REVIEW ARTICLE

# Hypoglycemia in patients with insulin-treated diabetes

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**KEY WORDS**

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**ABSTRACT**

Hypoglycemia is the major barrier for optimal glycemic control in patients on maintenance insulin therapy. It is widely known that good glycemic control leads to prevention of or delay in the development of microvascular complications, and can reduce macrovascular events. It is thought that hypoglycemia may predispose patients to cognitive deterioration and may negatively affect the cardiovascular system. Hypoglycemia per se can contribute to a blunted counterregulatory response and disabling hypoglycemia, while hypoglycemia avoidance restores normal response to low blood glucose levels. There are some new approaches to reducing the incidence of hypoglycemia occurrence, including education programs, insulin regimens, the type of insulin used, as well as new technologies for insulin delivery and blood glucose measurement. However, none of these approaches have been able to eliminate the incidence of hypoglycemia completely. The current paper summarizes the physiology and major aspects of hypoglycemia-related health consequences and possible ways to avoid hypoglycemia.

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**Introduction** Patients with diabetes treated with insulin must maintain euglycemia, which often takes years of delicate balancing between avoiding hyperglycemia and hypoglycemia. It is hypoglycemia that seems to be the main barrier for obtaining optimal glycemic control in both type 1 and type 2 diabetes.[1-3] Good glycemic management of diabetes prevents or delays microvascular complications and may reduce the risk of macrovascular events.[2,3] For many years, a target hemoglobin $A_{1c}$ ($HbA_{1c}$) of less than 7% has been recommended in most adult patients. Since 2013, the American Diabetes Association (ADA) recommendation for the treatment of diabetes proposed patient-centered glycemic goals, in which the general aim is to lower $HbA_{1c}$ below 7% (as previously) but to compromise to $HbA_{1c}$ below 8% when there is a high risk of hypoglycemia occurrence (ie, patients with a history of severe hypoglycemia, limited life expectancy, advanced micro- and macrovascular complications) and strengthen it to $HbA_{1c}$ below 6.5% when it can be reached without significant hypoglycemia.[4,5]

The incidence of hypoglycemia differs between studies, and that is why it is difficult to compare data due to different study designs, populations, and definitions of hypoglycemia used. Available studies indicate that the event rates for severe hypoglycemia range from 110 to 320 per 100 patient-years for patients with type 1 diabetes and from 10 to 70 per 100 patient years for patients with type 2 diabetes.[6,7] Fatal episodes of hypoglycemia are presumably the outcome of ventricular cardiac arrhythmias, not brain death, perhaps mediated by sympathoadrenal activation and possible hypokalemia, even though profound and prolonged hypoglycemia can be a cause of brain death.[8,9] Regardless of the type of diabetes, the pathophysiological mechanism of hypoglycemia, its associated risk factors, and interventions to reduce its occurrence must be understood by health care providers to minimize the risk of hypoglycemia. Therefore, in this article, we summarize the physiology of hypoglycemia, as well as some major aspects of hypoglycemia-related health consequences and possible ways to avoid them.

**Definition and physiology of hypoglycemia** Healthy people without diabetes maintain a plasma glucose concentration in the range of 70 to 99 mg/dl in the fasting state, and less than 140 mg/dl in the postprandial state.[5] Traditionally, hypoglycemia is defined by the following 3 factors (also known as the Whipple's triad): 1) the development

of clinical symptoms likely to be caused by a drop in plasma glucose level; 2) a low plasma glucose level at the time the symptoms occur; and 3) relief of the symptoms when the blood glucose level restores to normal.

The symptoms of hypoglycemia cover activation of the autonomic central nervous system (autonomic symptoms) and neuroglycopenic symptoms that are caused by reduced cerebral glucose absorption. Autonomic symptoms are the result of perception of physiological changes triggered by hypoglycemia, including tachycardia, palpitations, shakiness, sweating, diaphoresis, anxiety, hunger, arability, pallor, and nausea. Neuroglycopenic symptoms include reduced concentration, blurred vision and dizziness, headache, weakness, fatigue, confusion, amnesia, focal neurologic deficits, seizures, and coma as a result of low glucose levels in the brain.[8]

