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Hypoglycaemia unawareness in patients with type 1 diabetes

Nieświadomość hipoglikemii u pacjentów z cukrzycą typu 1

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Abstract

Hypoglycaemia unawareness, defined at the onset of neuroglycopenia before the appearance of autonomic warning symptoms, is a serious problem in type 1 diabetes mellitus. It is often caused by recurrent or severe hypoglycaemia, which leads to the failure of the autonomic nervous system (hypoglycaemia-associated autonomic failure – HAAF). The hypoglycaemia awareness can be restored by avoiding episodes of hypoglycaemia. Management of hypoglycaemia unawareness is complex, and can only be achieved by a multifactorial intervention of clinical care and structured patient education. In patients in whom functional intensive insulin therapy with insulin analogue, continuous subcutaneous insulin infusion using insulin pumps are ineffective in the prevention of hypoglycaemia the implementation of continuous glucose monitoring (CGM) is advisable. CGM systems equipped with low glucose alarms and prediction alarms not only significantly reduce the risk of severe hypoglycaemia, but also significantly reduce the fear of hypoglycaemia and improve the quality of life of patients and their families. The insulin pumps integrated with CGM automatically suspending insulin infusion when glucose is predicted to soon be low (PLGS) should be preferred in patient with hypoglycaemia unawareness. Hypoglycaemia management is complex and should also include structural education. Particular attention should be paid to the management of hypoglycaemia and appropriate use of modern therapy.

The hypoglycaemia unawareness is very common among children under the age of 6 years who are unable to observe the early symptoms of hypoglycaemia by themselves. This induces a high risk of frequent and severe hypoglycaemia, which can lead to structural changes in the brain, cognitive dysfunctions, poor mental abilities and behavioral disorders later in life.

Słowa kluczowe:

type 1 diabetes, hypoglycaemia unawareness, continuous glucose monitoring, insulin pump.

Streszczenie

Nieświadomość hipoglikemii, definiowana jako brak możliwości rozpoznania objawów hipoglikemii przez pacjenta, stanowi istotny problem kliniczny wśród chorych na cukrzycę typu 1. Najczęściej jest spowodowana nawracającymi niedocukrzeniami, które prowadzą do wystąpienia niewydolności autonomicznego układu nerwowego związanej z hipoglikemią (*hypoglycaemia-associated autonomic failure* – HAAF). Unikanie hipoglikemii może przywrócić zdolność do jej odczuwania. U pacjentów, u których zastosowanie funkcjonalnej intensywnej insulinoterapii z użyciem insulin analogowych oraz ciągłego podskórnego wlewu insuliny za pomocą pomp insulinowych jest nieskuteczne, wskazane jest wdrożenie ciągłego monitorowania glikemii. Systemy ciągłego monitorowania wyposażone w alarmy niskich glikemii i alarmy predykcyjne nie tylko znacznie redukują ryzyko wystąpienia ciężkich hipoglikemii, lecz także istotnie zmniejszają lęk przed hipoglikemią oraz poprawiają jakość życia zarówno pacjentów, jak i ich rodzin. Pompy insulinowe połączone z ciągłym monitorowaniem glikemii (*continuous glucose monitoring* – CGM), automatycznie wstrzymujące infuzję insuliny w przypadku zagrożenia niskim poziomem glikemii (*predictive low-glucose insulin suspend* – PLGS), powinny być preferowane u pacjentów z nieświadomością hipoglikemii. Leczenie nieświadomości hipoglikemii jest złożone, a jego integralną częścią jest edukacja

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zdrowotna. Szczególną uwagę należy zwrócić na postępowanie w hipoglikemii i odpowiednie wykorzystanie nowoczesnych metod terapii.
Nieświadomość hipoglikemii jest bardzo częsta wśród dzieci poniżej 6. roku życia, które nie są w stanie same zaobserwować wczesnych objawów niedocukrzeń. Wiąże się to z dużym ryzykiem występowania częstych i ciężkich hipoglikemii, które mogą prowadzić do strukturalnych zmian w mózgu, upośledzenia funkcji poznawczych i rozwoju zaburzeń zachowania w późniejszym życiu.
Key words:
cukrzyca typu 1, nieświadomość hipoglikemii, ciągłe monitorowanie glikemii, pompy insulinowe.

