]

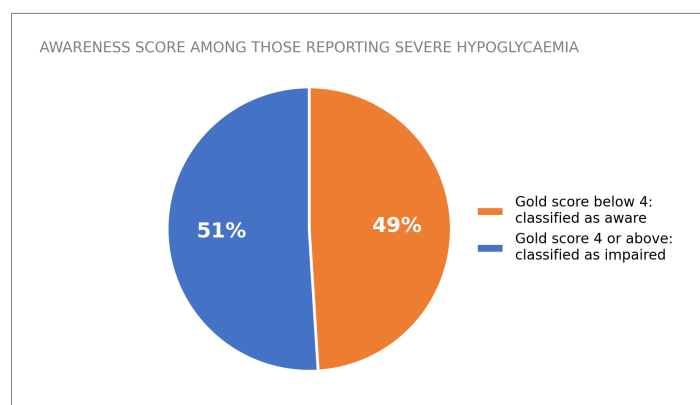


Figure 3: Awareness score among people reporting severe hypoglycaemia [16]

Read together, the two panels describe the same limitation from opposite directions: the questionnaire identifies a group at genuinely raised risk, and it leaves behind a group of similar size whose risk it did not detect. A screening tool with those properties supports escalation when positive but cannot license reassurance when negative [16].

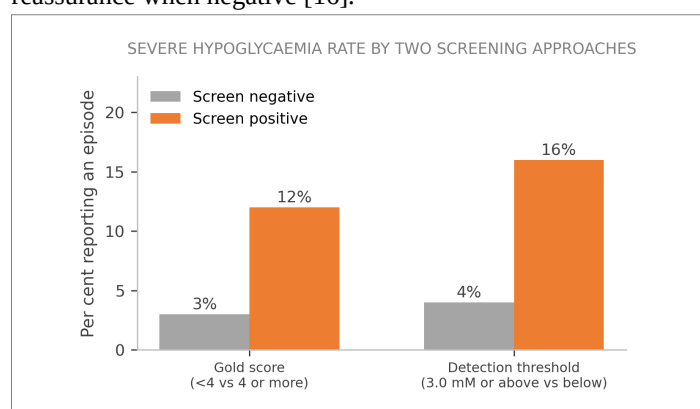


Figure 4: Severe hypoglycaemia rate by two screening approaches [16]

Instrument	Threshold	Prevalence in one cohort	Risk increase
Gold score	4 or more of 7	33.3%	6.00-fold
Clarke score	4 or more of 8	43.7%	4.63-fold
Pedersen-Bjergaard	Classified unaware	77.0%	5.83-fold

Associations beyond physiology: Impaired awareness by Gold score was independently associated with socioeconomic deprivation (OR 1.9, $p = 0.002$), female sex (OR 1.8, $p = 0.002$) and a positive depression screen (OR 2.1, $p = 0.007$). A hypoglycaemia detection threshold below 3.0 mM was associated with older age and with a positive depression screen (OR 2.7, $p < 0.001$), while severe hypoglycaemia itself was associated with greater glucose variability, a positive anxiety screen (OR 3.0, $p = 0.031$) and a low detection threshold (OR 6.7, $p < 0.001$) [16]. In a separate tertiary clinic cohort of 189 adults with median diabetes duration of 19.3 years, 17.5 per cent had impaired awareness and deprivation was again associated with both impairment and severe hypoglycaemia [17].

