Features of the Metabolic Syndrome and Type 2 Diabetes Mellitus in Schizotypal Disorder

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ABSTRACT

Objective: To describe the features and mechanisms of development of metabolic syndrome (MS), type 2 diabetes melitus (DM2) and intermediate states of glycemia in psychosis the occurrence of these disorders, the values of total cholesterol (TC), fractions of high density lipoproteins (HDL), very low density lipoproteins (VLDL), triglycerides (TG), values of atherogenic coefficient (AC), insulinemia, C-peptidemia, insulin resistance (IR) the level of glycated hemoglobin (HbA1c) in a sample of patients with schizophrenia and in mentally healthy individuals.

Materials and methods: The frequency of carbohydrate metabolism disorders (CMD) was studied. Fasting glycemia was determined, and in the presence of its violation, a glucose tolerance test was performed. MS components were studied in patients with DM2, plasma concentrations of TC, HDL, VLDL, TG, C-peptide (CP), insulin and HbA1c were determined in patients with DM2, AC values and IR indices were calculated using HOMA-IR and CARO criteria.

Results: CMD in schizophrenia are more common than among mentally healthy subjects, amounting to 13.1% (p=0.02), and the main condition here is a significant number of individuals with impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT) among women (CMD p=0.01; IGT p<0.001; IFG p=0.03). A feature of psychiatric sampling is a decrease in HDL by 16.4% (p=0.03) and an increase in AC by 52% (p=0.02). Mentally ill men with MS are characterized by a significantly large value of AC (p=0.019), insulinemia (p=0.02), CP level (p=0.02), HOMA-IR (p=0.01) and CARO (p=0.04) values than in mentally ill patients with DM2 without MS. In comparison with the control, regardless of gender, the schizophrenic patients with DM2 have significantly lower values of insulin (p=0.03), C-peptidemia (p=0.04) and IR, according to the criteria of HOMA-IR (p=0.01) and CARO (p=0.03).

Keywords: schizophrenia, metabolic syndrome, diabetes mellitus, dyslipidemia, insulin, insulin resistance, C-peptide, glycated hemoglobin.

INTRODUCTION

The problem of metabolic syndrome (MS), as well as type 2 diabetes mellitus (T2DM), still remains relevant, despite the current, more advanced than before, diagnostic and treatment programs. Thus, T2DM is often a clinical outcome of MS it has acquired the character of an epidemic. The number of such patients in 2016 alone increased by 3.6% (Dedov et al. 2016; Kryzhanovskij 2002). There is a tendency to "rejuvenation" of MS and diabetes (Kurpatov & Aver'yanov 2006). This type of pathology determines a significant physical, psychological and social maladaptation, contributes to the early disability of patients. Moreover, the problems of the pathogenesis of MS and T2DM are not completely solved, and the treatment of such patients remains an extremely difficult and economically expensive procedure.

It is known that many socially significant diseases are of anthropogenic nature. Evaluation of MS and T2DM from the standpoint of their anthropogenicity determines the need to consider the central mechanisms of regulation and participation of the higher nervous system in the formation of pathology. This approach is not accidental and is based on the importance of these mechanisms in controlling a number of physiological processes, including those responsible for the metabolism and state of the endocrine system (Kryzhanovskij 2002; Kurpatov & Aver'yanov 2006). An important role in the methodology of studying somatic pathology is played by the analysis of its population features. Using it, data were obtained and refined on the causes of the development of diseases, factors aggravating their course, it became possible to predict the subsequent evolution and degree of curability of somatic pathology, to build adequate preventive programs, etc.

This population principle of research in our work is reflected in the analysis of the natural sample of patients - patients with schizophrenia. Due to the characteristics of mental disorder, higher neurogenic functions are not carried out correctly, the hierarchical integrity of the central integrative mechanisms of regulation is violated. This peculiarity of endogenous prerequisites is supplemented by an exogenous modulator - the practice of prolonged or episodic drug therapy of psychosis. This population model makes it possible to examine from a different angle the role of the central nervous system in the formation of somatic pathology, in our case, MS and T2 (Álvarez-Jiménez et al. 2008; Caro et al. 2003; Gianfrancesco et al. 2003; Pourmousa et al. 2018; Tel et al. 2018).

