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## **INTERRELATIONSHIPS BETWEEN AFFECTIVE DISORDERS IN THE FORM OF DEPRESSION AND OBESITY AND OVERWEIGHT**

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**ABSTRACT:** Both depression and obesity are significant health, social and economic problems.

Depressive disorders were the second most common psychiatric disorder in 2017 after anxiety disorders. According to data published by the World Health Organization (WHO), depression affects about 280 million people worldwide, which is about 3.8 percent of the population. The etiology of depressive disorders is very complex and still not fully understood. The theories described so far complement each other. The factors underlying the development of depressive disorders can be divided into biological, psychological and other factors. Eating disorders in the form of overweight and obesity result from a loss of balance between anabolic and catabolic processes. This is most often led by insufficient physical activity and excess caloric intake. Hormonal disorders, genetic factors and environmental factors may also play an important role in the pathogenesis of obesity. The steadily increasing number of people suffering from depression and obesity prompts the search for links between these two seemingly unrelated disease entities. According to current knowledge, these diseases are bi-directionally linked by genetic, psychological, metabolic and social factors. Depression is associated with an increase in the risk of obesity by about 37% relative to those without depression. Obesity is associated with an increase in the risk of depressive disorders by about 18%. Understanding the links that exist between depressive disorders and obesity enables the search for new therapeutic options. The most important conclusion from the scientific research conducted so far is the

advantage of simultaneous treatment of obesity and depression over treating these disease entities individually.

KEY WORDS: depression, obesity, overweight.

#### INTRODUCTION:

The ever-increasing prevalence of depressive disorders and obesity and their many consequences have made these diseases of great interest to researchers. Of particular interest is the link that exists between these two disease entities. In order to determine the mechanisms linking depressive disorders and obesity, we reviewed medical articles published over the past 5 years. The collected information is presented in the following section of the article.

#### DISCUSSION:

##### DEPRESSION BASIC INFORMATION

Among affective disorders in the form of depression, we distinguish between a single depressive episode and recurrent depressive disorders. To diagnose a depressive episode, it is necessary to confirm the presence of at least 2 of the 3 main symptoms and at least 2 additional symptoms for a period of 2 weeks. Main symptoms include lowered mood, loss of interest and ability to feel joy, and decreased energy. Additional symptoms include sleep and appetite disturbances, feelings of guilt and punishment, impaired concentration, low self-esteem, pessimistic thinking about the future and also suicidal thoughts and acts. Depending on the number of symptoms present and their severity, mild, moderate and severe depressive episodes are distinguished [1]. The etiology of depressive disorders is very complex, and the theories described so far are complementary. The factors underlying the development of depressive disorders can be divided into biological, psychological and other [1], [2], [4]. The first theory regarding the development of depression was proposed in the 20th century by Joseph Schildkraut in the 20th century. According to it, deficiency of serotonin, dopamine and

norepinephrine and increased cholinergic conduction are responsible for its development [1],[4],[5]. Pharmacotherapy for depressive disorders is based on it [3]. The development of depression may also be influenced by excessive activation of the hypothalamic-pituitary-adrenal axis caused by chronic exposure to external and internal stressful triggers [1], [6]. The main hormone of this axis is cortisol, excess of which causes a number of unfavorable changes such as an increase in blood pressure, hyperlipidemia, immunosuppression [1], [6]. There are also reports of an inhibitory effect of hypercortisolemia on the processes of neurogenesis [6]. In addition, as a result of excessive influx of calcium ions, apoptosis of hippocampal cells occurs [1]. Structural changes within the brain underlying the development of depression involve not only the aforementioned hippocampus. In a study group including patients diagnosed with depressive disorders, scientific studies have shown reduced volume in the frontal lobes, anterior cingulate, orbital prefrontal cortex and amygdala [1]. Depression also results in excessive activation of the pro-inflammatory response. Levels of pro-inflammatory cytokines such as interleukin 1b (IL-1b), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 18 (IL-18), and tumor necrosis factor (TNF- $\alpha$ ) increase. Some patients also show an increase in acute phase proteins such as haptoglobin, C-reactive protein and acid  $\alpha$ 1-glycoprotein. Pro-inflammatory cytokines affect the synthesis and metabolism of neurotransmitters which explains the influence of the inflammatory process on the development of depressive disorders [1]. Oxidative stress and increased levels of reactive oxygen species may also be important in the development of depression [1]. A theory that links excessive activation of the hypothalamic-pituitary-adrenal axis and abnormal immune responses is the kynurenine pathway disruption theory. Inflammation is responsible for excessive activation of indoleamine-2,3-dioxygenase. This enzyme converts tryptophan into kynurenine. There is a reduced synthesis of serotonin and melatonin. In addition, kynurenine is characterized by neurotoxic and neurodegenerative properties [1]. The transformations of tryptophan are shown in the diagram below [Fig.1].

