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Diabetes mellitus in patients using psychotropic medications: How does it work?*

Cukrzyca u pacjentów stosujących leki psychoaktywne – jak to działa?

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Summary: Diabetes mellitus (DM) is not a single disease, but a group of diseases that are characterized by chronic hyperglycemia and risk of damage to tissues and organs. The mechanisms of its development are different and due mainly to disorders of insulin secretion or its effects. For this reason, 4 types of DM have been distinguished. One of them is a specific type of DM, determined, inter alia, by the use of certain psychotropic medications. Chronic hyperglycemia often occurs in association with some of these drugs, but in many cases it is categorized erroneously as type 2 (T2DM) or 1 (T1DM). The relationship between DM and psychiatric disorders is bi-directional, involving two mutually independent risk factors for the development of the disease. However, not all patients with a mental illness develop carbohydrate metabolism disorders, which is due to a varied diabetogenic potential and mechanisms of action of psychotropic medications. In clinical practice, questions concerning the frequency of this type of DM, risk factors of its development and hyperglycemic mechanism of psychotropic medications arise. Therefore, the aim of this article is to attempt to answer these questions. From a practical point of view, obtaining such information should allow for the development of appropriate diagnostic and therapeutic procedures.

Keywords: **specific type of diabetes, psychotropic drug-related diabetes mellitus, hyperglycemic mechanism of psychotropic drug**

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INTRODUCTION

Diabetes mellitus (DM) is not a single disease, but a group of diseases that are characterized by chronic hyperglycemia associated with impaired secretion or activity of insulin, resulting in the risk of damage to the tissues and organs (eyes, kidneys, nerves, heart and blood vessels) [26]. Four types of diabetes are distinguished based on the clinical presentation and the different, often overlapping, mechanisms of development of the disease. The third type, specific diabetes, has various clinical presentations, because it develops as secondary to all kinds of disorders and syndromes, genetic, endocrine, pancreatic diseases, or drugs leading to relative or absolute insulin deficiency [3].

It has been suggested that the main risk factors for drug-related DM include the dose of the diabetogenic medication, the duration of its use, as well as the standard risk factors such as the patient's age, the DM-related family history and the body mass index (BMI) value. It should be noted that the mechanism of diabetogenic effect of drugs is not completely understood, and the case is complicated by the diversity of hyperglycemizing potential within the same group. Psychotropic medications are also found among the potentially diabetogenic drugs [9, 25]. In everyday medical practice, patients who are diagnosed with de novo diabetes are often observed, and the collected medical history indicates the presence of mental disorders and the use of various types of psychotropic drugs. Such information raises questions about the type of diabetes. In order to dispel these doubts, it is worth knowing the answers to the following questions:

1. How often does such type of DM develop and which patients are at higher risk of developing it?
2. Is the risk associated with the groups of drugs, or with the specific substances?
3. What are the potential mechanisms of development?

Therefore, the objective of this work is to attempt to answer the above questions, associated with the use psychotropic medications.

From a practical point of view, obtaining such information may allow the development of diagnostic algorithms for carbohydrate disorders in patients with mental disorders. Additionally, understanding the pro-diabetic mechanisms of antipsychotic medications should enable the use of appropriate hypoglycemic drugs.

INCIDENCE AND RISK FACTORS OF DIABETES IN PSYCHIATRIC PATIENTS

Answer to question 1

Carbohydrate disorders is a major health issue that has reached alarming levels. The epidemiological data estimate that in 2019 there were 463 million adults (aged 20-79 years) with DM worldwide, with approximately 50% of that population not aware of the disease. They also point to a large number of patients with "prediabetic conditions", including 374 million people with impaired glucose tolerance. However, the data on the prevalence of specific type DM, especially associated with the use of specific drugs, are scarce [39]. It should be noted that epidemiological studies often qualify drug-related DM as type 2 diabetes mellitus (T2DM) or type 1 (T1DM). The above qualifications are mostly associated with a mild course of the disease and the absence of clinical signs (misdiagnosed as T2DM). In some cases, however, the process is rapid, with diabetic ketoacidosis and hyperglycemic coma (misdiagnosed as T1DM) [15]. On the other hand, epidemiological data indicate that psychotic disorders (schizophrenia, non-affective psychosis, persistent delusional disorders, acute and transient psychotic disorders, schizoaffective disorders, schizotypal disorder, induced delusional disorder) affect approximately 4 per 1000 subjects per year [35].