In 2005, the ADA agreed on how hypoglycemia should be defined and verified the guidelines in the year 2012.[10,11] According to the ADA, hypoglycemia is defined as an episode of an abnormally low plasma glucose concentration that leads to patient harm. It was agreed that there is no single threshold value for plasma glucose concentration that can define hypoglycemia. This is because the glycemic threshold for symptoms of hypoglycemia changes to lower plasma glucose concentrations after recent antecedent hypoglycemia and to higher plasma glucose concentrations in individuals with poorly controlled diabetes and few hypoglycemic events. However, according to the ADA an alert value for hypoglycemia should be recognized when plasma glucose level is equal to or falls below 70 mg/dl (3.9 mmol/l) because this is the level at which hormonal counterregulation is activated in patients without diabetes, and it is the level that can cause a reduction of secretion of the counterregulatory hormones in response to a subsequent episode of hypoglycemia. Several types of hypoglycemic episodes have been classified, including asymptomatic and symptomatic hypoglycemia, and severe hypoglycemia. Asymptomatic hypoglycemia is recognized when the measured plasma glucose concentration is 70 mg/dl or lower without typical hypoglycemic symptoms, and symptomatic hypoglycemia is recognized when typical symptoms occur. Hypoglycemia is defined as being mild or severe depending on the ability to self-treat. Self-treated episodes are categorized as "mild". Severe hypoglycemia is defined as an event requiring assistance of another individual and plasma glucose measurement may not be available but neurological betterment due to the restoration of plasma glucose levels to normal is thought to be sufficient enough to recognize an event.[1,10,11]

It is also important to be aware of hypoglycemic episodes that can occur at night, even though the episodes may not be detected by blood glucose self-measurement and often go unrecognized. Based on information obtained by the Diabetes Control and Complication Trial (DCCT) Research Group, ~55% of severe hypoglycemic episodes occur during nocturnal sleep.[12] Nocturnal hypoglycemia is asymptomatic in most cases but such episodes can affect health and well-being, and may be fatal.[13] Therefore, it is important to address strategies to prevent nocturnal hypoglycemia, including regular blood glucose measurements at bedtime, consumption of appropriate bedtime snacks when necessary, implementation of certain insulin regimens and new technology that may limit the hypoglycemic episodes occurrence (eg, long-acting insulin analogues, insulin pumps with hypoglycemia blockade), among others. There are several risk factors for nocturnal hypoglycemia, such as daytime exercise, tight glycemic control, previous episodes of nocturnal hypoglycemia, and low bedtime glucose levels.[14-16]

**Glucose homeostasis and counterregulation** In order to develop therapies or methods aimed at limiting the frequency of hypoglycemia, it is essential to know the homeostatic mechanisms of hypoglycemia detection and why they fail over time in both type 1 and type 2 diabetes.[17] Glucose homeostasis, as described by Watts and Donovan,[18] is maintained through a classic sensory integrative pathway, where glucose variations are monitored carefully by glucose-sensing cells in the periphery (hepatic portal and mesenteric vein) and some of the brain regions (especially in the hindbrain and hypothalamus). Glucose homeostasis is restored due to a direct connection to downstream integrators that allow the glucose signal to be influenced by inputs from brain regions (like circadian rhythms) before a motor output is generated by some of the effector mechanisms (eg, epinephrine or glucagon). Glucose-sensing neurons are unique because they are able to use glucose as a signaling molecule that regulates its activity. The main step in the translation of the glucose signal seems to be glucokinase, AMP-activated protein kinase, and the SUR-1 subtype of the ATP-sensitive potassium channel. Even though these neurons release neurotransmitters or neuropeptides, but not insulin, they act similarly to pancreatic β cells (the classic glucose sensors), which indicates that they may share a similar mechanism for detecting fluctuations in extracellular glucose concentrations.[18]

When glucose level falls, the counterregulatory response is triggered, which involves several physiological defense mechanisms. The first defense mechanism in the hierarchy of counterregulation is a reduction of insulin secretion from β cells, and the second is an increase in the levels of all counterregulatory hormones (glucagon, adrenaline, cortisol, growth hormone) that can promote endogenous glucose production and restrict peripheral glucose usage. When there is a further decrease of a plasma glucose level, behavioral changes occur as a result of subjective awareness of hypoglycemia leading to carbohydrate consumption.[19] The glycemic threshold for a decrease in insulin is approximately 80 mg/dl. When the glucose concentration falls just below

