International Journal of Community Medicine and Public Health
Abdullah MY et al. Int J Community Med Public Health. 2025 Feb;12(2):1054-1060
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20250066

Review Article

Hypoglycemia awareness and its clinical implications in insulin-treated patients

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Received: 02 January 2025
Accepted: 21 January 2025

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ABSTRACT

Hypoglycemia is a significant complication of diabetes treatment. If left untreated, serious complications may occur. Mild hypoglycemia occurs in approximately 30% to 40% of those with insulin-treated type 2 diabetes. Overall prevalence of severe hypoglycemia in insulin-treated type 2 diabetes is 0.28 episodes per patient per year. Impaired awareness of hypoglycemia (IAH) is a possible complication of recurrent hypoglycemia episodes. Many prior studies have examined the prevalence of IAH in patients with type 1 diabetes, while there is limited data on the prevalence of IAH in insulin-treated type 2 diabetes. The following databases were used in systematic research: Medline (PubMed), Web of Science, and Scopus. Summaries of the found studies were exported by EndNoteX8, and duplicate studies were removed. Various mechanisms have been proposed in recent studies, such as the brain glucose transport hypothesis and the brain glycogen supercompensation hypothesis. It is important to assess the risk factors of IAH to avoid its significant complications. To successfully assess the risk factors, three methods of measuring are being used: Clarke, Gold, and Pedersen Bjergaard methods. The aim of this review is to discuss the prevalence, mechanisms, measurement, and clinical implications of IAH in insulin-treated type 2 diabetic patients.

Keywords: Hypoglycemia, IAH, Type 2 diabetes mellitus, Clinical implications

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is estimated to affect 438 million people globally by the year 2030.[1] Hypoglycemia is a complication of diabetes treatment, and if hypoglycemia is severe and left untreated, many complications may occur, such as impaired cognitive function, vascular injury, severe cardiac arrhythmia, temporary focal deficits, and death.[2] The prevalence of hypoglycemic events in insulin-treated type 2 diabetes patients varies widely. It is determined by both the duration and intensity of treatment. Mild hypoglycemia occurs in approximately 30% to 40% of those with insulin-treated type 2 diabetes.[3] Studies reported that the prevalence of hypoglycemia in patients with type 2 diabetes treated with oral anti-hyperglycemic agents could reach 50%, as indicated by findings from Argentina, and 42.2%, based on data from Romania.[4,5]

Patients with T2DM treated with insulin for <2 years typically experience an average of four non-severe episodes annually, whereas those treated for over five years' experience an average of 10 episodes per year.[6] In addition, in the early years after the start of insulin therapy, severe hypoglycemia, which is an event requiring external help to recover, is uncommon. However, it becomes more common during later years.[7] The overall prevalence of severe hypoglycemia in insulin-treated T2DM patients in secondary care was estimated to be 0.28 episodes per patient per year.[8] One of the complications of hypoglycemia is impaired awareness of hypoglycemia (IAH). IAH is the reduced ability to detect the onset of hypoglycemia. It increases the risk of severe hypoglycemia by more than fivefold.[9] IAH is associated with recurrent hypoglycemia, and various mechanisms have been discussed lately, such as counterregulatory failure, cerebral adaptations, and habituation to hypoglycemia. IAH can lead to various adverse events, such as motor vehicle crashes and falls.[10]

Numerous prior studies have examined the prevalence of IAH in patients with type 1 diabetes, revealing moderate variability, with a prevalence of 20% to 25%.[11] In contrast, there is limited data on the prevalence of IAH in type 2 diabetes; however, various single-center surveys have addressed this subject lately.[12,13] Different factors can affect IAH in type 2 diabetes including duration of diabetes, duration of therapy, type of therapy, age, BMI and others. Three measurement methods have been widely used to assess IAH: Gold, Clarke, and Pedersen Bjergaard methods.[14-16] Although these tools were initially designed to assess hypoglycemia awareness in patients with type 1 diabetes, their application in type 2 diabetes patients has not been extensively studied. The aim of this review is to discuss the prevalence, mechanisms, measurement, and clinical implications of IAH in insulin-treated type 2 diabetic patients.