MATERIALS AND METHODS

The study included patients with schizophrenia, observed in a psychiatric clinic and able to cooperate with a doctor. The control group was formed from patients who were treated in somatic departments of multidisciplinary clinics (excluding endocrinology departments), and did not receive drugs that affect carbohydrate metabolism (glucocorticosteroids, β-blockers, etc.). All patients had fasting glycemia. Carbohydrate metabolism disorders were evaluated in accordance with the clinical recommendations of the Russian Association of Endocrinologists in 2015 ("Algorithms for specialized care for patients with diabetes mellitus"). Venous blood plasma glucose levels of <6.1 mmol/L on an empty stomach and <7.8 mmol/L 2 hours after glucose loading were taken as normal values. In the presence of impaired fasting glycemia (plasma glucose concentration> 6.1 mmol/L), an oral test was performed with a glucose load of 75 g. Fasting glycemia of 6.1-7.0 mmol/L and 7 were used as a criterion for impaired glucose tolerance 8-11.1 mmol/L 2 hours after glucose loading. The diagnosis of diabetes was established in the presence of fasting glycemia> 7.0 mmol/L or > 11.1 mmol/L after glucose loading. Then 2 cohorts of patients with T2DM were formed: the study (patients with schizophrenia) and the control (mentally healthy persons). In patients with T2DM, lipid profile parameters (HDL, OXc, TG, VLDLP were determined, an atherogenic coefficient - KA=(OXc-HDL)/HDL)) was additionally calculated, a Cobas c-311 analyzer, Roche, Switzerland, plasma concentrations of insulin and insulin in the blood by immunoelectrochemiluminescent analysis (Cobas E-411, Roche, Switzerland), glycated hemoglobin (HbA1c, Cobas b 101, Roche, Switzerland). The insulin resistance indices (IR) were calculated: HOMA-IR=[fasting insulin (μU/ml)× fasting glycemia (mmol/l)] / 22.5 and CARO=fasting glycemia (mmol/l) / fasting insulin (μI/ml). Then, HbA1c levels were assessed among patients with schizophrenia without MS, T2DM, and intermediate glycemic states under various PFT regimes, and in mentally healthy individuals.

The results were processed using variational-statistical methods using the statistical programs STATISTICA 10.0 (StatSoft, Inc.) and Primer of Biostatistics, 4.03. To compare quantitative traits (described by the median, 25% and 75% quartile), the Mann–Whitney T-test was used for pairwise comparison.

When using the Kruskal–Wallis test, differences of several samples were detected, they were compared by the Dunn test. When comparing qualitative characteristics, the χ^2 criterion was used for an arbitrary contingency table (in the 2×2 table with Yates correction).

RESEARCH AND DISCUSSION

Assessment of the specificity of T2DM consisted in the formation of a psychiatric group, n=336: 165 men (49.1%), 171 women (50.9%). In 21 (6%) patients - 8 men and 13 women, the diagnosis of T2DM was indicated initially, in 4 (2 women and 2 men) was established during our supervision. In addition, there was a state of NTG in 11 women (3.4%), and another 8 women (2.3%) had IHT. Thus, NUOs were present in 44 people (13.1%) with schizophrenia.

The main anthropometric and demographic characteristics of the groups in which the occurrence of NUO was evaluated are shown in Table 1. In order to exclude the influence of these factors on carbohydrate metabolism, the cohorts were formed homogeneous.

Table 1: Demographic and anthropometric characteristics of psychiatric and somatic sampling

	Schizophrenic patients n = 336 (husband / women, 165/171)	Mentally healthy, n = 602 (husband / wives, 207/395)	p
Age	47 [37-56]	52 [40-59]	n / a
Weight, kg	75 [70-80]	78 [67-90]	n / a
Height, cm	167 [160-173]	168 [162-175]	n / a
Body mass index kg / m2	27.1 [24.8-29.1]	27.5 [24.2-31.6]	n / a

Me [lq-uq], median and interquartile values, reliability p by T Mann – Whitney criterion

The control group included 602 people: 395 women (65.6%), 207 men (34.4%). Total, T2DM was present here in 39 (6.45%) people (17 men, 22 women), of which 24 (9 men (1.5%), 15 women (2.5%)) were diagnosed earlier and in 15 people (8 (1.3%) men, 7 (1.2%) women) in the course of our study, another 4 (0.7%) examples accounted for cases of NTG (2 men and 2 women), and NGN (0.7%) (1 man and 3 women). The total number of NLD was 47 (7.8%): of which T2DM 39 and 8 with NTG and NGN - table 2.