the physiological range, glucagon and epinephrine secretion is increased. Glucagon plays the leading role in increasing the glucose levels, while adrenaline (in the presence of glucagon) plays a secondary role. In the case of a more severe decrease of glucose levels, there is an additional increase of cortisol, growth hormone, and other neurotransmitter levels. At lower plasma glucose concentrations, neurogenic and neuroglycopenic symptoms occur. The glycemic threshold for neurogenic symptoms is ~55 mg/dl, and for disorders in mental function, it is ~46 mg/dl.[20,21] All 3 of these mechanisms are compromised in type 1 diabetes mellitus and advanced type 2 diabetes.[22] The etiology of the defect remains to be elucidated; however, it has been suggested that the inability to secrete glucagon during hypoglycemia in type 1 diabetes is due to an intraislet defect, namely, failure in the local regulation of β- to α-cell signaling by insulin, zinc, and probably the inhibitory neurotransmitter γ-aminobutyric acid.[23] Besides the inability to secrete glucagon, there is also an impaired autonomic response to hypoglycemia, impaired awareness of hypoglycemia, and a reduction in catecholamine release occurrence.[17] The pathophysiology of glucose counterregulation is the same in type 1 and type 2 diabetes, but it develops rapidly in type 1 diabetes and slowly in type 2 diabetes.[19]

A few experimental studies have assessed the counterregulatory responses to nocturnal hypoglycemia. Results from an earlier study suggested that sleep changes the glycemic threshold for the onset of the neuroendocrine counterregulatory response to lower glucose levels.[24] A later study by Banarer et al[25] concluded that patients with type 1 diabetes have reduced autonomic responses to hypoglycemia during sleep, most probably due to reduced sympathoadrenal responses, and thus, are less likely to be awakened by a hypoglycemic episode.[25] However, these studies examined hypoglycemia counterregulation solely during the early nocturnal sleep, which differs markedly from late sleep in sleep stage architecture. Therefore, Jauch-Chara et al[26] assessed whether the counterregulatory response differs between sleep stages (early and late), and found that late nocturnal sleep reduces the extent of neuroendocrine counterregulation and may contribute to hypoglycemic episode accumulation in the latter part of the night.

**Hypoglycemia unawareness** The awareness of hypoglycemia and the same behavioral defense (hunger) is mainly the result of perception of neurogenic symptoms, which are triggered through the activation of the autonomic nervous system by hypoglycemia.[27] Hypoglycemia is not only unpleasant and dangerous but, if persistent, may lead to the syndrome of hypoglycemia unawareness: a condition where neuroglycopenia is present before autonomic warning symptoms occur, or when a significant reduction in blood glucose level below normal is not sensed.[28,29] It is now known that hypoglycemia per se causes pathophysiological changes resulting in suppression of counterregulatory hormonal and symptomatic responses to another episode of hypoglycemia occurring 12 to 24 hours after the first episode.[30] The size of the suppression is related to the depth, duration, and frequency of previous hypoglycemia episodes.[31] It is suggested that in type 1 diabetes, hypoglycemia unawareness occurs in 10% to 15% of patients and impaired awareness in 40% to 50%.[32] It should also be mentioned that hypoglycemia unawareness increases the risk of severe hypoglycemia by 6-fold for patients with type 1 diabetes and by 17-fold for those with type 2 diabetes.[33,34] Approximately 10% of patients with type 2 diabetes present impaired hypoglycemia awareness.[34] There is also a term, hypoglycemia-associated autonomic failure (HAAF), which is a form of functional sympathoadrenal failure that increases the risk of severe hypoglycemia occurrence. This term describes the association between the 3 phenomena linked to disabling hypoglycemia, namely, defective hormonal counterregulation, altered counterregulatory hormone discharge, and impaired hypoglycemia awareness. It is essential to differentiate HAAF from classic autonomic neuropathy, in which HAAF is limited to the response to hypoglycemia, and autonomic activities in other organs such as the heart, gastrointestinal tract, and bladder remain unaffected.[10,35] The sequence of events described above explains why striving for good glycemic control with intensive insulin therapy leads to impaired symptom awareness and counterregulatory defense against hypoglycemia and to higher incidence of severe hypoglycemia both among patients with type 1 and type 2 diabetes.[36,37] It has been proved that avoidance of hypoglycemia may lead to reversal of counterregulation, which demonstrates that it is an antecedent hypoglycemia that plays the key role in this phenomenon.[38]