The association between DM and psychiatric disorders is bi-directional, involving two mutually independent risk factors for their development [1]. It is estimated that DM can affect 1 to 25–50% (on the average, ca. 13%) of patients, including 8.7% with major depressive disorders, 6.2% with bipolar disorders and 12% of patients with severe mental illnesses (schizophrenia, depression, bipolar and psychotic disorders). It should be noted that most of the patients (even as much as up to 70%) are not aware of the presence of DM [23, 44, 47, 49]. British data suggest that the risk for the coexistence of these diseases is highest in the group of patients aged 18–34 years (RR 9.99) compared with those 35–54-year-old (RR 2.89) and ≥55-year-old (RR 1.16) [12].

A high (19%) incidence of "prediabetic conditions" in patients with various types of psychoses has also been observed. However, it is noteworthy that not all psychiatric patients develop different types of carbohydrate metabolism disorders. It has been suggested that the main risk factors include elderly age of the patients, their sense of ill-health, obesity, weight gain, dyslipidemia, unhealthy diet or the use of hypolipemizing medications, the history of DM running in the family, sedentary lifestyle, impairment of cognitive functions, the regional economic situation, high blood pressure, or the use of antihypertensive drugs, increased 5-year cardiovascular risk, the presence of psychosis itself, its duration, severity, the presence of stress associated with the persistent elevation of hypothalamus-pituitary-adrenal axis activity resulting in an increase in cortisol release, as well as some antipsychotic agents used alone or in combinations. As it follows from the above data, the main predictors of developing carbohydrate metabolism disorders in these populations are the common risk factors for T2DM. It has been demonstrated that these factors can exert a stronger influence on the development of "prediabetes" than the used antipsychotic therapy [18, 36, 49]. Patients with psychoses are at risk of developing DM if they have a family history of DM or are currently using antipsychotic drugs [19].

There are more than 20 drugs registered for the treatment of psychotic disorders. Their main mechanism of action is

associated with the mitigation, or blocking of dopamine impact on the D2 receptors. These medications are used to alleviate the symptoms of the disease, although their effectiveness also depends on the safety profile. They include the typical 1st generation drugs (chlorpromazine, haloperidol, fluphenazine, loxapine, promazine, sulpiride, trifluoperazine), characterized, inter alia, by the risk of extrapyramidal side effects and atypical, 2nd generation ones (aripiprazole, clozapine, iloperidone, olanzapine, quetiapine, paliperidone, ziprasidone), which pose the risk of weight gain and adverse effects on the carbohydrate and fat metabolism [30]. As demonstrated by clinical studies, despite the presence of the total risk of developing DM during their use, the diabetogenic potential of psychotropic drugs is very diverse [45]. It has been suggested to result from the mechanisms of action of the particular substances [40].

The above information indicates the potential of psychotropic drugs as the most important risk factor for the development of DM and an indication for the assessment of carbohydrate disorders.

DIABETOGENIC POTENTIAL OF PSYCHOTROPICMEDICATIONS

An answer to question 2

The hyperglycemic potential of different psychotropic medications has been proven to be varied. An analysis of medical databases from 2004-2007 points to 6 antidepressants associated with the risk of DM. They include nortriptyline (with reported odds ratio (ROR) –2.21), doxepin (1.97), imipramine (1.82), sertraline (1.47), mirtazapine (1.33) and amitriptyline (1.31). Bupropion, citalopram, paroxetine, trazodone and desvenlafaxine were less frequently (adjusted reporting odds ratio -aROR<1) associated with DM, while clomipramine, venlafaxine, duloxetine, fluoxetine, escitalopram, nefazodone, fluvoxamine and milnacipran were not associated with DM. Trimipramine, desipramine and maprotiline were associated with diabetes in fewer than three reports. The authors of this study point also to a strong positive correlation between occupancy and aROR for DM identified for the receptors M1, M3, M4, M5 and H1 [41].