METHODS

The following databases were used in systematic research: Medline (PubMed), Web of Science, and Scopus till December 28, 2024. The MeSH database was used to retrieve the synonyms of the search strategy. Search terms were then combined by ("AND" and "OR") Boolean operators according to the Cochrane Handbook for Systematic Reviews of Interventions as follows: "hypoglycemia awareness" or "hypoglycemia unawareness" or "impaired awareness hypoglycemia" or "awareness of hypoglycemia" or "unawareness of hypoglycemia" and "type 2 diabetes mellitus" or "insulin-treated type 2 diabetes" or "type 2 diabetes treated with insulin" or "insulin-treated patients".[17] Summaries of the found studies were exported by EndNote X8, and duplicate studies were removed. Any study that discusses hypoglycemia awareness/unawareness in insulin-treated type 2 diabetic patients and is published in peer-reviewed journals was included with the inclusion of full-text articles, abstracts, and case series with the related topics included. All languages are included. Animal studies, case reports, letters, and comments were excluded.

DISCUSSION

Mechanism of IAH

A counter-regulatory response occurs in response to hypoglycemia. It includes inhibiting insulin secretion and activation of hormones such as glucagon, cortisol, catecholamines, and growth hormone. This stimulates the hepatic production of glucose and reduces glucose utilization by tissues. When blood glucose level decreases, the autonomic nervous system activates, leading to various symptoms such as sweating, tremors, palpitations, and hunger. The recognition of these symptoms is called hypoglycemia awareness.[18] The failure in reduction of insulin and an increase in glucagon and other hormone secretion leads to a failure in the counter-regulatory response, which in turn leads to IAH. Furthermore, the weak response of the sympathoadrenal activity enhances the condition. Recurrent hypoglycemia episodes lead to the maintenance of IAH.[19,20]

During a hypoglycemia episode, catecholamines play a role centrally by regulating the response to hypoglycemia and play a role peripherally by maintaining blood glucose levels. Recurrent hypoglycemia episodes lead to a blunted catecholamine response in subsequent episodes.[18] A study demonstrated that intravenous infusion of adrenergic blockers during a hypoglycemia episode can prevent counter-regulatory failure in the following episode.[21] However, catecholamines can't be used as a protective pharmacologic treatment against subsequent hypoglycemia episodes, as their influence in the peripheries will increase the severity of hypoglycemia. Selective adrenergic receptor modulators that work centrally without affecting beneficial peripheral effects of the sympathoadrenal response need to be developed.[18]

Another hypothesis is the brain glucose transport or glucose metabolism hypothesis. This hypothesis demonstrates the effect of changes in the uptake of glucose by the brain on hypoglycemia awareness. Brain regions such as the bilateral ventral striatum, the subthalamic area, and the left amygdala show increased uptake of glucose analogues such as fluorodeoxyglucose (FDG) during hypoglycemia in patients with hypoglycemia awareness.[22] On the other hand, patients with IAH show a remarkable reduction in glucose uptake, which may lead to an attenuated counter-regulatory response.[23] This reduction can be explained by a habituation to frequent hypoglycemia occurring in IAH patients, which means that the brain adjusts to recurrent episodes and reduces the hormonal and behavioral responses to low glucose levels.

In type 1 DM patients with IAH, a correlation between thalamic activation and the epinephrine response during hypoglycemia was found.[24] A reduced blood flow in the thalamus and hypothalamus was recorded during

hypoglycemia in this type of patient, which may impair glucose sensing, confirming the role of the thalamus in coordinating the body's counter-regulatory response to hypoglycemia.[24] In summary, recurrent hypoglycemia contributes to IAH by altering brain glucose uptake and metabolism through two mechanisms: diminishing the brain's ability to sense hypoglycemia and impairing the activation of counter-regulatory mechanisms. However, these results still need to be demonstrated in type 2 DM patients.

The brain glycogen supercompensation hypothesis assumes a link between increased brain glycogen levels and IAH. During periods of low systemic glucose, the brain stores glycogen as a backup energy source. The hypothesis suggests that by storing glycogen, the brain can maintain its energy needs during hypoglycemia without the need of the counter-regulatory responses, which can lead to 'supercompensation' of glycogen in the brain after recurrent hypoglycemic episodes. This excess glycogen can decrease the reliance of the brain on external glucose, thus reducing the signals that activate counter-regulatory responses, which may result in the development of IAH.[18] A few studies have examined this hypothesis, showing a discrepancy between results. Elevated brain glycogen levels after hypoglycemia were found in experimental studies, supporting the supercompensation theory.[25,26] While other studies found lower brain glycogen content in patients with type 1 DM, suggesting that glycogen supercompensation does not contribute to the development of IAH.[27] Current research focus is directed towards how adjusting brain glucose levels can maintain counter-regulatory responses and prevent IAH.[18]