**Hypoglycemia and the brain** The brain is the organ that is most exposed to the adverse effects of hypoglycemia, as it is totally dependent on the continuous supply of glucose. The brain cannot synthesize glucose, and reserves stored as glycogen are limited and sufficient only for a few minutes.[39] Different techniques of neuroimaging have been tested to better understand the way glucose is metabolized in the brain.[40] It has been proved that recurrent hypoglycemia leads to brain adaptations on many different levels.[40] These include changes in blood flow and transport of glucose to the brain, as well as administration of glucose within the brain, but also activation or deactivation of brain areas engaged in behavioral responses.[40] Concern has been raised as to whether exposure to recurrent severe hypoglycemia causes premature intellectual decline, and some controversy has emerged around this subject.

The outcomes from a large cohort study performed among older adults with type 2 diabetes suggest that a history of severe hypoglycemia is

linked to greater risk of dementia.[41] Similarly, in a recent 7-year follow-up study among patients with type 2 diabetes, a significantly increased risk of dementia among patients with prior hypoglycemia was documented.[42] Furthermore, in a prospective study among a diverse group of older patients (mean age, 74 years) with type 1 or type 2 diabetes initially free of dementia, a link between severe hypoglycemia and increased risk of dementia was found.[43] An important observation coming from the study is that the authors found evidence for a bidirectional association between severe hypoglycemia and dementia, where reduced cognitive function may increase the risk for hypoglycemia, which can further compromise cognition.[43]

On the other hand, there is also evidence coming from the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) trial that there is no relationship between long-term decline in cognitive functioning over an 18-year period and relatively high rates of recurrent severe hypoglycemia episodes in a large group of patients with type 1 diabetes of short disease duration.[44] However, it must be noted that the study cohort consisted of relatively young patients with short duration of the disease, so the outcomes cannot be transformed directly to elderly patients and ones that become diabetic before the age of 5 years, as well as patients with impaired awareness of hypoglycemia. The high selectivity of the studied group limited the power of cognitive impairment.[45] However, an association between hypoglycemia and impaired cognitive function in patients with type 1 diabetes has been shown in some studies, and there are also a few studies suggesting that severe hypoglycemia in very young children is associated with mild impairments in cognitive function.[46-48] Taking this information together, it seems plausible that recurrent severe hypoglycemia may influence cognitive function of people with diabetes, but the groups of people at risk (age of diabetes onset, time of the disease duration, and rates and depths of hypoglycemic events) remain to be elucidated.[49]

**Hypoglycemia and the heart** Diabetes elevates the risk of cardiovascular events to a similar level observed in people without diabetes, who have already suffered a myocardial infarction.[50] It is important to note that patients with type 1 diabetes have a similar risk of developing premature cardiovascular disease to those with type 2 diabetes when matched for age.[51] Hypoglycemia causes sympathoadrenal activation and counterregulatory hormone secretion, which in turn exert pronounced cardiovascular effects with a potential to superimpose on coronary vascular walls that are already diseased and on dysfunctional cardiac conductive systems, provoking serious cardiovascular events.[52]

The potentially life-threating effects of hypoglycemia on the cardiovascular system seem to have been overlooked for many years, until the announcement of the outcomes of 3 large clinical trials regarding type 2 diabetes: ACCORD, ADVANCE, and VADT.[53-55] A meta-analysis of 4 large, randomized controlled trials (ACCORD, ADVANCE, VADT, and UKPDS), in which intensive glycemic control was compared to standard glycemic control, revealed a modest reduction of major macrovascular events with intensive glucose-lowering treatment in the short-to--medium term; however, all-cause and cardiovascular mortality were not benefited.[56] Additionally, the ACCORD trial was prematurely interrupted because of excess mortality among intensively treated patients.[53] A post hoc analysis of the ACCORD trial could not establish a relationship between the higher mortality rate and tight glycemic control with certainty.[49] The current opinion is that the beneficial effect of strict glycemic control on cardiovascular events is probably limited to patients without the presence of cardiovascular disease and less strict glycemic targets should be recommended for patients with a longer duration of diabetes, shorter life expectancy, advanced macrovascular complications, and those prone to hypoglycemia.[5] Further analysis of the ACCORD study found a week inverse association between the annualized number of hypoglycemic episodes and risk of death.[57,58]

