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Lidia Witek[1], Irina Kowalska[2], Agnieszka Adamska[3]
[1]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok Clinical Hospital, Poland
[2]Department of Internal Medicine and Metabolic Diseases, Medical University of Bialystok, Poland
[3]Department of Endocrinology, Diabetology and Internal Medicine, Medical University of Bialystok, Poland

# The association between depression and diabetes — the role of the hypothalamo--pituitary-adrenal axis and chronic inflammation

## ABSTRACT

**Depression and diabetes belong to the most common diseases in the human population. Mood disorders are often diagnosed in patients with chronic diseases, including type 1 and type 2 diabetes. Patients suffering from both diseases have been observed to have poorer blood glucose control, an increased risk of complications and mortality compared to the group with diabetes alone. The association between diabetes and depression is complex. Their frequent co-occurrence may be influenced by psychological factors, hormonal and immunological disorders. In depression, hypothalamo-pituitary-adrenal axis dysregulation is observed, which causes peripheral hypercortisolemia. The excess of cortisol leads to hepatic glycogenolysis and reduction in insulin sensitivity of peripheral tissues. It has been proven that depression is accompanied by chronic subclinical inflammation. In this review we present the data regarding the relation between hypercortisolemia, subclinical inflammation and depression in patients with type 1 and type 2 diabetes. (Clin Diabetol 2019; 8, 2: 127–131)**

**Key words: depression, diabetes, hypercortisolemia, inflammation**

Address for correspondence:
lek. Lidia Witek
Klinika Endokrynologii, Diabetologii i Chorób Wewnętrznych
Uniwersytecki Szpital Kliniczny
ul. Marii Skłodowskiej-Curie 24a, 15–276 Białystok
Phone: 85 746 86 07, 85 746 82 39
e-mail: lidiawitek@tlen.pl
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## Introduction

DAWN (Diabetes Attitudes, Wishes and Needs) and DAWN 2 belong to the largest international psychosocial research studies on diabetes [1, 2]. The aim of the projects was to provide new information on the feelings and needs of patients, as well as to determine the direction of changes in health policy. The first edition of the study took place in 2001. The participants were randomly selected from 13 countries, including those suffering from type 1 and 2 diabetes (5104 patients), but also primary care physicians, endocrinologists, diabetologists and nurses (3827 people). Forty-one percent of respondents had poor psychological well-being, only 9% of patients with type 1 diabetes and 12% with type 2 diabetes reported receiving psychological treatment in the past 5 years. Only 42% of health care providers declared that they were able to identify and assess psychological needs of patients and meet those requirements [1]. The DAWN 2 study was conducted in 2011 in 17 countries. The questionnaire was completed by people suffering from diabetes (8596 people), health care workers, but also family members. The influence of diabetes on particular areas of life was evaluated. Over 62% of respondents declared negative effects on physical health, 44.0% on financial situation, 20.5% on relations with family, friends and peers, 38.2% on leisure activities, 35.4% on work or studies, 46.2% on emotional well-being. Over 13% of participants were likely to have depression (WHO-5 Well-Being Index, WHO-5 score $\leq$ 28) [2]. People from Poland also took part in the both studies. According to data from the DAWN 2 study, 19.2% people suffering from diabetes were likely to have depression. Only 8% assessed the organization of healthcare in Poland as good [2, 3].

The conclusions from the above-mentioned studies have contributed to the improvement of the situation of patients with diabetes in countries included in the project, also in Poland.

Since 2006, the guidelines of the Polish Diabetes Association have accentuated the influence of the mental state on therapeutic management in patients with depression and diabetes. Noncompliance with medical recommendations is often associated with psychological problems. Mental condition of a patient should be assessed during every medical visit. The authors of the guidelines suggest that as screening tests, doctors can use two online questionnaires: Well-being index (WHO-5) or Patient Health Questionnaire 9 (PHQ-9), or ask two important questions: "Did you often feel depressed or hopeless during the last month? Did you often lack interest in undertaking various activities or a feeling of pleasure during these activities?". A positive answer to one of the questions has a sensitivity of 97% and a specificity of 67% for the recognize of depression. In case of suspected depression, the patient should be referred for psychiatric consultation [4, 5].

