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Fear of hypoglycaemia — from normality to pathology. Diagnostic criteria and therapeutic directions

ABSTRACT

The aim of the article is to summarize the current knowledge on the phenomenon of fear of hypoglycaemia and its impact on the metabolic control and well-being of the population of diabetic patients. The article proposes a description of clinical criteria useful for the diagnosis of the fear of hypoglycaemia in a non-normative and harmful form. Therapeutic directions are presented that have been proven effective in the recent years in reducing the level of maladaptive fear of hypoglycaemia, while also protecting the mental health of the patients. Despite extensive knowledge and numerous clinical trials undertaken in other countries, further research on diabetes-related anxiety disorders in Polish patients is needed. It is also advisable to create a database of culturally adapted management protocols for specialists that could increase the quality and effectiveness of the assistance provided in the outpatient health care. (*Clin Diabetol* 2020; 9; 6: 479–484)

Key words: diabetes, fear of hypoglycaemia, diagnostic criteria, psychotherapy

Introduction

Hypoglycaemia has always been an important issue in the scientific discussions regarding the management of diabetes [1]. Hypoglycaemia is often described as

one of the greatest barriers on the patient's path to normoglycaemia and a risk factor that might lead to the development of life-threatening complications [2, 3]. The experience of hypoglycaemia may be incidental but very unpleasant, leading to lifelong memories of the event.

For reasons that are justified, the occurrence and perspective of experiencing hypoglycaemia may elicit strong emotions in patients. Fear of hypoglycaemia has its legitimate background and an adaptive meaning. Careful self-management and appropriate decisions when managing insulin therapy may successfully protect patients from hypoglycaemia and related consequences. However, fear is associated with some risk. Although it is a universal, primary and natural experience not only for humans, in specific settings it may acquire pathological features, initiate maladaptive mechanisms, and severely disorganize human's life. For good reason, fear has been termed the backbone of the most syndromes known in the contemporary psychiatric practice [4].

Multiple clinical studies have performed regarding the fear of hypoglycaemia and its effect on the therapeutic process, mental health, and subjective wellbeing of the diabetic population. Unfortunately, fear of hypoglycaemia remains very difficult to identify in the inpatient and outpatient practice, as no clear criteria are available to diagnose it in its non-normative, harmful form. However, the most troublesome is the lack of a culturally adapted management protocol that would be dedicated to that issue.

Hypoglycaemia — diagnosis and risk factors

Hypoglycaemia is a common phenomenon in diabetic patients treated with insulin and oral glucose-

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-lowering drugs such as sulphonylureas [5]. It has been estimated that hypoglycaemia, both symptomatic and asymptomatic, may occur thousands of times during the lifespan of an average patient [6].

According to the Polish Diabetes Association guidelines [7], hypoglycaemia should be categorized using three glycaemic/symptomatic thresholds. Alert blood glucose level (level 1) is defined as values below 70 mg/dL (3.9 mmol/L) regardless of the presence or absence of concomitant symptoms. Clinically significant hypoglycaemia (level 2) is defined as blood glucose level below 54 mg/dL (3.0 mmol/L). Severe hypoglycaemia (level 3) is diagnosed based on clinical symptoms associated with severe cognitive dysfunction, without any blood glucose level criterion. A third party intervention is required to terminate a severe hypoglycaemia episode.

At the physiological level, early response to hypoglycaemia involves activation of the autonomic nervous system. Early neurovegetative (adrenergic) symptoms include pallor, muscle tremor, profuse sweating, dizziness and/or headache, anxiety, and nervousness. Later, due to shortage of glucose in the central nervous system cells, neuroglycopenia ensues which is associated with cognitive dysfunction (e.g., confusion, disorientation, attention and memory deficits) and neurological symptoms (slurred speech, irrational or uncontrolled behaviours, loss of consciousness, seizures, nystagmus, reduced responsiveness to stimuli) [8]. The experience and recognition of the above clinical symptoms of hypoglycaemia may show large interindividual variation in the diabetic patient population [9].

The likelihood of an adverse fall in blood glucose level depends on many variables. The major iatrogenic risk factors are inadequate, excessive or maladjusted doses of insulin (or a substance that stimulates insulin release) in relation to the individual requirement, dietary intake (exogenous glucose) and/or planned physical activity [10].