Introduction

Hypoglycaemia, being the most common acute complication in patients with type 1 diabetes, is one of the major obstacles preventing restoration of good metabolic control of the disease [1]. Episodes of hypoglycaemia are observed in all patients because they are inherent in type 1 diabetes and its antihyperglycaemic therapy. The incidence of hypoglycaemia reported in clinical studies depends on the glucose level threshold accepted for hypoglycaemia episode detection [2].

The criteria for diagnosis of hypoglycaemia in patients with diabetes have evolved alongside progression of knowledge and the introduction of new therapeutic options. In 2017, the International Hypoglycaemia Study Group (IHSG) presented a joint statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), addressing the issue of classification of hypoglycaemia episodes. This statement was also accepted by the Polish Diabetes Association (*Polskie Towarzystwo Diabetologiczne*) (Table I) [3, 4].

Hypoglycaemia in its initial stage is associated with activation of the autonomic nervous system, which results in the occurrence of various symptoms. These symptoms usually allow patients to detect hypoglycaemia early. Patients can demonstrate one or more symptoms which are typical for hypoglycaemia [5]. In more severe hypoglycaemia, they can demonstrate symptoms that result from central nervous system glucose deprivation – symptoms of neuroglycopaenia [5]. Symptoms of hypoglycaemia can be diverse in different patients, and even in the same patient they may be different during subsequent hypoglycaemic episodes [6].

The perception of intensity of hypoglycaemia symptoms evolves over time. With disease progression, more and more patients demonstrate impaired perception of these symptoms, i.e. hypoglycaemia unawareness. Clinical observations and study results indicate that in some patients hypoglycaemia unawareness is a permanent condition [7].

Hypoglycaemia unawareness

Hypoglycaemia unawareness in diabetes is defined as the failure to detect hypoglycaemic symptoms of impending hypoglycaemia by a patient. Autonomic symptoms do not occur or occur too late, i.e. after the onset of neuroglycopaenia, and the patient is not aware of them [4, 8]. Hypoglycaemia unawareness affects as much as 17-40% of type 1 diabetes patients [9-11]. Significant differences in the incidence of this phenomenon are the result of two factors: various clinical manifestations and diagnostics problems.

Hypoglycaemia unawareness is a graduated phenomenon and not an "all or nothing" pathology. Thus, many patients with diabetes demonstrate partly impaired hypoglycaemia awareness. Almost 80 years ago, Lawrence *et al.* observed that

Table I. Classification of hypoglycaemia according to the International Hypoglycaemia Study Group [3]

Level	Criterion for glucose values	Comments
Hypoglycaemia alert value (or: glucose alert value) (Level 1)	≤ 70 mg/dl ≤ 3,9 mmol/l	Blood glucose level requiring treatment with simple carbohydrates. Indication for an adjustment of blood glucose lowering medication
Clinically significant hypoglycaemia (Level 2)	< 54 mg/dl < 3,0 mmol/l	Blood glucose level sufficiently low to indicate serious, clinically important hypoglycaemia
Severe hypoglycaemia (Level 3)	No specific glucose value	Hypoglycaemia associated with severe cognitive impairment requiring external assistance for recovery
*When detected by continuous glucose monitoring, a glucose level < 54 mg/dl (< 3.0 mmol) should last for at least 20 minutes		

a particular patient can in certain conditions demonstrate early prodromal symptoms, while in different circumstances he or she may be completely unaware of an "impending attack" [12]. Most patients demonstrate this clinical picture of hypoglycaemia unawareness. Another problem is different perception of hypoglycaemia while a patient is awake and while sleeping. Many patients easily identify diurnal hypoglycaemia but are unable to perceive hypoglycaemia overnight [13].

Diagnosing hypoglycaemia unawareness is very difficult. In most cases, patients themselves state whether they demonstrate this complication or not. In clinical practice as well as in scientific research, certain diagnostic tools are used. Gold's and Clark's questionnaires are most commonly applied [14, 15]. It should be emphasised that recurrent episodes of severe hypoglycaemia and clinically significant frequent hypoglycaemia episodes in a patient, particularly while awake, indicate hypoglycaemia unawareness.