A recent systematic review and meta-analysis, as well as cohort studies, have proved that severe hypoglycemia is associated with increased risk of cardiovascular disease and death among patients with type 2 diabetes.[59-62] Regarding patients with type 1 diabetes, it is suggested that repeated hypoglycemia could be related to worse prognosis in terms of preclinical atherosclerosis, as well as considered an aggravating factor for it.[63-65] Only a few studies have examined whether hypoglycemia may increase the risk of cardiovascular disease or death among patients with type 1 diabetes, and the results were ambiguous.[64,66-69] However, recently, a population-based study of all-cause mortality and cardiovascular disease in association with prior history of hypoglycemia among patients with type 1 diabetes was performed.[70] This study found that cardiovascular disease incidence is associated with severe hypoglycemic events that occurred in the preceding years, and that the risk of all-cause mortality was associated with severe hypoglycemic events that occurred in the preceding 5 years.[70] The authors concluded that repeated severe hypoglycemic events can lead to higher risk of mortality and cardiovascular disease.[70] Furthermore, a study among Swedish patients with type 1 diabetes found that those with prior severe hypoglycemic events presented an increased risk of mortality after a cardiovascular event.[71]

Unfortunately, the mechanism of hypoglycemia-related all-cause mortality and cardiovascular events is not fully known; it is only suspected that it is due to sympathetic-adrenal activations, prolonged cardiac repolarization, and increased cardiac arrhythmia risk.[72] Tsujimoto et al[73] showed that patients with type 1 and type

2 diabetes who suffered from severe hypoglycemia presented with critical problems, namely hypothermia, hypokalemia, and abnormal QT prolongation. The authors emphasized that hypothermia was often observed and it can lead to arrhythmias, such as ventricular tachycardia and atrial fibrillation, which were frequently observed.[73] It was also proved that patients with severe hypoglycemia presented with hypokalemia because hypothermia, hyperinsulinemia, and increased level of catecholamines may cause potassium transfer into the cell, while hypoglycemia and, in turn, hypokalemia increase the risk of lethal arrhythmias.[73] In the above study, authors report that patients with both type 1 and type 2 diabetes who had severe hypoglycemia exhibited an abnormal QT prolongation and it can cause new-onset atrial fibrillation; however, the causation in this study was not clear.[73] Similarly, Stahn et al[74] evaluated the risk of critical arrhythmias related to severe hypoglycemia in type 2 diabetes with cardiovascular disease and found that severe episodes of hypoglycemia are associated with increased risk of severe ventricular arrhythmias.

**Hypoglycemia avoidance** Hypoglycemia can be prevented when patients at risk of severe hypoglycemia are identified, appropriate insulin regimens and technical innovations (insulin analogues, continuous glucose monitoring [CGM], and insulin pumps, among others) are used, and patient education and empowerment is implemented. From a practical point of view, it is important to be aware of factors for increased risk of hypoglycemia occurrence, namely insulin excess (ill-timed and wrong type of insulin), decreased glucose intake (missed meals and overnight fast), decreased endogenous glucose production (after alcohol ingestion), increased glucose utilization (during exercise), increased insulin sensitivity (following exercise, in the middle of the night, and after weight loss), and decreased insulin clearance (as in renal failure).[1] Treatment goals and strategies should always be individualized, as indicated in the newest ADA/European Association for the Study of Diabetes guidelines.[75] It has been proved that blunted autonomic symptoms and counterregulatory hormonal responses can be improved when even mild hypoglycemia episodes are avoided.[76] Restoration of autonomic symptoms of hypoglycemia can be obtained within 2 weeks, and complete reversal of hypoglycemia unawareness—within 3 months.[10]

**Optimal insulin therapies for hypoglycemia avoidance** In patients with type 1 diabetes, the most adequate insulin therapy regimen that mimics normal physiology, adapts to the patient's lifestyle, and reduces hypoglycemia risk is multiple daily insulin injection (MDII) therapy with insulin analogues, or continuous subcutaneous insulin infusions (CSII) with the use of pump therapies.[5] In type 2 diabetes, β-cell dysfunction progresses with time, and insulin therapy is frequently required.[77,78] Typically, in this type of disease, basal insulin alone is added as an initial insulin regimen.[79] This therapy covers insulin needed throughout the day and night and lowers blood glucose levels mainly due to suppression of interprandial and night hepatic glucose production. Either intermediate-acting neutral protamine Hagedorn (NPH) or long-acting insulin analogues may be used, but the latter are linked to less frequent overnight hypoglycemia and possibly slightly less weight gain.[80,81] Eventually, due to the progressive character of the disease, some patients will need shorter-acting insulin before meals.[82] In summary, the insulin treatment approach among patients with type 2 diabetes should be individualized to meet the special requirements of an individual patient, namely, dietary and exercise habits, dominant glucose trends disclosed by self-monitoring, and expected individual treatment goals.[75]