The risk of hypoglycaemia is increased in the settings of reduced endogenous glucose production (e.g., following excessive alcohol intake or in liver failure), increased carbohydrate utilization, or reduced hepatic glycogen stores (e.g., during intense exercise or dieting). Additional risk settings include increased insulin sensitivity (e.g., during or immediately after exercise or during nocturnal rest) and reduced insulin clearance (e.g., in progressive renal failure) [11, 12]. Other risk factors are diabetes duration and type, patient age, reduced hypoglycaemia awareness, and past experience of severe hypoglycaemia [13–16].

Recurrent hypoglycaemia is associated with a risk of irreversible changes and may lead to further complications. Particular risks are associated with cardiovas-

cular changes and events induced by hypoglycaemia. Cardiovascular events may increase the likelihood of sudden cardiac death [13, 17, 18]. Severe hypoglycaemia may affect the vascular system and activate prothrombotic, proinflammatory and proatherogenic mechanisms [19]. Recurrent hypoglycaemia attenuates symptomatic and hormonal responses to the episodes of low blood glucose level, leading to the development of hypoglycaemia unawareness syndrome. The latter is characterized by a reduced or absent ability to identify the onset of hypoglycaemia despite blood glucose level lowering to the values usually associated with warning symptoms [20]. This significantly increases the risk of severe hypoglycaemia [14].

Hypoglycaemia has a major effect on worsened wellbeing and reduced quality of life of diabetic patients [21, 22]. It may also result in reduced professional productivity, increased absence from work, and increased overall costs related to health status [23]. Severe and recurrent hypoglycaemia may increase the overall level of anxiety [24]. Unfortunately, an increasing severity of anxiety is not always a desirable effect in these settings.

Fear of hypoglycaemia — from the norm to pathology

In general, anxiety may be described as a condition of unpleasant discomfort, tension and/or unrest which is accompanied by an increased level of excitation or even specific somatic experiences such as palpitation, tremor, and dyspnoea. In contrast to fear which is felt in response to a defined, recognizable stimulus, anxiety is an anticipatory reaction to an impending stimulus (may arise without a clear cause). From the functional perspective, human ability to feel anxiety is of major importance when safety of an individual is at stake — the protective or defensive reaction is a priority to ensure survival and protection of what is the most valuable [25].

Anxiety is a very complex phenomenon which depends on genetic factors, environmental influences, and combination of both [26]. It is an adaptive signalling-protective mechanism which is important from the perspective of the theory of evolution [27]. Already at the subconscious level, anxiety organizes perception systems, participates in processing information from the sensory channels, directs attention processes (e.g., selection) and memory, engages systems responsible for learning and leads to activation of body's physiological reactions — involuntary but dependent on the form of perceived danger. Most importantly, anxiety contributes much to the overall decision process in the context of choosing the best available behaviour in the situation of a perceived danger [28].

Clinically, non-normative anxiety is recurrent, persistent, and/or objectively inadequate for a given situation [27]. The criterion of inadequacy for a given situation may involve two forms — either excessive anxiety for a low level of danger (e.g., phobia), or inadequately low anxiety for a high level of danger (e.g., denial).

In the context of fear of hypoglycaemia, its adaptive nature depends on the criterion of adequacy of the felt anxiety in relation to the objective risk of hypoglycaemia [29]. Inadequately high level of anxiety in relation to a low risk of hypoglycaemia will lead to escalation of protective and avoidance behaviours. In this situation, the actual danger for the patient is chronic hyperglycaemia induced by interventions aimed to protect from blood glucose level lowering. Conversely, inadequately low level of anxiety in relation to a high risk of hypoglycaemia may also create danger. In this case, hypoglycaemia itself will be a major risk for the patient, as the patient will not try to protect from it, and with time he or she will not even recognize its symptoms due to habituation.