Table 2: The prevalence and forms of disorders of carbohydrate metabolism in psychiatric (n=336) and somatic (n=602) samples

	Schizophrenic patients n husband / n women- 165/171	Mentally healthy n husband / n women - 207/395	p
The total number of CID cases	44 (13.1%)	46 (7.6%)	0.02
Men	10	15	0.83
Women	34	31	0.01
Total number of cases of T2DM	25 (7.4%)	39 (6.3%)	0.69
Men	10	17	0.94
Women	15	22	0.68
The total number of cases of NTG	11 (3.4%)	4 (0.7%)	0.01
Men	0	2	0.75
Women	11	2	<0.001
Total number of cases of IUF	8 (2.3%)	4 (0.7%)	0.06
Men	0	1	0.47
Women	8	3	0.03

reliability p by $\chi 2$ criterion

It was found that the prevalence of these disorders here in women is significantly higher than in patients without a mental illness (p=0.011), and the leading role in this is played by NTG (p<0.001) and NGN (p=0.027). On the contrary, in men there was no such intergroup difference.

Further, in order to analyze the specifics of MS and T2DM in schizophrenia, 2 groups are formed: the main group consists of 25 patients with T2DM in a psychiatric hospital (10 men, 15 women). As a control, mentally healthy patients with T2DM (39 people) were: 17 men, 22 women. Against the background of almost coinciding main anthropometric characteristics, patients with schizophrenia, in contrast to the mentally healthy with T2DM, are characterized by significantly lower levels of HDL and higher value of CA. Thus, the HDL concentration by 16.4% (p=0.029) with psychosis was lower than the control values, and the CA indicator by 52% (p=0.017) exceeded them (table 3).

Table 3: Anthropometric and laboratory characteristics of patients with schizophrenia and mentally healthy with impaired carbohydrate metabolism

Criterion	Schizophrenic patients n=25	Mentally healthy n=39	p
Age	54 [48-60.5]	54 [43-62]	n / a
Waist circumference, cm	108.5 [97-115]	103 [95-116]	n / a
Weight, kg	88 [70-104]	96,5 [80-105]	n / a
Height, cm	164 [157-174]	168 [161-178]	n / a
Body mass index, kg/m2	31,8 [26.4-36.5]	32,5 [30,2-37,6]	n / a
Diabetes experience, years	4 [2-5]	3.5 [0-7]	n / a
HDL, mmol/l	1.1 [1.0-1.2]	1.28 [1.1-1.5]	0.03
Holesterol, mmol/l	5.4 [4.6-6.2]	4.6 [4.1-5.8]	n / a
TG, mmol/l	1.9 [1.6-2.1]	1.6 [1.2-2.6]	n / a
KA, units	3.8 [3.0-4.5]	2.9 [1.9-3.7]	0,02
VLDL, mmol/l	1.0 [0.8-1.2]	0.7 [0.6-1.2]	n / a
Glycemia, mmol/l	6.3 [5.6-7.8]	7.3 [6.1-9.6]	n / a

AlcHb, %	6.2 [5.9-7.6]	6.9 [6.3-9.7]	0.02
C-peptide, ng/ml	2.8 [2.1-3.5]	3.1 [2.7-3.9]	0.04
Insulin, mced/l	8.2 [4.2-13.9]	12.2 [9.0-17.1]	0.03
HOMA-IR	2.6 [1.3-4.1]	5.5 [2.6-6.8]	0.01
CARO	1.0 [0.6-1.4]	0.6[0.5-0.9]	0.03

Me [lq-uq], median and interquartile values, reliability p by T Mann – Whitney criterion

The group of mentally ill patients, unlike mentally healthy individuals with T2DM, is also characterized by a significantly lower value of insulinemia and the level of CP. Thus, insulin concentrations by 32.8% (p=0.031), and CP by 10.9% (p=0.037) in psychosis were inferior to control values. Additionally, the HOMA-IR and CARO values for psychosis differed from the figures in the group of mentally healthy individuals by 53.3% (p=0.013) and 37.5% (p=0.034), respectively, indicating a lower level of IR in schizophrenia. In addition, another important characteristic of schizophrenia with comorbid T2DM in our case was HbAlc, which is on average 13.2% lower than its level in patients without mental pathology (p=0.017). In the study, all patients in both groups had abdominal type of obesity, while in some men it was absent. In order to analyze the specifics of lipid and carbohydrate metabolism in schizophrenia in men with and without abdominal type of obesity, 2 groups were formed: in 4 men with schizophrenia there was no abdominal obesity, and in the remaining 6 patients, OT met the main criterion of MS. Significant heterogeneity of these cohorts was demonstrated: mentally ill men with MS were characterized by a significantly higher CA value (p=0.019), insulinemia (p=0.018), CP level (p=0.019), HOMA-IR values (p=0.010) and CARO (p=0.038).