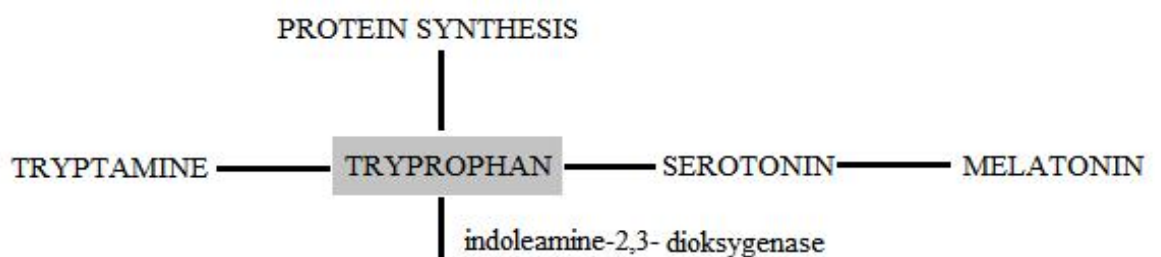


Fig.1. Tryptophan metabolism, the kynurenin pathway.

Genetic factors can also contribute to the development of depressive disorders. Scientific studies provide rather divergent data on the percentage risk of depression if a relative is burdened with it. The risk depends on the degree of consanguinity and ranges from about 10% if a parent develops depression to as much as 40-50% if a monozygotic twin develops depression [1], [7], [8]. Genetic background is most strongly correlated with the development of severe depression [4]. They should be suspected especially in the early development of depression, which occurs during childhood, adolescence and early adulthood [4]. Genetic factors affect not only the risk of developing depression, but also its course by determining, among other things, the response to the pharmacotherapy used. Psychological factors also influence the risk of developing depression. People who are overly sensitive, have difficulty resolving conflicts and dealing with stress, are overly critical of themselves and have low self-esteem are more prone to developing depression. Its occurrence may also be related to the experience of traumatic events [1].

## EPIDEMIOLOGY OF DEPRESSIVE DISORDERS

Depression is a very significant problem both because of its high prevalence and because of the socioeconomic burden it generates. The Global Burden of Disease study conducted by the Institute for Health Metrics and Evaluation-IHME-showed that depressive disorders were the second most common psychiatric disorder in 2017 after

anxiety disorders [9]. According to data published by the World Health Organization (WHO), depression affects about 280 million people worldwide, which is about 3.8 percent of the population. Depression affects about 50% more often women than men. About 4% of men and 5% of women suffer from depression [10]. The increase in the prevalence of depression over the years in both the general population and among children and adolescents is alarming. In 1990, there were about 172 million cases of depression worldwide, about 100 million fewer than today [11]. In 2020, depression was the second most commonly diagnosed disease in the world and, according to estimates by the World Health Organization, in 2030 it could top the list. A factor that has had a significant impact on the increase in the recognition of depression in addition to increased awareness and social change has been the COVID-19 pandemic [12]. Despite well-known treatments for depression, still as many as 75% of people diagnosed with depression in low- and middle-income countries go untreated [10]. Depression places a heavy burden not only on the individual it affects, but also on society as a whole. The financial burden of depression stems not only from the cost of treating it, but also from costs caused by inability to work or accidents and emergencies related to it [13]. In 2019, the excess financial burden caused by depression in the United States amounted to more than \$333 billion [14]. In Poland, according to a report by the National Health Fund, the reimbursement costs of antidepressants in 2013-2018 ranged between PLN 99 and 135 million per year [9]. The exact figures, along with a breakdown by year, are shown in the chart below [Fig.2].