Psychopathologically, anxiety disorder is said to occur when the subjective severity of anxiety, its intensity and frequency lead to disorganization of the individual's life, resulting in suffering [30]. The diabetes self-management process itself should protect the patient from suffering, and at the same time allow active social and professional functioning tailored to the patient's needs, as well as pursuing pastime hobbies and other activities aimed at achieving individual wellbeing and adequate mental health status. Unfortunately, inadequate fear of hypoglycaemia and associated behaviours generate secondary effects in many areas important for the patient, affecting the subjective assessment of quality of life and the severity of depression in both adults and children [30].

Diagnosis of non-adaptive fear of hypoglycaemia

Inadequate fear of hypoglycaemia may be identified based on observation and history taking [32] and may be reflected by laboratory test results (haemoglobin A_{1c} [HbA_{1c}] level) [33]. Studies on the relation between fear of hypoglycaemia and metabolic control of diabetes provided strong evidence that fear may motivate patients to actions directed at preventing hypoglycaemia, thus leading to chronic hyperglycaemia. Obviously, this association is much more complex and involves interactions with many variables, and thus not all studies may be expected to confirm the relation between metabolic control and the severity of fear of hypoglycaemia [29, 34]. For example, some patients

may present with adequate metabolic control, while fear of hyperglycaemia may be reflected in excessive blood glucose level measurements, home isolation, and lifestyle restrictions that preclude professional activities.

The risk of developing non-normative fear of hypoglycaemia is associated with many patient personality features, such as the overall severity of the anxiety as a general feature and the level of neuroticism [29]. However, as shown in multiple studies, the strongest risk factor is patient's previous experience of hypoglycaemia. Fear of hypoglycaemia is associated with both the severity and frequency of previous hypoglycaemia episodes [34, 35]. This phenomenon affects not only diabetic patients but also their close persons (e.g., family members, caretakers of minors with diabetes, partners) [36, 37].

Based on the current studies, one of the best known self-descriptive tools to measure the severity of fear of hypoglycaemia is the Hypoglycaemia Fear Survey (HFS and HFS-II) developed by Cox, Irvine, Gonder-Frederick et al. [38]. This questionnaire includes 33 items measuring the behavioural and affective-cognitive dimensions of the fear of hypoglycaemia. Other screening tools have also been developed during the last 20 years, including the Quick Screening for Fear of Hypoglycaemia (QSFH) [39], an abbreviated and improved version of HFS known as the Fear of Hypoglycaemia Scale (FH-15) [40], and the paediatric version known as the Children's Hypoglycaemia Index (CHI) [41]. Despite their promising psychometric properties, neither HFS-II, its abbreviated versions, nor QSFH and CHI have been adapted to or validated in the Polish population. As result, it is difficult to use them as screening tools in the outpatient diabetes care settings.

Further studies are recommended to identify the special at-risk group in which the problem of non-normative fear of hypoglycaemia might be revealed during the therapeutic process. As indicated by Böhme et al. [42], as healthcare professionals we still do not know enough about our patients, and our patients are too often reluctant to disclose their fear of hypoglycaemia.

Therapeutic directions in the management of fear of hypoglycaemia

Currently, the main therapeutic model in the management and prevention of recurrent hypoglycaemia in the context of non-normative fear of hypoglycaemia is holistic education and increasing awareness of individuals at risk of hypoglycaemia in regard to the risk, diagnosis and management of future hypoglycaemia episodes. Studies confirmed a significant effect of education on self-monitoring of blood glucose and avoidance of hypoglycaemia [43, 44].

The best known psychoeducation protocols targeted at hypoglycaemia include the Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT), HyPOS, and Blood Glucose Awareness Training II (BGAT-2) [45–47]. The common feature of these programs is combining home-based self-monitoring (e.g., keeping a hypoglycaemia diary) with group sessions over several weeks targeted at patient education covering the principles of insulin therapy management, planning actions directed at maintaining normoglycaemia, and coping with extreme situations (e.g., hypoglycaemia and ketoacidosis). Studies on these protocols showed that they are satisfactorily effective in increasing patients' hypoglycaemia awareness and reducing the number of hypoglycaemia episodes. In addition, the BGAT-2 program was also shown to be effective in reducing fear of hypoglycaemia and depressive symptoms and improving the perceived quality of life in patients with diabetes type 1 subjected to this intervention [48].