Measurement of IAH

Three methods have been widely used to assess IAH: Clarke, Gold, and Pedersen Bjergaard methods.[14-16] These methods were originally developed to assess hypoglycemia awareness among type 1 diabetes patients but have yet to be thoroughly interrogated among patients with type 2 diabetes. Ang et al investigated potential similarities and differences between these tools, particularly in insulin-treated type 2 diabetic patients.[28] Although IAH has been extensively studied in diabetes patients, there remains a lack of consensus on the most effective tool for assessing its prevalence in T2DM. Investigators often rely on the Clarke and Gold questionnaires, assuming insights from hypoglycemia research in type 1 diabetes can be applied to type 2 diabetes.[29,30] A study evaluated IAH prevalence in T2DM using these tools and observed a stronger association between the Clarke and Gold methods, consistent with findings from other researchers.[31-33] However, a recent study suggested that the Gold and Clarke questionnaires may not be interchangeable for assessing hypoglycemia awareness in type 1 diabetes.[34] This prompted Ang et al to investigate potential similarities and differences between these tools, particularly in insulin-treated T2DM patients.[28]

The Gold and Clarke questionnaires show variability in the prevalence of IAH, prompting the need for standardized tools and established protocols to compare IAH prevalence across regions and treatment regimen accurately. The Gold-TW questionnaire is a more focused approach, which makes it more suitable for confirmatory diagnostics where specificity is needed. The Clarke-TW may be more suitable for screening due to its ability to identify more cases, even at the risk of false positives. This is attributed to the ability of this questionnaire to capture multiple domains with higher sensitivity. So, the choice of tool depends on the clinical aim. For precise diagnostics or research requiring consistency, the Gold-TW should be used, while the Clarke-TW is preferred for population-level screening or preventive strategies.

Prevalence of IAH

Insulin-related hypoglycemia accounts for nearly 98,000 emergency department visits and 30,000 hospitalizations annually in the USA. Notably, over 75% of these visits are middle-aged or elderly individuals, suggesting that the majority of these people suffer from type 2 diabetes.[35] IAH is well-documented in type 1 diabetes and affects approximately 25% of people with type 1 diabetes, a prevalence that remains relatively stable across different cohorts and over time.[32,36] Furthermore, in type 1 diabetes, IAH is associated with a three- to six-fold increase in the incidence of severe hypoglycemia compared to those with intact awareness.[14,15,32] It is also associated with a higher frequency of asymptomatic biochemical hypoglycemia.[14,15] In contrast, IAH in type 2 diabetes is only discussed in single-center surveys, which report a wide range of prevalence rates among insulin-treated individuals, varying from 7% to 46%.[7,8,12,13] However, more recent studies show that the prevalence of IAH in patients with insulin-treated type 2 diabetes approximately 5.93% to 22.9%.[29,30,37,38]

In Asia, the prevalence of IAH determined by the Gold-TW criteria among patients with insulin-treated type 2 diabetes was 19.6% in Singapore and 5.93% in Jordan. While the prevalence of IAH determined by the Clarke-TW criteria among patients with insulin-treated type 2 diabetes was 13.7% in Singapore and 17.01% in Jordan.[29,37] Cheng et al showed higher percentages in comparison to previous studies, based on the Gold-TW criteria, 41% of type 2 diabetic insulin users had IAH, while the prevalence was 28.2% based on the Clarke-TW criteria.[39] Another study conducted in Spain stated that 12.0% of type 2 diabetic insulin users had IAH using Gold-TW criteria, while 10.2% of them had IAH using Clarke-TW criteria, demonstrating a significant correlation between the two methods with good concordance.[38]

There are differences in IAH prevalence found between clinics and hospitals. This suggests the need for tailored hypoglycemia awareness interventions based on the healthcare setting. More intensive monitoring and

education should be directed towards hospitalized patients to reduce the observed prevalence of IAH.[28,29]

Risk factors of IAH

Several factors are associated with IAH in type 2 diabetes including severe hypoglycemia events in the past year, higher frequency of hypoglycemia in the past 6 months, lower education, lower medication adherence, diabetes-related comorbidities.[29,40] Considering duration, Cheng et al reported that IAH prevalence was higher in people using insulin for less than 1 year compared to those using insulin for 5 or more years, regardless of the criteria used.[39] A possible explanation is that clinicians often provide effective education on hypoglycemia risks and prevention to patients initiating insulin therapy.

