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## Are metabolic disorders part of a severe mental illness? Historical and current perspective

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### Abstract

**Introduction and purpose:** People with severe mental illness (SMI) live shorter lives than general population. The main cause of mortality in this group is not psychiatric tax diseases, but comorbidities, which are mainly classified as diseases associated with metabolic disorders, such as: obesity, metabolic syndrome (MetS), diabetes type 2, CVDs, coronary artery disease (CAD), cerebrovascular disease. The aim of this review was to identify the factor relating to relationship between metabolic disorders and mental illness.

**Description of the state of knowledge:** People with SMI are characterized by a higher level of adipose tissue in the visceral region (abdominal obesity) compared to the control group, without any mental disorders. Current studies indicate, that persons with SMI have a genetic tendency of to accumulate adipose tissue in the abdominal area. They are also characterized by higher level of body mass index (BMI), overweight or obesity, than general population. This is mostly caused by

lifestyle and specific pharmacological treatment using antipsychotic drug, especially atypical (second generation), which cause weight gain and disturbed carbohydrate metabolism. The fact is, that carbohydrate metabolic disorders were observed in patients with schizophrenia before the first neuroleptic was discovered. Last studies indicated that overweight, obesity may have the same genetic loci as SMI.

**Summary:** SMI seems to be part of a metabolic disorder. This relationship mostly results from the lifestyle, pharmacological treatment, and also the genetic factors. It should be taken into account that the treatment of SMI always requires monitoring of metabolic indicators. Additionally, motivating patients to a healthy lifestyle and physical activity should be the standard of treatment.

**Key words:** metabolic syndrome, diabetes type 2, obesity, severe mental illness

### **Introduction purpose**

Mental illness, due to its long-term character, contributes to the decline in the quality of life [1]. People suffering from severe mental illness (SMI) often experience cognitive difficulties such as: weakened range of attention and memory, psychomotor skills, problems with decision making and reasoning [2]. This often makes it difficult for them to function in everyday life as well as at work. It happens that they are forced to give up their professional career. Often the disease is a barrier to acquiring appropriate professional qualifications and thus taking up employment in the open market. Most psychiatric patients experience financial problems [3]. This often affects the quality of family and interpersonal relationships. As a result, they withdraw from the sphere of social life [4].

Somatic factors also affect the deterioration of quality of life of a person with mental illness. Patients who have experienced psychotic disorders (e.g. schizophrenia) and mood disorders (affective disorder, depression), statistically live shorter than the population without

mental disorders [5]. Viron et al. showed that patients with psychotic and mood disorders live an average of 25 years shorter than the rest of population. According to researches the main cause of death in these groups are complications of cardiovascular diseases (CVDs) [6].

The most common somatic disorders and diseases occurring in people suffering from mental disorders include: obesity, metabolic syndrome (MetS), diabetes type 2, CVDs, coronary artery disease (CAD), cerebrovascular disease, viral diseases such as: human immunodeficiency virus (HIV), jaundice, pneumonia, chronic obstructive pulmonary disease (COPD), cancer, dental diseases [7].

The most important factors leading to health deterioration of people with SMI are: difficulty in accessing adequate medical care - due to persistent symptoms of the underlying disease (e.g. positive and negative), unhygienic lifestyle: low physical activity, inadequate diet, nicotine and addiction to psychoactive substances, usage of neuroleptic drugs - adversely affecting, inter alia, lipid and carbohydrate metabolism and weight gain [8].

Another factor contributing to the deterioration of health of the mentioned above group is the fact that they receive a lower standard of primary care. Often, the comorbid somatic disorders of persons with mental illness are not properly treated or not treated at all by general practitioners and specialist doctors [9-10].

The aim of this study is to find an answer to the question of whether metabolic disorders are part of the SMI picture. PubMed/MEDLINE and Google Scholar data bases were searched for publications describing relationship between metabolic disorders (overweight, obesity, dyslipidemia, carbohydrate metabolism disorders and diabetes) and SMI (schizophrenia and schizoaffective disorder, major depression and bipolar disorder).

## **Description of the state of knowledge**

### **Metabolic disorders and SMI**

#### **Overweight and obesity**

Numerous clinical studies have shown that people suffering from mental disorders are more prone to overweight and obesity, as well as diseases resulting from them, such as: type 2 diabetes, cardiovascular diseases, metabolic syndrome [11], [12]. The first scientific reports in

this regard came from studies conducted on a group of people suffering from schizophrenia. Already at the beginning of the 20th century, long before the appearance of the first neuroleptics, it was observed that people suffering from schizophrenia exhibit more metabolic disorders than people without mental disorders. At the end of the 20th century, a number of studies were carried out in which metabolic disorders in mentally ill people were mainly associated with the effects of neuroleptics [13].