Fear of hypoglycaemia may also be addressed with cognitive-behavioural therapy (CBT)-based psychotherapy programs which were shown to be highly effective in the treatment of a wide spectrum of anxiety disorders [49]. The 8-week *StyrKRAFT i Ditt Liv*© (Power to Choose your Direction) program developed by Amsberg, Anderbro et al. [50], consisting of 2-hour CBT group sessions and support and monitoring interventions following the end of group sessions, was shown to be associated with significantly lower HbA_{1c} levels in the intervention group at 8, 24 and 48 weeks after program conclusion. In addition, significant beneficial differences between the CBT and control group were also noted in the mean assessment of wellbeing, perceived distress, level of anxiety, and severity of depressive symptoms [51]. Similar effects of individual CBT psychotherapy were shown in a case study by O'Donnell et al. [52]. Graded exposition combined with CBT interventions employed in a patient with diagnosed fear of hypoglycaemia resulted in a reduced fear of hypoglycaemia and lower frequency of protective behaviours targeted at maintaining high blood glucose levels during the day. As a result, the intervention improved self-monitoring of blood glucose parameters and contributed to better mental functioning of the patients (reduction in generalized anxiety and depression).

An important component of the above psychoeducation programs and CBT interventions is an access to modern blood glucose monitoring technologies. These solutions play an important role, providing biofeedback to the patients' therapeutic efforts, which undoubtedly had an effect on the final therapy effect. For example, the HAATT protocol used Accucheck Easy BG, Medtronic's CGMS Gold was used in group CBT, and continuous

glucose monitoring was used in the CBT case study. However, caution is advised in the available literature regarding the use of continuous glucose monitoring systems (CGMS) in patients suspected of anxiety disorders, as this may paradoxically increase their anxiety and lead to treatment discontinuation [52].

Unfortunately, despite many successes in the international arena, there are no Polish adaptations of programs such as HAATT, HyPOS, and BGAT-2 and thus, despite large demand, they are not available for the Polish population of diabetic patients. Developing such culturally adapted psychoeducation protocols is a desired future direction of work for the healthcare community involved in diabetes care and education. Promising results may be obtained with CBT-based psychotherapy. It is important, however, that these interventions be developed based on cooperation of certified psychotherapists and a wide community of specialists involved in diabetes care and education. Controlled access to modern technologies may be a helpful addition to the psychoeducation process and therapy, allowing the patients to monitor changes which highlight the effect of their decisions on the ultimate biopsychophysical outcomes.

Conclusions

Normative fear of hypoglycaemia is consistent with situations where a patient is able to self-identify the existing hypoglycaemia based on clinical symptoms and/or use of blood glucose level measurement technologies, which allows an adequate response to restore normoglycaemia. Adaptive fear of hypoglycaemia will also motivate the patient to plan future behaviours with the aim of maximizing the likelihood of maintaining normoglycaemia and minimizing the occurrences of both hypo- and hyperglycaemia. It will play a regulatory role in terms of daily functioning of the patient (his or her professional, personal, and social activities), his or her physical and mental health, and the subjective wellbeing and satisfaction from life.

Non-normative fear of hypoglycaemia may be diagnosed if it is inadequate to the individual risk of hypoglycaemia. It will induce a harmful effect on the patient's health which may be identified by observation, history taking and/or results of self-monitoring of blood glucose. The pathological component of fear of hypoglycaemia is said to be present when the non-adaptive level of fear and its consequences pose a threat for the patients' wellbeing and mental health, leading to a subjective suffering.

The diagnosis of harmful, non-normative fear of hypoglycaemia in the outpatient or inpatient setting should be preceded by detailed history taking regard-

ing the previous disease course and patient actions in the context of hypoglycaemia. Patients presenting with severe fear of hypoglycaemia should receive adequate medical and psychotherapeutic care. The issue of diagnosing and managing fear of hypoglycaemia should be an inherent component of the recommendations for healthcare personnel caring for diabetic patients. Prompt intervention and help offered to patients with non-normative fear of hypoglycaemia may contribute to better treatment outcomes and preservation of what is most important in the patient's life. Further research is needed on the possible directions of help and support for Polish diabetic patients affected by non-normative fear of hypoglycaemia.

Conflict of interest statement

The authors declare no conflict of interests.

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