In the study of Erickson et al., it was demonstrated that the use of atypical antipsychotics, such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone, paliperidone and ziprasidone, in patients aged 65 years and above is associated with a significant risk (OR 1.63) of the patient developing DM. The most commonly used drugs in that study were risperidone (30-42%), quetiapine (31-40%) and olanzapine (21-26%). Exposure to aripiprazole, clozapine and ziprasidone was minimal. After taking into account the comorbidities, such as hypertension, hyperlipidemia, obesity and dementia, this risk still remained (OR 1.32). It is noteworthy that only the presence of earlier anxiety disorders was associated with a lower frequency of hypoglycemizing medications [14].

Long-term studies indicate a higher prevalence of DM in patients treated with olanzapine patients than in those receiving clozapine. The study was carried out for an observation period sufficient to prove that risk, i.e. for 8 years, and the studied population consisted of 50 patients diagnosed with schizophrenia and/or schizoaffective disorder [16].

In the STAR (Schizophrenia Trial of Aripiprazole) study, using the Stern model, the risk of DM associated with the use of aripiprazole in patients with schizophrenia was estimated to be 23.4 lower that that associated with the standard therapy based on quetiapine, olanzapine and risperidone [6].

A study that compared the efficacy of olanzapine therapy administered orally or as slow-release injections – for 24 weeks showed that the use of both of these drug forms is associated with a mild but significant increase in glucose levels tested after overnight fasting (fasting glucose – FG). A comparison of the two groups of patients receiving the different forms of the drug demonstrated no significant difference in their effect on the FG levels. The difference was noted at the time of comparison of different FG concentration values at the beginning of the test. In patients whose FG showed borderline values at the beginning of the study, a significant average decrease was observed in the course of olanzapine treatment administered orally, whereas in those receiving injections there was a slight, insignificant average increase, which resulted in a significant difference in relation to the group treated orally. Patients with high levels of FG at the beginning of the study did not show a significant difference in the change from the baseline to the endpoint [33].

In a study by Hardy et al. comparing 12-week olanzapine therapy with risperidone therapy, a significant increase in the concentration of FG in the group of patients treated with olanzapine only was noted, without a significant impact on the percentage value of glycated hemoglobin in the compared groups of patients. There was, however, no significant effect of both drugs on the low-insulin phase. In contrast, there was a significant reduction in the high--phase only in the case of olanzapine medication. These changes correlated inversely with the changes in body weight, obesity and were more significant in the group of patients taking olanzapine [21].

In a study by Stroup et al. carried out in the patients with cardiometabolic risk factors (elevated body mass index (BMI) ≥27 kg/m2 and a non-HDL-C ≥3.37 mmol/L (if non--HDL-C was 3.37 to 3.60, then LDL cholesterol was required to be ≥2.59 mmol/L), a significant reduction in the risk of coronary heart disease was observed, despite the fact that there had been no significant reduction in the concentration of FG. Comparing the different therapeutic groups, the highest reduction in the concentration of FG during the 24-week therapy was reported in the quetiapine group (difference of 5.4 mg/dl) vs. the group using olanzapine (2.0 mg/dl) and risperidone (2.8 mg/dl) [43].

During the 5-year follow-up carried out by American scientists in a group of patients treated with clozapine due to

schizophrenia or schizoaffective disorders, the total daily dose of this drug was not found to be associated with a significant risk of patients developing DM, although that disease was diagnosed during the follow-up in 36.5% of the patients. During the 60-month study, 43 of the 82 patients (52.4%) experienced at least one episode of elevated FG (FG value greater than or equal to 7.77 mmol/L) [22].