The definition of hypoglycaemia unawareness – failure to detect a significant decrease in glycaemic level below normal values – bears no information about what glucose level should be considered "normal" [16]. Because the definition of hypoglycaemia is being modified and due to restricted accuracy of glucose meters, many diabetes scientific associations do not state a glycaemic threshold for the diagnosis of the condition [4, 16, 17]. There are arguments for adopting the value of 70 mg/dl – a hypoglycaemia alert value of glucose level, below which simple carbohydrates should be consumed, as well as the value of 54 mg/dl, which corresponds to a clinically significant hypoglycaemia.

Mechanisms of hypoglycaemia unawareness

A decrease in blood glucose concentration results in activation of counterregulatory responses. Counterregulation, preventing further decrease in blood glucose concentration, involves: decreased secretion of insulin, increased secretion of glucagon, catecholamines, cortisol, and growth hormone, increased production of glucose by the liver, and its decreased metabolism. This leads to an increase in glucose concentration [5]. Autonomic nervous system activation, which accompanies a decrease in the blood glucose level is clinically manifested by adrenergic symptoms of hypoglycaemia, e.g. hyperphagia, sweating, a feeling of rapid heartbeat [18].

Patients with type 1 diabetes demonstrate impaired physiological ability to prevent hypoglycaemia. This means that secretion of endogenous insulin cannot be suppressed, because exogenous insulin is present in the bloodstream, and in the course of the disease the ability of glucagon and catecholamine secretion in response to decreasing glucose concentration becomes disturbed. In some patients, glucagon secretion can be impaired already at the initial stage of the disease, and five years after type 1 diabetes diagnosis the majority of patients demonstrate this impairment [19, 20]. Further disturbances of the counterregulatory mechanisms are observed over 10 years of disease duration [21].

Recurrent episodes of hypoglycaemia, which impair sympathoadrenal responses, pose a serious problem. Cryer proposed a concept of hypoglycaemia: associated autonomic failure (HAAF) [22], according to which, antecedent hypoglycaemia disturbs not only glucose counter-regulation but also awareness of hypoglycaemia [23, 24]. This leads to a vicious circle of recurrent hypoglycaemia [18]. From the scientific point of view, HAAF is identified as an adaptation of the central nervous system to recurrent hypoglycaemic episodes.

Functional neuroimaging studies revealed that damage to the nucleus of the ventromedial hypothalamus (VMH) contributes to a 75% reduction of hormonal reaction to hypoglycaemia. VMH contains two types of glucose-induced neurons: GE neurons (glucose-excited neurons), which become activated when the glucose concentration increases, and GI neurons (glucose-inhibited neurons), which are less active when the glucose concentration increases [25]. Possibly, there is a similarity between GE neurons and beta cells of pancreatic islets, as well as between GI neurons and pancreatic alpha cells. GE neurons are active during euglycaemia and hyperglycaemia and inhibit hormonal counter-regulation, whereas GI neurons are active during hypoglycaemia and activate counter-regulatory hormonal mechanisms. In recurrent hypoglycaemia, GI neurons become less active due to a decreased glucose threshold at which the neurons start to be excited and GE neurons become more active [26]. This hypothesis explains the pathogenesis of impaired counter-regulatory mechanisms, which is observed in recurrent hypoglycaemia. The adaptation of the central nervous system to the current glucose concentration involves: changes in cerebral blood flow, changes in cerebral transport and metabolism of glucose, use of alternative energy sources by a brain, and changes in neurotransmitter activity [25].

Positron emission tomography studies revealed significantly lower uptake of labelled glucose analogue 18-F-fluorodeoxyglucose (FDG) in the hypothalamic region during hypoglycaemia in type 1 diabetic patients with hypoglycaemia unawareness in comparison to patients without hypoglycaemia unawareness. Different levels of FDG uptake during hypoglycaemic episodes in patients with hypoglycaemia unawareness were observed in many regions, which seems to confirm the hypothesis that an extensive cerebral network plays a role in the pathogenesis of HAAF in diabetes [27]. Transient changes in cerebral perfusion may be responsible for weakened symptoms of hypoglycaemia in patients with hypoglycaemia unawareness.

Glucose is the main source of energy for the brain. During hypoglycaemic episodes, alternative fuels, including lactates, are utilised [28]. Cerebral lactate concentration is several times higher in patients with type 1 diabetes, who demonstrate recurrent episodes of hypoglycaemia than in people not affected by diabetes. However, increased lactate oxidation during hypoglycaemia was not confirmed.