For example, Allison et al. used the data from National Health Interview Survey (NHIS), (N = 80,130 nonschizophrenic and 150 schizophrenic individuals) showed that overweight and obesity as measured by the body mass index (BMI) occurred more often in people with schizophrenia than in the general population, especially in women. The gains in body weight were primarily related [14].

Current research indicates that not only antipsychotic drugs cause metabolic disorders in person with mental illness [15]. Metallize of 136 study, showed that drug naïve patients of schizophrenia have a higher level of adipose tissue in the visceral region (abdominal obesity) compared to the control group, without any mental disorders [16]. This indicates the genetic tendency of people suffering from schizophrenia to accumulate adipose tissue in the abdominal area. Currently, it is assumed that metabolic disorders are a part of the picture of schizophrenia [17].

The tendency to increase body weight also occurs in the group of people suffering from mood disorders. Research by Maina et al. conducted in a group of 76 patients with bipolar disorder who had not been treated pharmacologically so far, showed that compared to a control group of people suffering from obsessive-compulsive disorder (also untreated), patients with bipolar disorders are more likely to be overweight and obese. Interestingly, the depressive episode was much more common in overweight people than in non-overweight people [18].

The above conclusions imply the relationship between overweight and obesity and depressive disorders. In the research of Lin et al. from 2014, a positive correlation was found between obesity and depression. This means that symptoms of depression increase with increasing body weight [19]. Similar relationships were shown earlier. Roberts et al. study conducted in a group of 2,123 people over 50 years of age showed, that after 5 years of obesity, the risk of developing depressive disorders increased. It has been noted that obesity may contribute to depression, but depression does not increase the risk of obesity [20].

A slightly different picture emerges from the long-term studies by Marmorstein et al. from 2014, conducted in a group of teenagers from early youth to late adolescence. It has been shown that young women who experienced a depressive episode in early adolescence were prone to obesity in late adolescence. As the researchers themselves say, the relationship between depression and obesity requires further detailed research [21].

Undoubtedly, the prevalence of overweight and obesity is greater in the group of people suffering from psychotic and mood disorders, especially in SMI. The following factors are associated with the development of overweight and obesity in this group of people with SMI: unhygienic and inactive lifestyle, antipsychotic drugs play a large role, the effects of which will be discussed in detail later [22].

Recent studies show that genetic factors play an important role in the development of overweight and obesity in the group of people with SMI [23]. Tyrrell et al. using data from the UK Biobank, tested 48,791 individuals with depression and 291,995 controls looking for links between BMI and depression. The responses have been explored as to whether the relationship between BMI and depression is a result of the metabolic consequences of obesity. They showed that obesity increased the incidence of depression, especially in women, and it was not due to the metabolic consequences of an increased BMI. According to researchers, genetic predisposition seems to be important in this respect [24].

## **Dyslipidemia**

Lipid metabolism disorders, also known as dyslipidemia, are manifested by an increased concentration of lipids and lipoproteins in plasma. In clinical practice, its two forms are most often diagnosed: hypercholesterolaemia and atherogenic dyslipidemia. Hypercholesterolemia is diagnosed when the concentration of LDL cholesterol in the blood exceeds 115 mg / dl or the total cholesterol (TC) exceeds 190 mg / dl. In contrast, atherogenic dyslipidemia, otherwise known as the lipid triad, is related with coexistence of increased triglycerides (TG > 150mg / dl), low HDL levels (HDL <40mg / dl in men and 45mg / dl in women) and abnormal LDL cholesterol levels [25-26].

It is known that the increase in lipids is associated with excess body weight and is one of the main factors in the development of cardiovascular diseases. These conditions are the leading

cause of death for sufferers for mental disorders. In psychiatrically treated patients, the increase in serum lipids is a consequence of both lifestyle and a tendency to overweight and obesity as well as a consequence of long-term usage of antipsychotic drugs [27].

Wirshing et al. Long-term studies carried out in a group of 215 psychiatric patients before and after the initiation of treatment with antipsychotic drugs, i.e. olanzapine, clozapine, risperidone and haloperidol, showed statistically significant differences between the effects of individual drugs

on the lipid profile of patients. The highest increase in triglyceride levels was noted after the use of olanzapine and clozapine [28].

However, it is disturbing that psychiatric patients are often untreated due to dyslipidemia. It has been shown that only 12% of adults with SMI and diagnosed dyslipidemia received treatment in this area [29-30].

### **Carbohydrate metabolism disorders**

People with SMI tend to be overweight and obese. These diseases contribute to the formation of disturbances in carbohydrate metabolism, which in turn leads to the formation of insulin resistance and, as a result, type 2 diabetes. Many researchers indicate that the prevalence of diabetes in the group of people with mental disorders is higher than in the general population [31].