Particularly noteworthy are the results of a study carried out by Mackin et al. in a group of 90 patients (35.6%; schizophrenia, 30.0%; schizoaffective disorder, 10%; other disorders, 24.4%). The study enrolled 90 participants, including 78 with normoglycemia at the start of the observation, and 6 with IFG and DM. During the therapy, lasting 600 days on the average (SD±235.4; range 328-1175), with different psychotropic substances, it was found that among the patients with normoglycemia only one person had developed DM, and 5 IFG. Its occurrence was associated with the use of quetiapine, amisulpride and risperidone. It should be emphasized that those drugs had already been used at the start of the observation. The only person, who after the follow-up period was diagnosed with DM, had been using olanzapine also at the time of inclusion in the study. In as many as 5 out of 6 patients qualified for the study with diagnosed IFG (receiving olanzapine and clozapine) a regression of carbohydrate metabolism disorders was observed, which was, however, not associated with the reduction of body weight. Such an association was reported in one person with DM treated before and during the study with flupentixol, who was found to have reduced the carbohydrate disorders – IFG [31].

In the case of a study comparing the metabolic safety of sertindole and risperidone, neither of these drugs was shown to affect significantly the increase of glucose levels. It is noteworthy that during the 60 weeks of follow-up, no new onsets of diabetes were observed either in the sertindole or risperidone treatment groups [13].

Quetiapine XR has not been proven to have a significant impact on the concentration of glucose and the risk of developing DM during the 12-week therapy of bipolar depression in the 10–17 years age group [17]. Ziprasidone is another SGA that has been associated with severe hyperosmolar hyperglycemia [28].

The data obtained from NIH (Korean National Health Insurance) and MA (Medical Aid) indicate that more than 10% of children and young people receiving treatment for mental disorders use atypical antipsychotics, which are associated with a higher risk of developing DM. Although that risk was dependent on the age of the patients, their use in the past was not found to be associated with the risk of developing DM. The risk concerned only the recent use of psychoactive substances and was highest in the case of the use of many atypical antipsychotics among schoolchildren (aOR 3.07), higher than in adolescents (aOR 1.78). It should be emphasized that the risk of developing DM was 3.47 times higher in clozapine users, 2.67 times higher in zotepine users, and 2.14 times higher in olanzapine users, and increased in a linear manner with the daily dose of risperidone. Aripiprazole or quetiapine users did not show a distinct learner relationship like that of risperidone, but the adjusted OR for developing DM tended to increase more with heavy doses than with small doses. As a result of the subgroup analysis by psychiatric diagnosis, patients with nonorganic sleep disorders, somatoform disorders, or anxiety showed high adjusted ORs, and it was statistically significant. Otherwise, there was no statistical difference in the adjusted ORs of patients with ADHD or other neurotic disorders [29].

Burcu et al. have demonstrated that in the 5-20 years age group of patients, the addition of SSRIs/SNRIs (selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors) to the treatment with atypical antipsychotics is associated with an increase in the risk of developing DM. Such a correlation was not observed in the case of their addition to the combination therapy with other antidepressants or stimulants. Moreover, a correlation was found between the risk of developing DM and the cumulative dose (RR=1.99 for >2.700mg vs. 1–2.700mg fluoxetine dose equivalents) and the duration of SSRI/SNRI treatment (RR=2.35 for ≥180 days vs. 1-180 days). Such a correlation was not observed in the case of the administration of stimulants. The long duration of the study, 24.8 months, and the large number of patients who started treatment with atypical antipsychotics, 73,224, should be emphasized [7].

A small-scale study carried out by van Keulen et al. (29 hospitalized, elderly patients) revealed that no substantial increase in glucose is noted in short-time preventive haloperidol therapy [48]. It was found, however, that the use of even low doses of lithium for a period of two years increases the risk of DM in patients with mild cognitive impairment and dementia [4].

The recently published results of the GOMAP (Genetic Overlap between Metabolic and Psychiatric disease) study have shown that the prevalence of DM in patients with schizophrenia is significantly higher in the case of treatment with at least three different psychiatric drugs as compared to one or two drugs, after adjustment according to age, BMI, gender, duration of the disease, and the number of schizophrenia-related hospitalizations [32].