Choi *et al.* [29] and Saez *et al.* [30] observed that neurons of the central nervous system have their own source of glycogen, which, during hypoglycaemic episodes, protects cells against oxidative stress. Quantitative studies revealed that cerebral glycogen content is decreased in patients with hypoglycaemia

unawareness in comparison to patients who are aware of hypoglycaemia. Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. During hypoglycaemia the GABA concentration in the interstitial fluid of the ventromedial hypothalamic nucleus decreases. Recurrent hypoglycaemia leads to a substantial increase in the level of GABA in VMH. This correlates with impaired secretion of glucagon and catecholamines, which is a consequence of hypoglycaemia [18].

The incidence and clinical implications of hypoglycaemia unawareness make it a serious problem in diabetes therapy. Reports from professional literature indicate that the most important risk factors of hypoglycaemia unawareness include: longer diabetes duration, older patients' age, past but, in particular, recurrent antecedent hypoglycaemia, intensive hypoglycaemic therapy, and high glucose variability [31].

Patients with autonomic neuropathy demonstrate impaired secretion of counter-regulatory hormones, particularly adrenaline, which might lead to permanent hypoglycaemia unawareness.

Risk of hypoglycaemia unawareness increases significantly while sleeping. During night-time rest, adrenergic response to hypoglycaemia considerably decreases, and alarming symptoms are often not strong enough to wake up the patient [18]. Due to lack of perceivable symptoms and infrequent blood glucose measurements, nocturnal hypoglycaemia is hardly ever detected and can last even a couple of hours [32].

Results of studies using continuous glucose monitoring indicate that during sleep, biochemical hypoglycaemia occurs in 50% of adult patients and in almost 80% of paediatric patients treated with insulin [32]. Patients with type 1 diabetes experience the majority of severe hypoglycaemic episodes during sleep [33].

Genetic factors may also contribute to hypoglycaemia unawareness. In patients with type 1 diabetes, hypoglycaemia unawareness is observed 3-4 times more frequently in homozygotes Gly16 (GG) patients compared to people with other variants of Arg16Gly polymorphism of β2-adrenergic receptor gene (ADRB2) [34].

Consequences of hypoglycaemia unawareness

Hypoglycaemia unawareness significantly increases the risk of severe hypoglycaemia. Severe hypoglycaemia is a health and life hazard for patients with diabetes. Hypoglycaemia-induced injuries, incidents, arrhythmias, and cerebral oedema may result in the patient's death.

Poor concentration, memory disturbances, and slowed reactions, which accompany hypoglycaemia, might have a negative impact on learning processes, professional life, or sports activities. Intellectual activity and physical efficiency are decreased not only during hypoglycaemic episodes but also later, in the recovery period. The most recent studies performed with the use of advanced imaging techniques revealed that type 1 diabetes adult patients experiencing hypoglycaemia must recruit more cerebral regions in order to maintain cognitive functions than people without the disease.

Moreover, both severe and recurrent minor hypoglycaemia episodes are risk factors for chronic vascular complications of diabetes (both macro- and microvascular), which significantly affects patients' lifespan and quality of life [35]. Patients' experiences related to hypoglycaemia, affect their quality of life and influence therapeutic decisions. Fear of hypoglycaemia is an extremely serious problem [36]. This fear is experienced by patients, their families, caregivers, as well as diabetologists. The patients are afraid of neurological consequences of hypoglycaemia and cardiovascular complications. The fear of hypoglycaemia influences self-management and may impair glycaemic control. Due to fear of potential further episodes of hypoglycaemia, patients and their physicians may diminish insulin doses, which results in persisting hyperglycaemia. Hypoglycaemia-related fear significantly affects the quality of life of the patients and their families and often requires psychological and sometimes even psychiatric therapy.

The economic aspect is of great importance, too. Hospitalisations and work absence of patients (or the patients' parents/guardians) due to severe hypoglycaemia generate additional costs and constitute a burden for the health care system and the state economy [37].

Management of hypoglycaemia unawareness

Perception of hypoglycaemic symptoms can be improved by avoiding episodes of hypoglycaemia. It is possible due to identification of particular risk factors of hypoglycaemia, establishing individual therapeutic goals and application of new technologies in the management of diabetes (Table II) [23]. The effectiveness of these interventions will greatly depend on providing patients with proper education.