Irregularities in carbohydrate metabolism are observed three times more often in SMI patients than in the general population [32]. The relationship between schizophrenia and hyperglycemia was observed at the beginning of the 20th century. The first publication by Kooy appeared in 1919, much earlier than the first neuroleptics were used [33]. Subsequent publications from 1921 (Drury and Farron-Ridge), 1922 (Lorenz), 1924 (Barrett & Serre), 1926 (Kasanin), 1944 (Freeman et al), 1945 (Braceland et al) also indicated the relationship between mental disorders and impaired glucose tolerance [34].

This phenomenon was increasingly observed with the use of the first neuroleptics in 1952. It was then that the effect of chlorpromazine administered to 38 patients with psychotic diseases was described for the first time [35]. This has radically changed the effectiveness of the treatment of mental disorders. However, it was quickly noticed that, in addition to significantly improving

the quality of life, neuroleptics led to adverse metabolic changes. As early as in 1954, Dobkin et al. published the results of an experiment in which 7 healthy volunteers were administered chlorpromazine. It was noticed that in these people the level of glucose in blood significantly increased [36]. It is now known that some antipsychotic drugs disturb the carbohydrate metabolism, which in turn contributes to the development of type 2 diabetes. [37].

Both diabetes type 2 and schizophrenia are disorders with a complex, multi-gene and multi-factor inheritance model. Glucose intolerance was noted in patients with the first episode of the disease who had not yet started pharmacological treatment. Abnormal glucose values were noted in family members of patients, it is possible that the same genetic loci are responsible for the tendency to manifest these diseases [38].

Suvisaari et al. conducted research among 8,028 people suffering from schizophrenia and other psychotic and non-psychotic diseases. Researchers point out that type 2 diabetes is one of the main health problems of people suffering from psychotic disorders, and the fact of taking antipsychotic drugs increases the risk of developing type 2 diabetes. The prevalence rate of type 2 diabetes was as follows: 22% among people with schizophrenia, 13.4 % among people with psychoses without affective disorders, 3.4% with psychotic disorders of an affective nature, 6.1% in the group of people without psychotic disorders [39]. Hackinger et al. identified 29 genes associated with diabetes type 2 and schizophrenia. They postulated, that both disorders have the same genetic loci [40].

Calkin et al. maintain that type 2 diabetes is three times more common in patients with bipolar disorder than in those without bipolar disorder, becoming one of the leading causes of death in this group [41].

Another issue is the relationship between type 2 diabetes and depression. Carnethon et al. in long-term studies have shown that the severity of depression symptoms is associated with an increased risk of developing type 2 diabetes. The risk of developing hyperglycemia is 37% higher in people suffering from depression than in people without depressive disorders [42]. It has been shown that depressive disorders have a negative impact on glucose metabolism through increased secretion of hormones that control glucose transport disorders and increased activity of inflammatory factors, which may lead to the phenomenon of insulin resistance [43]. It should be

added that people suffering from depressive disorders tend to lead an unhygienic lifestyle that may lead to the development of chronic diseases [44].

### **Metabolic syndrome**

In recent years, there have been many scientific publications on the subject of metabolic disorders in people with mental illness. This is undoubtedly related to the growing awareness that some antipsychotic drugs contribute to weight gain in patients suffering from mental disorders, which in turn leads to the development of many interrelated somatic factors such as: abdominal obesity, impaired glucose tolerance, hypertriglyceridemia and hypertension [45-46].

MetS is more common in people with mental disorders. It is assumed that in the group of people with SMI about three times more often than in the population of people without SMI [47].

The highest incidence rate is noted in patients with schizophrenia, schizoaffective disorders, then in people with bipolar disorder and also in people with depression. Knowledge of MetS prevalence in other psychiatric diseases is very low and requires further research [49].

It is assumed that the prevalence of individual MetS components in the group of people with schizophrenia is obesity (45% -55%), hypertension (19% -58%), type 2 diabetes (10% - 15%), and lipid disorders (25% -69%) [50]. In the meta-analysis of Malhotra et al. it has been shown that the incidence of MetS in the group of patients treated for schizophrenia ranges from 11% to 69%, and in those not taking antipsychotic drugs from 4% to 26% [51].

MetS prevalence in affective disorder ranges from 16.7% up to 67%, depending on various studies [52]. There are fewer publications in the presence of MetS in depression. Extensive German study in the group of 1,673 people with depression showed that the prevalence rate of MetS was 2.4 times higher than in the control group and amounted to 41% [53].

### **Summary**

SMI are linked with metabolic disorders. Cause of this association is mostly determined by pharmacological treatment, especially using atypical antipsychotics, which lead to weight gain and induced proinflammatory process which can lead to some metabolic disorders like: obesity, diabetes type 2, CVDs. On the other hand, metabolic disorders, are observed in persons with SMI



before starting treatment. It is assumed, that some persons with SMI can have genetic predisposition to overweight and obesity.

The scientists' reports described above imply that there is a relationship between depression, mental disorders and type 2 diabetes, and this fact should be taken into account in the treatment of these diseases.

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