In the newest report, an ADA workgroup recommends that, in order to restore recognition of hypoglycemia in patients with HAAF, rapid-acting insulin analogues to decrease the risk of interprandial hypoglycemia and basal insulin analogues to decrease the risk of nocturnal hypoglycemia should be used.[10] A meta-analysis by Monami et al[83] indicates that long-acting insulin analogues are associated with a significant reduction in the rate of nocturnal hypoglycemia in type 1 diabetes. The cost of long-acting analogues is higher compared with that of NPH insulin, but it must be remembered that the indirect cost of decreased hypoglycemia risk may be reduced, which is why it is the physician's responsibility to balance between costs and the clinical benefits that may be obtained.[83] Furthermore, a recent observational study showed that while the use of insulin analogues versus human insulin may predispose to more frequent episodes of mild hypoglycemia, it does not increase the incidence of severe hypoglycemia in patients on intensive insulin therapy.[84]

Recently, a newer ultra-long-acting insulin analogue (ie, insulin degludec) has been developed, and, since September 2015, it has been approved by the US Food and Drug Administration for glycemic control in adults with type 1 and type 2 diabetes.[85] This insulin demonstrates a different pharmacokinetic/pharmacodynamic profile compared with insulin glargine and detemir and a longer duration of action (up to 42 hours with approximately 25-hour half-life at steady state), which can lead to potential benefits.[86] As revealed in a recent review by Thuillier et al,[87] insulin degludec shows good long-term efficacy in providing glycemic control and reducing nocturnal hypoglycemia in patients with type 2 diabetes.

**The role of education programs in hypoglycemia avoidance** Beside insulin therapy itself, structured education programs that help people understand the ways in which they can manage their insulin therapy are important, as self-management is essential for successful diabetes treatment. An example of a structured training program designed

to maintain glucose control while enabling dietary freedom among type 1 diabetes patients was a multicenter randomized controlled study, DAFNE.[88] It has been carried out in the United Kingdom and resulted in improved $HbA_{1c}$ levels and quality of life with no significant increase in severe hypoglycemia incidence.[88] A similar education and training program for intensified insulin therapy on type 1 diabetes has been run in Düsseldorf and was linked to a reduction of $HbA_{1c}$ value from 8.1% to 7.3% and a decrease of severe hypoglycemia occurrence from 0.37 to 0.14 events per patient per year.[89]

In 2016, outcomes of a pragmatic, cluster-randomized controlled trial of the CASCADE intervention that assessed efficacy of a clinic-based structured educational group incorporating psychological approaches to improve long-term glycemic control, quality of life, and psychological functioning in children and adolescents with type 1 diabetes was published.[90] The results indicated that delivering such educational programs remains challenging and that standardized training failed to demonstrate improvement in $HbA_{1c}$ values among patients with poor diabetic control.[90] One of the reasons for that is a high rate of lack of response to invitations and failure to attend meetings among young people and their families.[90] Therefore, although the benefits of education are clear, determining the optimal educational program to provide insulin-treated patients with the correct information on how to manage diabetes well requires further investigation. All patients with diabetes should obtain precise information on how to recognize and treat hypoglycemia and should know how to prevent it. Physicians should always ask patients about hypoglycemia incidence and talk over strategies for its management.

**New technology in hypoglycemia avoidance** Technical innovations in insulin delivery and glucose monitoring are becoming increasingly important in the improvement of glycemic control with avoidance of hypoglycemia episodes, especially the development of new CSII and CGM systems, including real-time continuous glucose monitoring (RT-CGM) or "closed-loop" systems. Self-monitoring of blood glucose (SMBG) is a critical part of insulin therapy. However, several factors limit adherence to SMBG (namely, pain, motivation, and cost), which is why RT-CGM systems have been developed. RT-CGM allows patients to observe the direction and rate of change of plasma glucose in real time via an electrode inserted into the interstitial fluids of subcutaneous tissue, and it was proved that this technical support leads to an improvement of $HbA_{1c}$ levels without increased risk of hypoglycemia in adults on intensified insulin therapy.[91]