The presented data indicate the selected groups of psychotropic drugs with a strong diabetogenic effect, which may be the cause of the development of DM and at the same time constitute indications for diagnostics in carbohydrates disturbances. On the other hand, in patients with risk factors for the development of DM, the hyperglycemic potential should be the criterion for choosing the treatment of mental disorders.

MECHANISMS OF DEVELOPMENTOF DM

Answer to question 3

A few direct and indirect key mechanisms responsible for the development of carbohydrate metabolism disorders in patients taking antipsychotics are currently suggested.

Insulin resistance

This mechanism can develop directly, or in connection with weight gain and obesity. The effect independent of the impact on body weight has been proven in clinical studies and by using animal models for olanzapine and clozapine therapy. These drugs have been demonstrated to be able to inhibit insulin-signaling pathways at different levels in the muscles, hepatocytes and adipose tissue. The association between the presence of obesity, weight gain and the risk of DM has been shown for clozapine, olanzapine and risperidone. It has been proven to be more strongly pronounced in the female sex. Moreover, this effect was found to be associated rather with excessive appetite and food intake than with a reduction in energy expenditure. This is due to the antagonistic effect of antipsychotics on the serotonin 5-HT2C, histamine H1, and dopamine D2 receptors and changes in the gut microbiome. Not without significance is the fact that locomotor activities were reduced by olanzapine and risperidone and reduction of thermogenesis of brown adipose tissue by olanzapine [10].

A study by Teff et al. demonstrates that 9-day treatment with olanzapine increases significantly the postprandial insulin, glucagon and causes a rapid increase in glucagon-like peptide 1 (GLP-1) concentration with a decrease in insulin sensitivity compared with placebo. Aripiprazole induce salso IR, but has no statistical effect on postprandial hormones. It was also found that the metabolic changes occur in the absence of weight gain, increases in food intake and hunger, or psychiatric disease [46]. A meta-analysis conducted by Burghardt et al. indicates that atypical antipsychotics decrease insulin sensitivity and increase weight in healthy volunteers. It was found that decreases in insulin sensitivity were potentially dependent on treatment duration but not weight gain [8].

Animal models indicate that chronic administration of sulpiride is associated with an increase in insulin level and the homeostasis model assessment of insulin resistance (HOMA-IR), which is associated with the induction of fatty liver by phosphorylation of insulin receptor substrate-1 [51].

Antagonistic effect on M3 muscarinic receptors

Olanzapine and clozapine are drugs with the most antagonistic effects on cholinergic muscarinic M3 receptors, located not only in the pancreas, but also in the hypothalamus and brainstem (the areas of the brain that affect insulin levels via the parasympathetic innervation of the vagus nerve of the pancreas). Their inhibition has been shown to reduce the secretion of insulin. These drugs alter M3R density in discrete nuclei of the hypothalamus and caudal brainstem, the regions that regulate glucose homeostasis and insulin secretion through vagal innervation of the pancreas. In addition, the research suggests that the body's glycemic status affects the dynamic sensitivity of the hypothalamus and brainstem M3Rs [50].

Dysfunction and apoptosis of pancreatic β-cells

The devastating effect on the β-cells of the pancreas as the mechanism responsible for hypoinsulinemia and DM may be, in the case of this group of medications, both direct and indirect. The direct apoptotic effect, in which the mitochondrial route is involved, has been proven for clozapine and olanzapine. The indirect effect is related to the impact on the dopaminergic, histaminergic, serotonergic, adrenergic and muscarinic receptors and the consequent inhibition of insulin secretion [10]. In the study by Kopf et al., it was demonstrated that, despite the normal sensitivity of the peripheral tissues to insulin, even a small dose of the D2/D3 amisulipride antagonist, in contrast to olanzapine or placebo, has a stimulating effect on the production of insulin, as evidenced by an increase in the C-peptide secretion [27].