Risk factors of hypoglycaemia unawareness syndrome

In recent years, the following risk factors of hypoglycaemia unawareness syndrome have been identified: longer diabetes duration, older patient age, overly restrictive glycaemic control, and antecedent hypoglycaemia [38]. Reduction of modifiable risk factors of hypoglycaemia is the most important step in the prevention of hypoglycaemia. The main reason hypoglycaemia occurs in patients treated with insulin is because it is not easy to adequately adjust insulin doses to demand for it. Patients are still at risk of hypoglycaemia even if counter-regulatory mechanisms are efficient, because exogenous insulin is not subject to feedback regulation [30].

Hypoglycaemia might result from inadequate adjustment of insulin therapy to physical activity, dietary errors, or miscalculation of insulin doses.

A rapid increase in insulin sensitivity, caused by loss of body weight or more strenuous physical activity and simultaneous administration of inadequate insulin doses, contributes to hypoglycaemic episodes.

Concomitant disorders might also increase hypoglycaemia risk (e.g. endocrine disorders, such as adrenal cortical insufficiency or hypothyroidism. Disturbances of intestinal absorption may cause problems, including coeliac disease, being one of

Table II. Therapeutic guidelines for patients with hypoglycaemia unawareness

Avoiding episodes of hypoglycaemia by: • Reduction of modifiable hypoglycaemia risk factors • Establishing individual therapeutic goals • Use of insulin analogues • Implementation of continuous subcutaneous insulin infusion (CSII), i.e. insulin pumps • Continuous glucose monitoring use • Application of insulin pumps equipped with the function of automatic suspension of insulin infusion in the event of low glucose level (low glucose suspension – LGS) or with predicted low glucose algorithm (predictive low glucose insulin suspension – PLGS)
Therapeutic education concerning: • Frequent measurements of glucose levels, night-time glucose measurements, • Effective use of continuous glucose monitoring systems including proper interpretation of glucose concentration profiles and glucose trend arrows • Adjustment of insulin doses to meals, physical activity, lifestyle – in CSII therapy application of bolus calculator, taking "insulin on board" into consideration, • Causes and symptoms of hypoglycaemia – proper reaction to hypoglycaemia, necessity to constantly have simple carbohydrates (containing glucose or saccharose) by site.
Training in perception of hypoglycaemia
Psychological support

the most common autoimmune diseases concomitant with type 1 diabetes. Hepatic diseases associated with impaired glycogen storage also increase the risk of hypoglycaemia. Nutritional disturbances can contribute to high blood glucose variability and recurrent hypoglycaemic episodes. Proper management of concomitant diseases decreases the risk of hypoglycaemia.

Another factor increasing hypoglycaemia risk is concomitant medication, which may impair counterregulatory mechanisms; such effects are best known for beta-adrenergic receptor inhibitors.

Establishing individual therapeutic goals

Patients with hypoglycaemia unawareness syndrome should keep their glucose levels stable, without hypoglycaemic episodes, for 4-6 weeks to restore the proper glucose threshold at which the central nervous system starts reacting to hypoglycaemia, and thanks to this bring back adrenergic symptoms related to hypoglycaemia. Therapeutic goals should be established individually to prevent low blood glucose levels in particular patients, and therapy modifications aimed at reducing hypoglycaemia should be implement [3, 39, 40].

Insulin types

Currently, functional insulin therapy with the use of insulin analogues is recommended for patients with type 1 diabetes. Implementation of human insulin analogues, both rapid- and long-acting, substantially decrease the incidence of hypoglycaemia [41]. Rapid-acting analogues start acting more rapidly and are characterised by higher peak activity and shorter acting time. These characteristics allow better adjustment of insulin doses to meals and physical activity. They also decrease the risk of late post-meal hypoglycaemic episodes and physical activity-related hypoglycaemia. Low or no peak activity profile of long-acting insulin analogues reduces the incidence of nocturnal and diurnal hypoglycaemia [42].