A systematic review and meta-analysis performed by Poolsu et al[92] analyzed effectiveness of CGM and RT-CGM on glucose control among patients with type 1 and type 2 diabetes, and found that RT-CGM was more effective than SMBG in type 1 diabetes but retrospective CGM was not.[92] However, among patients with type 2 diabetes, retrospective CGM provided better glycemic control than SMBG.[92] Another study examined whether impaired awareness of hypoglycemia can be improved and severe hypoglycemia prevented with the use of CSII compared with MDII and RT-CGM compared with SMBG among patients with type 1 diabetes.[93] Similar biomedical outcomes were obtained with conventional MDI and SMBG regimens compared with CSII/RT-CGM; however, satisfaction was higher with CSII.[93]

Trang et al[94] performed a randomized trial to determine the incidence of severe and moderate hypoglycemia with sensor-augmented pump therapy with a low-glucose suspension function compared with standard insulin pump therapy among patients with type 1 diabetes with impaired awareness of hypoglycemia. It was proved that the use of sensor-augmented pump therapy with low-glucose suspension reduced the rate of severe and moderate hypoglycemia in patients with type 1 diabetes and impaired hypoglycemia awareness over a 6-month period; however, no associated change in $HbA_{1c}$ values was observed.[94]

Another randomized, controlled, multicenter, open-label trial was performed in patients with type 1 diabetes and nocturnal hypoglycemia (the ASPIRE study,) who received sensor-augmented insulin pump therapy with or without the threshold-suspend feature for 3 months.[95] This study showed that the therapy with the threshold-suspend feature reduced nocturnal hypoglycemia without increasing $HbA_{1c}$ values.[95] The first step in developing an artificial pancreas is a quite recent advance in insulin treatment technology, which is a sensor-augmented insulin pump with automatic low-glucose suspension of the basal rate of the insulin for up to 2 hours once the interstitial glucose concentration reaches a preset threshold. This innovation is especially important for people who sleep through alarms, because it can potentially reduce severe hypoglycemic episodes at night.[96]

**Conclusions** It is well known that good glycemic control prevents or delays microvascular complications and may reduce macrovascular events. Iatrogenic hypoglycemia is the major barrier for optimal glycemic control because it is associated with morbidity and risk of death. In order to eliminate the risk of hypoglycemia in insulin-treated patients, the treatment should be patient-centered, which means that glycemic targets and insulin regimens, as well as any technical support used, should be individualized according to the patient's age, life expectancy, comorbidities, and preferences. It is currently not possible to maintain euglycemia without hypoglycemia occurrence over the lifetime of most patients with diabetes mellitus, regardless of the type of disease. A great deal of hope is placed in technical investigations that might help manage this situation.

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ARTYKUŁ POGLĄDOWY

# Hipoglikemia u pacjentów leczonych insuliną

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**SŁOWA KLUCZOWE**

cukrzyca,
hipoglikemia,
insulinoterapia

**STRESZCZENIE**

Hipoglikemia jest główną barierą w uzyskaniu optymalnej kontroli glikemii u pacjentów leczonych insuliną. Jak wiadomo, prawidłowa kontrola glikemii zapobiega lub opóźnia wystąpienie powikłań mikronaczyniowych, a także może zmniejszać ryzyko wystąpienia powikłań makronaczyniowych. Przypuszcza się, że hipoglikemia może prowadzić do upośledzenia funkcji poznawczych i wpływać negatywnie na układ sercowo-naczyniowy. Hipoglikemia *per se* może prowadzić do osłabionej odpowiedzi kontregulacyjnej na hipoglikemię i nieświadomości hipoglikemii, a unikanie hipoglikemii prowadzi do powrotu prawidłowej odpowiedzi organizmu na zbyt niskie stężenie glukozy we krwi. Istnieją nowe metody mające na celu redukcję występowania hipoglikemii: programy edukacyjne, schematy insulinoterapii, rodzaj stosowanej insuliny oraz nowe technologie podawania insuliny i pomiaru glikemii. Żadna z tych metod nie prowadzi jednak do całkowitego wyeliminowania hipoglikemii. W artykule zawarto podsumowanie fizjologii hipoglikemii, główne aspekty zdrowotne związane z jej występowaniem, a także sposoby jej unikania.

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