A study comparing the direct effects of haloperidol and clozapine on an animal model demonstrated that these drugs, respectively, increase and decrease β-cell input conductance, an index of K+ permeability. Despite this, neither clozapine nor haloperidol affected basal insulin release, although clozapine inhibited glucose-induced insulin release [5].

Increase in glucagon secretion

The animal model demonstrated that administration of lithium causes a greater increase in glucose level at the time of the coexistence of DM. It has also been shown that intravenous therapy with that drug in the presence of DM is associated with the second increase in glucose levels after 60–90 minutes, without any response from the changes in insulin levels, in contrast to weaker insulin response. During the therapy, an intravenous administration of glucose is associated with a weaker decrease in glucagon level when DM coexists with a similar drug-related glucose level increase. The hyperglycemic effect of lithium is stronger when hypoinsulinemia is present, which is associated with the stimulation of glucagon secretion [24].

Genetic abnormalities

Research indicates that polymorphisms contribute to the development of DM. It has been shown that the polymorphism of cytochrome P450 gene CYP1A2 (alleles of CYP1A2*1C and/or *1D), responsible for the metabolism of clozapine, is associated with an increase in insulin levels and the presence of IR [34]. The studies indicate also the risk of the development of DM in the case of risperidone medication and the coexistence of specific gene polymorphisms (rs741780, rs483082, rs429358, rs7412, rs10119, rs439401 and rs405509) for apoE [11].

It is suggested that the serotonergic system genes are involved in adverse reactions to antipsychotics, including DM. For example, the genotype distribution of the TPH2-366 (T/C) polymorphism (the gene coding for the enzyme, tryptophan hydroxylase subtype 2, which plays a role in the biosynthesis of serotonin) was found to be significantly associated with the presence of DM [2].

Leptin and another cytokines

A link between leptin, a hormone involved in the body's energy homeostasis, and the presence of DM in patients with depression has been confirmed [20]. A study by Srisawasdi et al. demonstrated that in patients with autistic disorders, along with an increase in the daily dose of risperidone, there is a significant decrease in glucose tolerance (increase in the concentration of FG, insulin and HOMA-IR), as well as an elevated concentration of prolactin and leptin. It should be noted that the highest (270%) difference between the groups of patients using a low and a high dose of risperidone was reported for leptin [42]. The relationship between antipsychotic drugs and elevated leptin are also confirmed by the results of the meta-analysis of 42 studies, carried out by Ragguett et al. They have shown that the highest increase in leptin occurs during olanzapine treatment, lower after clozapine, and the lowest after quetiapine and aripiprazole. It should be noted that the type of mental disorders was also significant in the concentration of leptin (more affected in the case of bipolar disorders, less in schizophrenia) [38].

It has been proven that antipsychotic-induced weight gain (secondary to exposure to risperidone) is connected with increased C-peptide, glucose-dependent insulinotropic polypeptide and adipsin concentration. No such impact was found in comparison to adiponectin, ghrelin, GLP-1, glucagon, insulin, leptin, resistin concentration. To the contrary, visfatin, which has insulin-mimetic activity, was significantly higher in the untreated obese patients [37].

Currently, there are no guidelines for the pharmacotherapy of diabetes associated with psychotropic drugs. Understanding the above-mentioned mechanisms of development of this type of diabetes not only allows us to determine therapeutic possibilities, but also indicates the need to determine the influence of antihyperglycemic drugs on these mechanisms.

CONCLUSION

DM often coexists with mental disorders, but it is important to determine its type. DM associated with psychotropic medications is a quite common type of carbohydrate metabolism abnormalities, in many cases qualified incorrectly as T2DM or T1DM. The potential of psychotropic drugs is the most important risk factor for the development of DM and an indication for the assessment of carbohydrate disorders. There are numerous mechanisms responsible for the development of DM, with the main ones including insulin resistance, pancreatic β-cells dysfunction and the M3 muscarinic receptor antagonism. These mechanisms can play a key role in the choice of hypoglycemic therapy.

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