ANs have a number of metabolic effects, including weight gain, effects on carbohydrate metabolism and IR. In this regard, in order to concretize the influence of the PFT factor on the characteristics of T2DM in schizophrenia (insulinemia, SP and IR assessment), two groups of patients were formed: in one, more patients did not use AN, in the latter they were used independently, or together with first-generation antipsychotics (table 4). The average duration of AN therapy was 40 days.

Table 4: Characterization of drug correction of schizophrenia in patients with impaired carbohydrate metabolism

Criterions	Schizophrenic patients, n=25
AN, n (m/f)	6 (2/4)
NPP, n (m/f)	1 (1/0)
NPP + NPP + AN, n (m f)	1 (0/1)
NPP + NPP + Ts, n (m/f)	8 (2/6)
NPP + AN + AD, n (m/f)	2 (1/1)
NPP + C, n (m/f)	6 (3/3)
NPP + C + HELL, n (m/f)	1 (1/0)

AN - atypical antipsychotic, NPP - first generation antipsychotic, C is cyclodol, AD is an antidepressant.

It turned out that such a period of taking AN is not enough to form any noticeable changes in the concentration in the blood serum of HDL, OHC, VLDL, insulin and CP, as well as changes in the parameters of IR and CA (p> 0.05).

Modern population studies indicate a higher prevalence of MS in schizophrenia compared with the general population. Among the factors of this population specificity, two main groups are indicate. On the one hand, a number of retrospective and prospective studies have shown that their occurrence is associated with side effects of using atypical antipsychotics (AN) in the treatment of psychosis (Álvarez-Jiménez et al. 2008; Caro et al. 2002; Gianfrancesco et al. 2003; Lieberman et al. 2005; Lindenmayer et al. 2003). On the other hand, it was established that during therapy and with some NPP, the frequency and degree of visceral obesity, dyslipidemia, and intermediate states of glycemia can increase (Allison et al. 1999; Hwang et al. 2001; Parez-Iglesias et al. 2008). In parallel with this, a wide spread of MS and NUO was found in patients with the first episode of psychosis who were not receiving drugs (De Hert et al. 2006; Sengupta et al. 2008; Thakore et al. 2002). According to the authors, this evidence is in favor of the fact that such metabolic disorders are an integral part of the mental illness itself.

NUOs for schizophrenia are, to some extent, specific. Firstly, the clinical picture of psychosis is characterized by a cyclical course with the presence of exacerbations. These exacerbations, in turn, are accompanied by sympathicotonia and an increase in the level of catecholamines in the blood, mobilization of liver glycogen, hyperglycemia, and a change in tissue sensitivity to insulin.

Secondly, in the past decade and a half, the problem of CID in schizophrenia has mainly been associated with the mechanisms of formation of IR and its metabolic effects as a result of the use of a new group of AN in psychosis. However, NPPs are known to act as modulators of 5-HT1A receptors, and thereby mediate changes in insulin secretio (Beettnger et al. 2000). For example, a hypoinsulinemic response to NPP was noted during experimental injections of high doses of chlorpromazine (chlorpromazine),

although prolonged use of the drug in a therapeutic regimen alone precluded a similar effect in the latter case, the level of glycemia remained stable (Erle et al. 1977). In addition, the significance of AN in the genesis of IR also has an "age qualification": a correlation between the development of MR and the administration of AN is noted only among mentally ill patients under the age of 45 (Martynihin 2009). Additionally, in the nature of hypoinsulinemia in schizophrenia, the possible participation of altered, due to the specifics of the mental illness itself or its pharmacological correction, the alpha-adrenergic receptor link and the special organization of somatostatin production is considered (Li-Chun & Sibille 2013). For patients with type 2 diabetes suffering from schizophrenia, this multidirectional effect on PFT insulin levels is complemented by a similar effect of oral hypoglycemic agents.

CONCLUSION

In a prospective comparative analysis of a sample of patients with schizophrenia (n=336) and a group of mentally healthy individuals, a higher prevalence of carbohydrate metabolism disorders in psychosis was established due to cases of impaired fasting glycemia and impaired glucose tolerance in women. The metabolic syndrome in schizophrenia is characterized by a significant decrease in the level of high density lipoproteins and an increase in the atherogenic coefficient in comparison with a group of mentally healthy subjects. A feature of type 2 diabetes mellitus in psychosis is significantly lower than in the control, the magnitude of insulinemia, C-peptidemia and insulin resistance.

CONFLICT OF INTEREST

None

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