Factor	Association	Reported estimate
Socioeconomic deprivation	Impaired awareness	OR 1.9, $p = 0.002$
Female sex	Impaired awareness	OR 1.8, $p = 0.002$
Positive depression screen	Impaired awareness	OR 2.1, $p = 0.007$
Positive anxiety screen	Severe hypoglycaemia	OR 3.0, $p = 0.031$
Detection threshold below 3.0 mM	Severe hypoglycaemia	OR 6.7, $p < 0.001$

What technology has changed: Continuous glucose monitoring reduced the prevalence of impaired awareness by Gold score from 28.1 to 18.1 per cent in one follow-up, with restoration more likely in those with shorter diabetes duration. A prospective cohort starting intermittently scanned monitoring in 60 adults reported a 47 per cent reduction in impairment by Clarke score, and a Spanish cohort starting hybrid closed-loop therapy reported prevalence falling from 27 to 7 per cent, though using a non-standard Clarke threshold of 3 or more (Figure 5) [10,18,19]. Structured education and optimised delivery have randomised support [9,20,31]. Real-time monitoring has randomised support in those with impaired awareness [21], psychological approaches have been trialled where hypoglycaemia persists despite optimised self-care [23], and monitoring-led avoidance has restored counter-regulation directly [32].

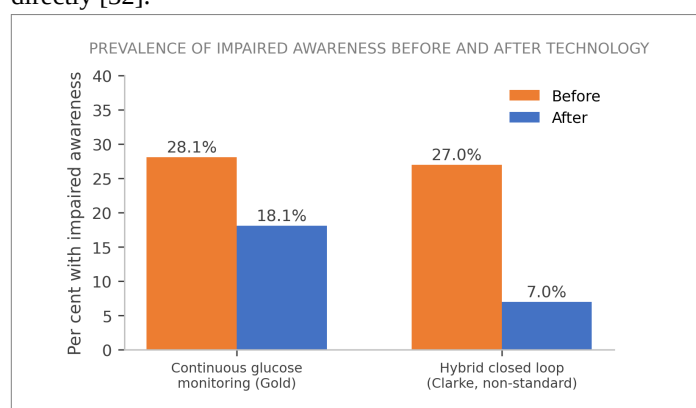


Figure 5: Prevalence of impaired awareness before and after technology [10,18,19]

Study	Design and cohort	Principal reported finding
CGM cohort study [15]	Adults using CGM, three instruments	Prevalence 33.3%, 43.7% and 77.0% in the same people
Contemporary survey [16]	782 adults, 89% CGM users	49% of those with severe hypoglycaemia scored below threshold
Tertiary clinic survey [17]	189 adults, median duration 19.3 years	17.5% impaired; deprivation associated with both outcomes
Technology review [10]	Review of technological interventions	Gold-defined impairment 28.1% to 18.1%
Yeoh et al. 2015 [9]	Systematic review and meta-analysis	Interventions can restore awareness
HypoCOMPaSS [20]	Randomised trial	Optimised delivery with education reduced severe episodes

Table 3: Principal studies reviewed, with the finding as reported by the original investigators

Restoring awareness: The condition is not fixed. Systematic review and meta-analysis of interventions concluded that awareness can be restored, most reliably through scrupulous avoidance of hypoglycaemia supported by education and optimised insulin delivery [9,12]. Randomised trials combining structured education with technology have reduced severe episodes in people with established impairment [20,21], and a psychological intervention aimed at the beliefs that sustain hypoglycaemia risk has been trialled in those for whom optimised self-care alone had failed [23]. Recovery is more likely in those with shorter diabetes duration, which argues for identifying the problem early rather than at the point of crisis [10,12].

What the detection threshold adds: Asking at what glucose concentration a person first notices symptoms may be more informative than asking whether they notice at all. A threshold below 3.0 mmol/L was reported in 10 per cent of one cohort and carried an odds ratio of 6.7 for severe hypoglycaemia, higher than the Gold score achieved in the same analysis [16]. It is a single question, it maps directly onto the physiology, and it is not part of either standard instrument [16,28].

Discussion

The instrument problem is the finding that should change practice. When three validated questionnaires are applied to one group of people and return 33.3, 43.7 and 77.0 per cent, the quantity being measured is not the same across them [15]. Any statement that impaired awareness affects a given proportion of people with type 1 diabetes is therefore incomplete without naming the instrument, and the widely quoted range of 20 to 40 per cent conceals this rather than expressing it.