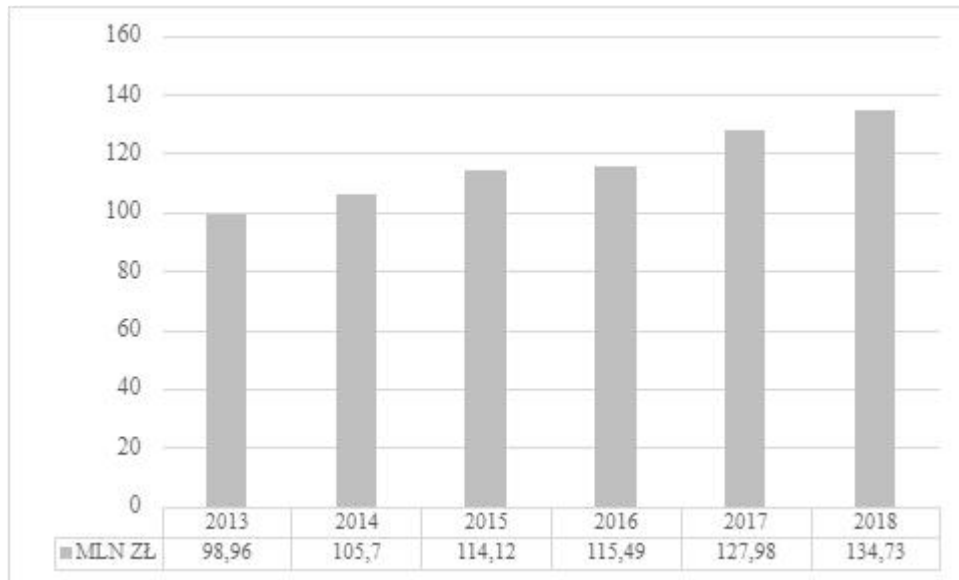


Figure2.

Refundation costs of antidepressants in Poland in 2013-2018.

However, the most serious consequence of depression is premature death by suicide. Every year, more than 700,000 people take their own lives. Suicide is the fourth most common cause of death in the age group between 15-29 years. Nonetheless, suicide is a global problem recorded in every age group [15]. Statistics on suicide in Poland by gender and year are shown in the chart below [Fig.3].