Furthermore, proper insulin usage, including accurate injection techniques, correct dosing, and appropriate timing, may help reduce the risk of hypoglycemia. Consequently, educating patients with type 2 diabetes on correct insulin administration is crucial, as it can lower hypoglycemia risk and enhance long-term survival.[41] In addition, Van et al reported a higher incidence of IAH with non-Caucasian ethnicity, complex insulin regimen, not having a partner, lower BMI and among patients with tighter glycemic control. They also found no significant differences in IAH prevalence between men and women or between primary and secondary/tertiary care settings.[30]

Although, it was reported that sulfonylurea is associated with lower incidence of IAH and severe hypoglycemia, a recent study demonstrated that sulfonylurea is associated with higher incidence of these conditions either alone or in combination with insulin.[30,39] Capre et al reported that IAH was not dependent on gender, age, duration of insulin therapy, duration of T2DM. IAH was positively associated with the frequency of hypoglycemia during the previous six months and the development of severe hypoglycemia within the past year.[38] No correlation was found between IAH and factors such as age, duration of diabetes, or insulin use by Schopman et al.[12]

Consequences of IAH on subjects with T2DM

The incidence of severe hypoglycemia in the patients with IAH was 9-fold and 17-fold higher respectively than people with hypoglycemia awareness.[12,14] Type 2 DM patients with IAH are susceptible to severe hypoglycemia which can lead to cardiovascular and neurological complications.[42,43] Severe hypoglycemia was linked to chest pain and ischemic electrocardiogram in patients with type 2 DM and coronary artery disease. It is also a risk factor for sudden mortality.[44]

Studies show that type 2 DM patients with IAH who experienced outpatient severe hypoglycemia have a 79% risk of acute cardiovascular events and a 65% increase in the risk of myocardial infarction.[45,46] Severe hypoglycemia due to IAH and may damage regions of the brain and can cause neuronal cell death especially in older people with type 2 DM.[47] Neurological complications of severe hypoglycemia secondary to IAH such as seizures, behavioral changes, cognitive impairment, and coma are estimated at between 4.9% and 9%.[18]

T1DM and T2DM patients with IAH suffer from reduced quality of life resulting in anxiety, depression, poor sleep, and reduced mobility.[48,49] This prompts them to do harmful compensatory behaviors, such as lowering insulin doses, worsening glycemic control, and increasing health risks to avoid hypoglycemia.[50] Many countries put driving restrictions due to hypoglycemia, however IAH has not consistently shown a higher risk of car accidents.[51,52]

Clinical implications

Patients on insulin combined with oral hypoglycemic agents have significantly higher IAH prevalence, which highlights the need for cautious use of combination therapies and considering alternative oral hypoglycemic agents with a lower risk of hypoglycemia. Continuous glucose monitoring, follow-ups, and patient education are important components of effective diabetes management. Both sulfonylurea and insulin users, who received regular diabetes-related medical care had decreased risks of IAH.[39] In addition, using Insulin over the long term is protective against IAH.[39] Therefore, comprehensive care as patient education and monitoring can improve outcomes for insulin users.

CONCLUSION

IAH is a serious complication in insulin-treated T2DM, arising from various physiological mechanisms such as counter-regulatory failure and alterations in brain glucose metabolism. Despite variations in measurement methods and patient populations, IAH in insulin-treated T2DM is consistently associated with an increased risk of severe hypoglycemia and its complications, including cardiovascular and neurological outcomes. It can occur due to different physiological mechanisms such as counter-regulatory failure and brain glucose metabolism alterations. Management strategies for IAH should standardize diagnostic tools, tailored education programs, and frequent monitoring to reduce the risks associated with IAH. This includes important implications for patient safety, quality of life, and healthcare outcomes. Further research is needed to understand its precise mechanisms in T2DM and optimize treatment protocols for better outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Abdullah MY, Yatimi AM, Aljamaan MB, Amoudi ZT, Alrefai NM, Bamajboor AS, et al. Hypoglycemia awareness and its clinical implications in insulin-treated patients. Int J Community Med Public Health 2025;12:1054-60.