Insulin therapy regimen

The model of intensive insulin therapy also plays a role in hypoglycaemia prevention. Continuous subcutaneous insulin infusion (CSII) with the use of personal insulin pumps is a method that provides an insulin supply that nowadays mimics best the physiological insulin secretion. This method allows a reduction in the number of hypoglycaemic episodes, including severe ones, compared to multiple insulin injections. Gimenez at al. conducted a study in which they evaluated the impact of CSII on hypoglycaemia awareness and the glucose concentration profile in patients with type 1 diabetes with hypoglycaemia unawareness, who experienced two or more episodes of severe hypoglycaemia within the previous 24 months [43]. They showed that CSII decreased the number of severe hypoglycaemia episodes, and improved patients' quality of life and their reaction to hypoglycaemia.

Continuous glucose monitoring

Continuous glucose monitoring (CGM), which provides comprehensive, continuous insight into glucose levels and into current trends of glucose concentration in the interstitial fluid, are widely used in clinical practice. They are nowadays an important tool, which helps to restore and maintain glycaemic control. Real-time continuous glucose monitoring (rtCGM), equipped with low glucose alarms and prediction alarms, can warn the user about hypoglycaemia. Broad application of these devices considerably decreases the incidence of hypoglycaemia in type 1 diabetes patients and significantly decreases duration of hypoglycaemic episodes. Real-time CGM also appears to be an effective tool in prevention of severe hypoglycaemia in patients with hypoglycaemia unawareness [44, 45]. It should be pointed out, however, that rtCGM itself does not prevent all episodes of hypoglycaemia, particularly nocturnal ones, because patients are not always woken up by the alarms [46].

Artificial pancreas

The first steps of constructing an artificial pancreas were focused on minimising the number and duration of hypoglycaemic episodes with the use of insulin pumps connected to rtCGM. At the first stage, automatic suspension of insulin infusion by the pump when the glucose level decreased below the alert glucose threshold (e.g. low glucose suspension function-equipped system – LGS) was applied. A study conducted by Bergenstal *et al.* revealed that therapy with the use of an insulin pump equipped with the LGS function significantly reduced the number of nocturnal hypoglycaemic episodes [47]. Ly *et al.* carried out a study in a group of patients with hypoglycaemia unawareness and observed that therapy involving the use of a pump with the LGS function contributed to a decrease in the number of moderate and severe hypoglycaemic episodes in comparison to therapy with the use of a personal insulin pump not equipped with the CGM [48]. Another model of an insulin pump was supported with a function of automatic suspension of insulin infusion in the event of predicted low glucose level (predictive low glucose insulin suspend – PLGS) [49]. This system appeared to be even more effective in prevention of hypoglycaemia than LGS. It should be emphasised that rtCGM systems used on their own do not fully prevent hypoglycaemic episodes, particularly events that occur overnight, when patients do not react to alarms of low glucose levels during sleep. Only the application of the PLGM function, involving automatic suspension of insulin infusion in the event of impending hypoglycaemia, gives a considerable decrease in the risk of hypoglycaemia occurrence [50]. Of all available technological solutions, infusion pumps equipped with the PLGS function should be preferred in patients with hypoglycaemia unawareness.

It must be pointed out, however, that studies on an artificial pancreas indicate that in order to restore normoglycaemia without episodes of hypoglycaemia, it will be required to use a bihormonal artificial pancreas, which, as well as supplying insulin, will also infuse glucagon [51].

Patient education

The main goal of therapeutic education programs for patients with hypoglycaemia unawareness is to decrease the incidence of severe hypoglycaemia by avoiding modifiable risk factors for hypoglycaemia and by restoring proper perception of hypoglycaemic symptoms [52]. Thus, education on self-control of diabetes as well as on hypoglycaemia itself should be provided. Patients should be aware of potential causes of hypoglycaemia because such knowledge will enable them to properly adjust insulin doses to their daily needs. During training sessions, clinical symptoms of hypoglycaemia should be thoroughly discussed. In the course of the disease, some patients start demonstrating different symptoms of hypoglycaemia than before. If a patient does not associate these "new" symptoms with hypoglycaemia, he or she starts to be unaware of hypoglycaemia episodes. Providing training sessions on appropriate management of hypoglycaemia is also important. Training on hypoglycaemia should also be provided to the patient's closest friends, relatives, etc.