More consequential for an individual patient is sensitivity. Half of the people who reported a severe episode requiring another person's help had a Gold score below the impairment threshold, and the score's sensitivity for severe hypoglycaemia risk was 51 per cent [16]. A clinician who screens with a single question and is reassured by a low score has excluded very little. That does not make the instrument useless: specificity was 80 per cent, so a high score is informative. It means the test is better at ruling in than ruling out, and it is frequently used as though the reverse were true.

There is also a measurement artefact worth naming in the intervention literature. The Clarke score counts exposure to severe episodes among its eight items, so an intervention that reduces the frequency of severe hypoglycaemia will mechanically improve the Clarke score whether or not symptomatic awareness has returned [10,15]. Reported falls in Clarke-defined impairment after starting new technology should be read with that in mind, particularly where a non-standard threshold has also been used [19]. Where clamp studies have looked directly at the adrenaline response, improvement has not always followed [10].

Finally, the associations with deprivation, depression and anxiety indicate that this is not a purely physiological phenomenon [16,17]. Some of that is plausibly causal in both directions: living with unpredictable severe hypoglycaemia is frightening, and fear of hypoglycaemia alters behaviour [24,25]. Severe hypoglycaemia also carries cardiovascular associations of its own [29], and autonomic dysfunction is implicated more broadly [33]. Some of it is likely to reflect access to technology, structured education and specialist review, none of which is evenly distributed [22,26,27]. A model of impaired awareness that is purely about counter-regulatory physiology will not explain why deprivation nearly doubles the odds.

A practical consequence follows from the sensitivity figure. If half of those who go on to have a severe episode screen as aware, then awareness scoring cannot be the only gate to escalation of care, technology or specialist referral [16]. Continuous glucose monitoring data offer a partial alternative, since time below 3.0 mmol/L and glucose variability are measured rather than recalled, and both were associated with risk in the cohorts reviewed here [15,16,32]. Combining a questionnaire with objective data is likely to outperform either alone, though no risk model of that kind has been prospectively validated [16].

The deprivation finding deserves a last word. Impaired awareness was independently associated with socioeconomic deprivation after adjustment, and so was severe hypoglycaemia [16,17]. Counter-regulatory physiology does not vary by income. What plausibly varies is access to continuous monitoring, to structured education and to specialist review, together with the ability to eat regularly and to take time off when unwell. Treating this as a purely biological phenomenon obscures the part of it that is a service-delivery problem [17,22,26].

Study limitations

The limitations belong to the underlying literature. Prevalence estimates derive from instruments that disagree substantially with one another, and no reference standard exists against which to adjudicate between them [15]. Severe hypoglycaemia is self-reported and subject to recall over six or twelve months, in a population that by definition may not have been aware of the episodes [16,17]. Survey cohorts are older, have longer diabetes duration, lower deprivation and higher technology use than non-responders, so they are not representative [16]. Intervention cohorts are small, frequently uncontrolled, and several use non-standard thresholds [19]. The Clarke score responds mechanically to changes in severe hypoglycaemia frequency, which confounds its use as an outcome measure [10]. Clamp-based physiological confirmation is rarely performed [10]. And the evidence is drawn almost entirely from specialist clinics in high-income countries with routine access to continuous glucose monitoring [15,16].

Conclusion

Impaired awareness of hypoglycaemia is common in long-standing type 1 diabetes and carries a substantially increased risk of episodes requiring another person's help. How common depends on which questionnaire is administered, to a degree that makes any single prevalence figure unreliable without its instrument attached. The more important point for the clinic is that roughly half of the people who go on to report a severe episode screen as aware, so a reassuring score is weak evidence of safety. The instruments are useful for identifying risk when positive and poor at excluding it when negative, and the associations with deprivation and with mood suggest that what they capture is not only a failure of adrenaline.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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