## Depression and diabetes

Depression and diabetes are among the most common diseases in the human population. According to the WHO report, in 2015 the proportion of the global population with depression was estimated to be 4.4%. The prevalence rates depend on age, peaking in older adults, and gender (5.1% among women and 3.6% among men) [6]. The exact number of people suffering from mental illness is difficult to assess. According to the literature, only 15% to 26% of depression cases are diagnosed [7]. Mental disorders often co-occur with chronic diseases such as diabetes, arthritis, asthma, chronic obstructive pulmonary disease, ischemic heart disease, and stroke [8]. The prevalence of depression is more than three-fold higher in people with type 1 diabetes and nearly twice as high in people with type 2 diabetes, compared to the general population [9]. The relationship between the diseases is bidirectional. Despite many studies, it is not yet explained whether depression is a consequence of diabetes or mood disorders are a risk factor for the onset of diabetes. A depressive episode is associated with a 60% increased risk of type 2 diabetes [10]. People with mood disorders are mostly characterized by low physical activity, which predisposes to obesity. It has been observed that depression is significantly associated with the occurrence of metabolic syndrome (in particular abdominal obesity) in people aged 60 years or over [11]. According to a meta-analysis by Luppino et al., obese persons had a 55% increased risk of developing depression, and depressed persons had a 58% increased risk of becoming obese [12]. Older people with depressive symptoms and prediabetes have an increased risk of developing overt diabetes, compared to those with only one disease [13]. People with type 2 diabetes have a 24% higher probability of developing a mental disorder compared with non-diabetic controls. A history of a depressive episode and the occurrence of diabetes-related complications are additional risk factors for the development of mood disorders. Among people with diabetes and major depressive disorder, episodes last longer and are more recurrent than in people without glucose metabolism disorders [14]. In patients with type 1 diabetes, it was observed that depression was associated with an 86% increased risk of severe hypoglycemic events and more than doubled the risk of severe hyperglycemic events causing hospital admission or emergency room care [15]. It was shown that depressed mood, sleeping difficulties, problems with appetite and suicidal ideation were significantly associated with higher glycated hemoglobin ($HbA_{1c}$) values [16]. In the South London Diabetes (SOUL-D) study, people with diagnosed type 2 diabetes were followed for two years. Patients suffering from depression and diabetes were more likely to have macrovascular complications, mainly coronary heart disease (measured by the number of myocardial infarctions and coronary artery bypass graft), and stroke, carotid/limb revascularization or amputations [17]. The coexistence of the two diseases was associated with increased mortality, compared to the group with diabetes alone [18].

It is possible that depression and diabetes are causally related. The coexistence of diseases may result from hormonal and immune system disturbances.

## Dysregulation of the hypothalamo--pituitary-adrenal axis

Chronic stress in depression causes hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis. As a result, it leads to excessive production of corticotropin-releasing hormone (CRH) by hypothalamus and then to secretion of adrenocorticotropin (ACTH) by pituitary gland and consequently, peripheral hypercortisolemia is observed. Physiologically, glucocorticosteroids affect the functioning of many tissues, but are also responsible for the feedback inhibition of the HPA axis — they inhibit the synthesis and release of CRH in the paraventricular nucleus and the secretion of ACTH by the pituitary gland, via glucocorticoid receptors (GR). The negative feedback is disturbed in depression. This phenomenon, called glucocorticoid resistance, is associated with GR dysfunction [19, 20]. A meta-analysis by Stetler and Miller showed that in patients with depres-