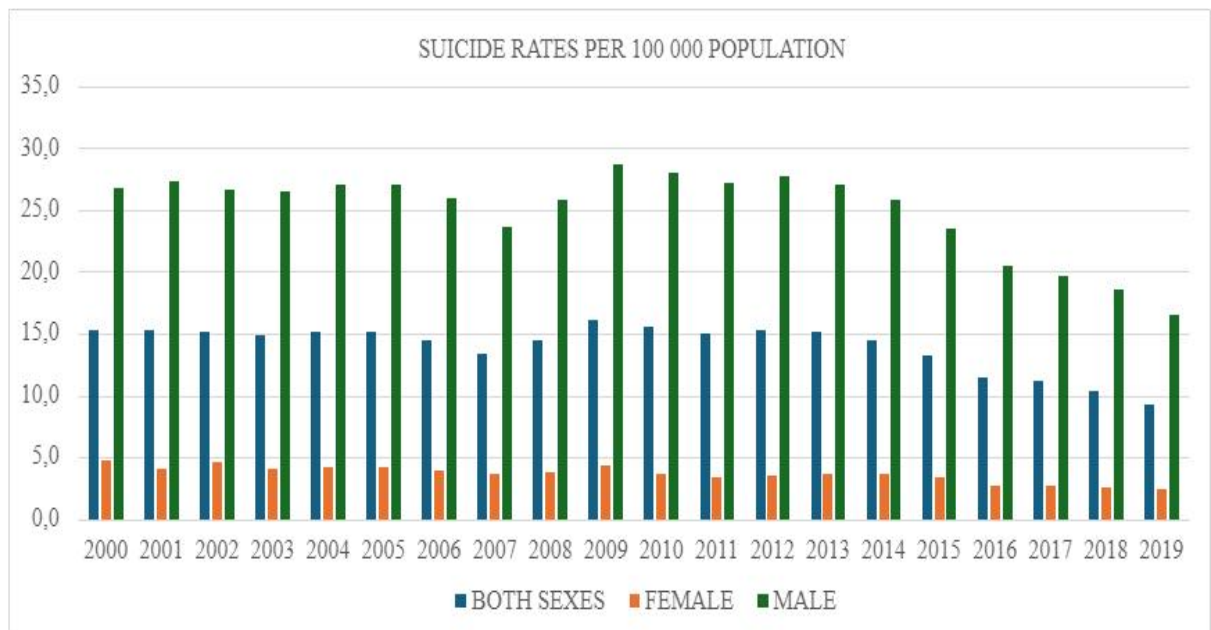


Figure 3 Suicide rates in Poland in 2000-2019

# OBESITY AND OVERWEIGHT

Eating disorders in the form of overweight and obesity result from an imbalance between anabolic and catabolic processes. This is most often led by insufficient physical activity and excess caloric intake. Endocrine disorders, genetic factors and environmental factors may also play an important role in the pathogenesis of obesity [16]. The basic parameter for the diagnosis of overweight and obesity is BMI (body mass index). To calculate it, divide body weight by height in meters squared. The BMI index has numerous limitations. It is characterized by high specificity, but low sensitivity. Above that, the BMI index does not allow differentiation of obesity types by fat distribution, is less reliable in the elderly population and in the male population it is more strongly related to lean body mass. Given the above, it is also important to use other indices such as waist circumference or the ratio of waist circumference to hip circumference [17]. According to the definition proposed by the World Health Organization, overweight is diagnosed when the BMI value is greater than or equal to 25, obesity is diagnosed when the BMI value is greater than or equal to 30 [16]. The prevalence of weight disorders in the form of overweight and obesity is constantly increasing worldwide. According to data published by the World Health Organization (WHO), in 2022, 16% of the world's adult population suffered from obesity and 43% were overweight [16]. In 2016, 13% of the world's adult population suffered from obesity and 39% were overweight [18]. These data are shown in the charts below [Fig.4].



Figure 4: BMI values among the adult population in the world in years 2016 and 2022.



Equally alarming are the data on the prevalence of overweight and obesity among children and adolescents. According to statistics from the World Health Organization (WHO), in 1990 only 8% of children and adolescents in the 5-19 age group were overweight and obese; by 2022 this percentage had more than doubled to 20%. In 1990, 31 million in the 5-19 age group were burdened with obesity, while in 2022 the number of children and adolescents burdened with obesity was as high as 160 million [16]. The data is shown in the charts below [Fig.5].



Fig.5 BMI values among children aged 5-19 in the World

CONSEQUENCES OF OVERWEIGHT AND OBESITY

Weight disorders in the form of overweight and obesity have numerous health, social and economic consequences for both the individual affected and the population as a whole. The economic burden generated by obesity stems from outpatient medical costs, costs associated with hospitalization, financial losses caused by increased sickness absenteeism, earlier retirement benefits and premature deaths. In 2016, obesity-related medical costs in the United States accounted for more than \$260 billion [19]. The annual health care cost incurred by an obese person in the United States was significantly higher than that of a normal-weight person. A significant relationship was observed between an increase in the degree of obesity and an increase in an individual's health care costs [19]. In contrast, the relationship between the degree of obesity with the costs incurred by the population is inverse. Overweight and first-degree obesity generate the highest costs due to the highest prevalence among the

population [20]. Research has shown a strong link between lost work productivity and abnormal BMI or waist circumference [21]. According to a study of more than 4,000 active adults in Portugal, obese people missed about 3.8 more days during the year than those of normal weight [22]. According to estimates, at current trends of increasing prevalence of overweight and obesity, the global costs caused by them will be \$3 trillion in 2030 and about \$18 trillion in 2060 [16]. Equally important are the health consequences of obesity. It increases the risk of developing many diseases such as type two diabetes, cardiovascular disease, fatty liver, chronic respiratory disease, and osteoarthritis [16], [23], [25]. Obesity is also an identified risk factor for bladder, endometrial, colorectal, gastric and liver cancer [24]. Obesity not only increases the risk of the aforementioned diseases, but also negatively affects their course.

## CONNECTIONS BETWEEN DEPRESSION AND OBESITY

The steadily increasing number of people burdened by depression and obesity, as well as the incompletely understood etiology of depressive disorders, have prompted the search for links despite these disease entities. According to current knowledge, these diseases are bi-directionally linked by genetic, psychological, metabolic and social factors [27]. Depression is associated with an increase in the risk of obesity of about 37% compared to those without depression [28]. Obesity is associated with an increase in the risk of depressive disorders by about 18% [26], [28]. The cited study did not find an identical association between overweight and depressive disorder [28]. The most common theory explaining the increased risk of depression among obese individuals is the inflammatory theory [29]. Adipose tissue has a storage and secretory function [30]. Adipokines secreted by adipose tissue are divided into pro-inflammatory and anti-inflammatory. In the course of obesity, there is an excessive secretion of pro-inflammatory adipokines such as leptin, TNF- $\alpha$ , IL-6 and resistin [30]. As a result, systemic inflammation develops, affecting brain structures such as the amygdala, hippocampus, brainstem, and cerebral cortex and, according to scientific studies, may contribute to the development of depression via multiple mechanisms [29], [31]. Pro-inflammatory cytokines can penetrate the blood-brain barrier causing disruption of