Providing training programs to patients with hypoglycaemia unawareness

Patients with diabetes, who do not perceive hypoglycaemic episodes or who perceive hypoglycaemia too late, can be provided with special training programs that will considerably improve their perception of hypoglycaemia and restore a sympathoadrenal response to it. The educator should pay particular attention to neuroglycopaenic symptoms of hypoglycaemia that can be observed even when sympathoadrenal response is diminished. The patient can be instructed how to identify various, typical for him or her, symptoms of hypoglycaemia. Particular attention should be paid to frequent self-monitoring of glucose levels. It is recommended that the patient analyses his or her "body cues" when the glucose measurement indicates hypoglycaemia and he or she does not perceive its evident symptoms. During the time of hypoglycaemia awareness restoration training it is advisable to eat regular meals. Also, physical activity sessions should be repeated during this training time to elaborate a model of exercise-related hypoglycaemia prevention.

Blood Glucose Awareness Training (BGAT) is an educational program based on behavioural therapy. The program was prepared by Cox *et al.* in 1995, and its efficacy has been confirmed in many studies [53]. Another training and therapeutic program is HyPOS, prepared by the Diabetes Academy in Bad Mergentheim. Its effectiveness was confirmed in a randomised controlled study [54].

The DAFNE-HART program successfully implemented psychological intervention into education of people affected by diabetes in order to treat hypoglycaemia unawareness. The structured educational program, including psychological intervention, appears to be a useful therapeutic tool in enhancement of perception of hypoglycaemic episodes in patients with a tendency for hypoglycaemia unawareness [55].

Achieving goals established in educational programs for type 1 diabetes patients with hypoglycaemia unawareness allowed to avoid episodes of severe hypoglycaemia, being a real health and life hazard. Studies confirmed that adequate training on health issues was the most effective tool in reduction of hypoglycaemia incidence. Currently used modern insulin pumps, equipped with the function of automatic suspension of insulin infusion in the event of predicted hypoglycaemia, will not be fully effective if the patients using them are not provided with relevant therapeutic education.

Hypoglycaemia unawareness in young children

Children under the age of six years are particularly prone to hypoglycaemia. Such young patients are usually unable to perceive or report hypoglycaemic symptoms. Due to this inability, they require round-the-clock care of their parents or guardians. A problem arises when a child with type 1 diabetes starts attending kindergarten. Kindergarten personnel, like children's parents, have to be provided with training on how to identify hypoglycaemic symptoms in a child. Day care institution personnel are often fearful of the child's disease, which in many cases results in not accepting the child with diabetes to a school or kindergarten. Besides, it should be emphasised that children aged 6-8 years are still at the stage of central nervous system development while recurrent and severe episodes of hypoglycaemia may contribute to structural changes in the brain, impairment of cognitive functions, and behavioural disturbances in later life [56-58].

The problem of hypoglycaemia unawareness during sleep relates to children of any age, as well as to older ones. Most patients in the developmental age do not wake up at night during a hypoglycaemic episode. Therefore, to prevent severe hypoglycaemic episodes, which most often occur at night, the children's parents/guardians have to control their glucose levels also during the night.

Reimbursement of continuous glucose monitoring (CGM) systems in Poland

Since March 2018, patients under the age of 26 years with type 1 diabetes and hypoglycaemia unawareness, treated with personal insulin pumps, have been entitled to partial reimbursement of the costs incurred for purchase of a CGM. In children who do not positively respond to the first stages of hypoglycaemia unawareness management (functional intensive insulin therapy with the application of insulin analogues, continuous subcutaneous insulin infusion), CGM use is indicated. CGM, equipped with low glucose alarms and prediction alarms, not only significantly reduces the risk of severe hypoglycaemia, but also significantly reduces the fear of hypoglycaemia and improves the quality of life of patients and their families.

Summary

Hypoglycaemia unawareness is a common health issue affecting patients with type 1 diabetes. The increased risk of severe hypoglycaemia poses a great threat for patients. This medical problem is also a great challenge for treating physicians and for whole therapeutic teams. Patients should be provided not only with modern technical solutions that help in diabetes management but also with therapeutic education, psychological support, and with hypoglycaemia awareness trainings. Broad application of CGM and insulin pumps, equipped with the function of automatic suspension of insulin infusion in the event of predicted hypoglycaemia (PLGS), considerably improve the safety and quality of life of patients with hypoglycaemia unawareness.

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