sion, especially in older people, cortisol and ACTH levels are increased [21]. The normal HPA axis diurnal rhythm consists of high morning and low afternoon-evening cortisol levels. Mood disorders are associated with flattening of the diurnal cortisol curve [22]. About 64% of people with psychotic depression and 41% of patients with nonpsychotic depression showed non-suppression of cortisol secretion in the low-dose dexamethasone test [23]. Exposure to cortisol promotes differentiation and proliferation of human adipocytes. The receptors for glucocorticoids are more plentiful in visceral than in subcutaneous tissue. This contributes to increased fat accumulation in visceral area, activates lipolysis and release of free fatty acids into the circulation [24]. Triglycerides and nonesterified fatty acids can accumulate in the pancreas and induce beta-cell failure. In addition, chronic exposure to glucocorticosteroids cause insulin resistance in skeletal muscle and hepatic tissues [25]. In a study by Oltmanns et al., a positive relationship between metabolic disturbances and salivary cortisol concentrations in patients with type 2 diabetes was found. Hormone levels were positively related to fasting and postprandial blood glucose and $HbA_{1c}$ [26]. In the group of men and women aged between 26 and 36 years it was found that a depressive disorder was significantly related to insulin resistance as indexed by HOMA-IR [27]. Hormonal dysregulation may lead to disorders in metabolism of carbohydrates. Alterations in the HPA system can be reversed by successful antidepressant therapy [28].

## The inflammatory theory of depression

Scientific evidence supports the role of the immune system in the etiology of depression. Chronic low-grade systemic inflammation can be reflected by increased concentrations of circulating inflammatory markers such as interleukin 6 (IL-6), interleukin 1 beta (IL-1$\beta$), tumor necrosis factor alpha (TNF-$\alpha$) and high sensitivity C-reactive protein (hsCRP). Inflammatory cytokines influence the metabolism of neurotransmitters, activation of the HPA axis and an increase in oxidative stress, which is responsible for degeneration of nerve cells, reduction in synaptic plasticity and activation of microglia [29]. Elevated levels of inflammatory markers are associated with somatic symptoms of mental disorders (fatigue, lack of energy, sleep disorders, changes in appetite) [30].

According to the results of the SOUL-D study, in a group of patients with newly diagnosed type 2 diabetes, symptoms of depression were associated with high concentrations of hsCRP, IL-1$\beta$, interleukin-1 receptor antagonist (IL-1RA), monocyte chemoattractant protein 1 (MCP-1) and leukocytes in the blood [31]. The results of a study by Herder et al. have shown that higher levels of hsCRP and IL-1RA in type 1 and 2 diabetes were associated with an increase in depressive symptoms. In addition, higher interleukin-18 (IL-18) levels and lower adiponectin levels were linked to the greater severity of mood disorders in type 2 diabetes. The associations were not found for IL-6 [32]. The results of another study proved that depression is associated with activation of proinflammatory cytokines, but also with endothelial dysfunction. It has been shown that depression in people with type 1 diabetes is associated with elevated levels of soluble intercellular adhesion molecule (sICAM-1) in the blood, and with elevated levels of hsCRP and increased ratio of high-molecular-weight/total adiponectin in the blood in patients with type 2 diabetes [33].

In addition, it is important to underline that the cytokines affect the HPA axis. Interleukin-1 increases the secretion of CRH and ACTH and leads to impairment of GR activation and translocation from the cytoplasm to the nucleus, resulting in reduced expression of GR. Antidepressants increase GR activation and function [19, 20, 34]. Not all depressed patients have increased inflammatory markers, but a group of severely depressed inpatients with treatment-resistant depression have been shown to have high IL-6, TNF-$\alpha$ and cortisol levels [20, 35]. In type 1 diabetes, a higher baseline level of hsCRP was associated with worse patient response to treatment (sertraline or cognitive-behavioral therapy) during the 3-month and 15-month follow-up [36]. Measurement of inflammatory markers may help in the choice of treatment method. Some antidepressants (escitalopram and fluoxetine) reduce CRP levels [37].

## Conclusion

Depression and diabetes often co-occur. Mental state has a significant impact on treatment of diabetes. Episodes of depression in patients with diabetes are often long-term, difficult to treat and recurrent. Patients suffering from both diseases have an increased risk of the occurrence of diabetes-related complications, including coronary heart disease. Data from literature review suggest that the co-occurence of depression and diabetes result in dysregulation of the HPA axis and chronic subclinical inflammation. Health care providers who care for people with diabetes should know how to recognize depression. Individual approach to each patient is a very important element of successful therapy.

## Conflict of interest

The authors declare no conflict of interest.

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