monoaminergic neurotransmitter secretion [29]. In addition, inflammation can interfere with neurogenesis and cause neuronal damage [29]. There are also reports of negative effects of obesity on the gut microbiota. According to scientific studies, the composition of the gut microbiota in people burdened by depression differs from that of normal-weight individuals. Decreased levels of anti-inflammatory sodium butyrate and increased levels of bacteria with potential pro-inflammatory properties have been observed [31]. Factors leading to the development of obesity, such as poor nutrition or chronic stressful stimuli, can increase intestinal permeability which enhances the development of inflammation [31]. The impact of disruption of the gut-brain axis on the development of depressive disorders, needs to be further explored for better understanding [29]. Excessive activation of the hypothalamic-pituitary-adrenal axis in response to chronic stress and also inflammation is another mechanism linking depressive disorders to obesity [31]. The adverse effects of cortisol on the brain were described in the previous section of this article. Hypercortisolemia is associated with abdominal obesity and also according to studies with visceral obesity [31]. Another important aspect is the association of depressive disorders with self-esteem [32],[33]. Nowadays, there is a very strong emphasis on physical appearance. In the virtual world, often unrealistic role models are spread, which is a goal that is often impossible to achieve. According to scientific studies, as BMI increases, satisfaction with appearance decreases with the consequence of which may be the development of depressive disorders [32], [33]. Obesity in the course of depression may result from lifestyle changes and decreased physical activity, and may also be a side effect of antidepressant or antipsychotic drugs [31]. It can also result from an increase in appetite in the course of depression. However, this is an uncharacteristic symptom of depression, occurring in the course of atypical depression [34].

## MANAGEMENT STRATEGIES

The ever-increasing prevalence of depressive disorders and overweight and obesity, as well as the significant consequences associated with them, leave no doubt about the need to take action to reverse this trend. The World Health Organization makes

recommendations covering all age groups starting from fetal life. According to them, the weight gain of pregnant women should be controlled, and after giving birth the child should be exclusively breastfed for the first 6 months of life and continued until at least 24 months. A very important role is the formation of healthy patterns from an early age. The role of regular physical activity, limiting time spent in front of a computer, not using stimulants such as tobacco or alcohol, adequate length and quality of sleep and a healthy, balanced diet should be emphasized. The WHO places great emphasis on limiting the consumption of highly processed foods, sugar, salt and fats. At the same time, fruit and vegetable intake should be increased [16]. Treatment of depression is based on psychotherapy combined with pharmacotherapy [10]. It is also important to undertake educational activities aimed at increasing the public's knowledge of depressive disorders, which will help reduce the stigmatization of sufferers and facilitate therapy. It is also important to establish support institutions such as helplines for children and adolescents. Understanding the links that exist between depressive disorders and obesity enables the search for new therapeutic options [31], [35]. A healthy balanced diet and normal body weight can reduce the risk of depression and anxiety disorders. Anti-inflammatory and Mediterranean diets seem to have a particularly beneficial effect [31]. Physical exercise also plays an important role in the treatment of depression combined with obesity. Research has shown positive effects of aerobic training and Pilates on the course of depression [31]. Abnormalities in the composition of the gut microbiota as mentioned earlier in this article may underlie depressive disorders. This has prompted researchers to consider the role of FMT, which is a potential treatment option, albeit one that requires further research [31]. Research has shown that probiotics and prebiotics can have positive effects in the prevention and treatment of depression and obesity [31]. The most important conclusion from the scientific studies conducted so far is the advantage of treating obesity and depression simultaneously over treating these disease entities individually.

## CONCLUSIONS

Both depression and obesity are significant health, social and economic problems. These diseases have been known for years, yet the exact underlying pathomechanisms and the links between them are still not fully understood. Due to the proven bidirectional relationship between depressive disorders and obesity, it is necessary to take measures to treat both diseases simultaneously. It is also important to continue scientific research aimed at better understanding and more effective treatment of them.

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