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Original article

Metabolic syndrome or glucose challenge in first episode of psychosis?

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ABSTRACT

Patients with schizophrenia exhibit a reduced life expectancy. Although unhealthy lifestyle or suicide risk plays a role, the main causes are diverse medical conditions such as cardiovascular diseases, type 2 diabetes mellitus and metabolic syndrome. Albeit pharmacological secondary side effects might also trigger previous conditions, studies in naïve patients reflect diverse anomalies at the onset. Patients with a first episode of psychosis, display a wide scope of metabolic abnormalities, ranging from normality till pathological values depending on the parameters studied. We attempted to evaluate the metabolic syndrome and glycemic homeostasis in a subset of antipsychotic-naïve patients with a first episode of non-affective psychosis. Patients (n = 84) showed a similar prevalence of metabolic syndrome compared with a matched control sample (n = 98) (6% vs 4%, P = 0.562), while glucose homeostasis values differed significantly (14% vs. 5%, P = 0.034). Our results suggest that metabolic syndrome is not a useful clinical condition to be evaluated in patients before pharmacological treatment. Abnormal glycemic homeostasis at the onset of the disease requires specific diagnostic tools and preventive measures in order to avoid future cardiovascular events. New strategies must be implemented in order to evaluate the cardiovascular risk and subsequent morbidity in patients at the onset of the disease.

1. Introduction

Schizophrenia is a complex medical disorder with approximately 20% reduction in life expectancy compared with the regular population [1]. This finding cannot solely rely on poor health care access [2], unhealthy lifestyle habits [3], suicide risk [4] or substance abuse [5]. Part of this excess of mortality comes from a constellation of metabolic risk factors called the metabolic syndrome (MetS), already described to be increased in treated patients [6], and correlated with clinical psychopathology [7]. This clinical situation promoted the implementation of physical health monitoring in patients with schizophrenia, as suggested by international societies [8–10] and systematic evaluations [11].

The MetS is strictly defined as a disorder of energy utilization and storage, diagnosed by the co-occurrence of five medical conditions which reflect the probability of developing a certain amount of medical events over time [12]. Although there is a discrepancy for its diagnosis between two major lines of research [13], both include the same five risk factors but differentiate the requirements to fulfill the criteria. Those criteria are described by the International Diabetes Federation (IDF) [14] (Table 1A) and the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) [15] (Table 1B).

Patients with schizophrenia exhibit an increased prevalence of the MetS compared with matched controls [16]. The high prevalence of the MetS in patients has assumed greater significance since the introduction of second-generation antipsychotics which have been associated with substantial weight gain [17], which is a major risk factor for Type 2 Diabetes Mellitus (T2DM) and Cardiovascular Diseases (CVD). Weight gain is more pronounced in antipsychotic-naïve patients at the onset of the disease as those

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Table 1A
Criteria for the metabolic syndrome definition according to the International Diabetes Federation (IDF) [14].

Central obesity: defined as waist circumference ≥ 94 cm for Europid men, ≥ 80 for Europid women. If body mass index (BMI) is > 30 kg/m^2, central obesity can be assumed and waist circumference does not need to be measured
Plus any two of the following four factors
Raised triglycerides: ≥ 150 mg/dL or specific treatment for this lipid abnormality
Reduced High Density Lipoprotein-Cholesterol (HDL-C): < 40 mg/dL for men, < 50 mg/dL for women, or specific treatment for this lipid abnormality
Raised Blood Pressure (BP): systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose: ≥ 100 mg/dL or previously diagnosed type II diabetes

Table 1B
Criteria for the metabolic syndrome definition according to the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP-III) [15].

Three of the following five factors
Central obesity: waist circumference ≥ 102 cm (male) or ≥ 88 cm (female)
Elevated triglycerides ≥ 150 mg/dL or on drug treatment for elevated triglycerides
Reduced High Density Lipoprotein-Cholesterol (HDL-C) < 40 mg/dL (male), < 50 mg/dL (female) or on drug treatment for reduced HDL-C
Blood pressure ≥ 130/85 mmHg or on antihypertensive drug treatment in a patient with a history of hypertension
Fasting plasma glucose ≥ 100 mg/dL or on drug treatment for elevated glucose

patients are more sensitive to secondary side effects [18,19]. Most of the studies in chronic treated patients have shown similar results confirming the MetS as being extremely prevalent [20,21].

However MetS studies in naïve patient with a first episode of psychosis have yielded contradictory results. While some reflect a ratio similar to the general population matched by age and gender [22–25] others reflect an increased prevalence [26,27]. A recent meta-analysis confirmed the low prevalence of the MetS in the early stages compared with chronic treated patients [28].

Glucose abnormalities are components of the MetS (fasting glucose values over 100 mg/dL) which have been historically described to be altered in patients with schizophrenia [29]. They have also been highlighted as an important predictor of mortality risk in patients [30]. Glycemic evaluation in psychiatric patients has received considerable attention in literature since the beginning of the 20th century, either evaluating baseline parameters after glucose challenge or during the studies regarding insulin shock [29]. As fasting glucose might have under-represented the risk of developing T2DM over time, glucose abnormalities were better observed after a metabolic challenge, such as an oral glucose tolerance test (oGTT) [31]. Baseline fasting glucose, the usual measure evaluated, does not differ between patients and healthy controls so the performance in naïve patients of an oGTT could be established as the most effective measurement to assure the risk of glycemic abnormalities [32].

With the previous rationale, we aim to evaluate the prevalence of the MetS in a subset of antipsychotic-naïve patients with a first episode of non-affective psychosis and describe their glycemic state after the performance of an oral glucose tolerance test. We decided to evaluate the MetS with both the NCEP-ATP-III and IDF criteria for epidemiological purposes.

2. Materials and methods

2.1. Subjects

Drug-naïve patients with non-affective psychosis were recruited at the time of their first contact with psychiatric services in a general academic hospital (Hospital Clinic of Barcelona). All subjects gave informed consent for participation in the study, which was conducted under the supervision of the authors' Institutional Review Boards, and came from a larger study of metabolic abnormalities and glucose dysregulation in neuropsychiatric disorders. Control group had no current or prior diagnosis of any Axis I DSM–IV psychiatric disorder, after being assessed with the structured clinical interview for Axis I DSM–IV psychiatric disorders (SCID–I). Additional inclusion/exclusion criteria, clinical and metabolic assessments for all participants have been described in previous articles [33].

Data regarding abnormal glucose homeostasis values has been previously published on 50 patients with psychosis and 50 control subjects [33] and 64 patients with psychosis and 85 control subjects [34] while data regarding two-hour glucose load has been previously published in 84 patients and 98 controls [35].

2.2. Metabolic assessments

All subjects were given a 2 h, 75-g oral GTT, which began between 8 and 9 AM after an overnight fast. Height and weight, while wearing underwear and without shoes, were recorded between the blood samplings. Body Mass Index (BMI) was calculated using the formula (weight [kg]/height [m]^2). Heart rate and blood pressure (in mm of Hg) were measured twice in the forearm, after 5 min of rest. Insulin resistance measured with the Homeostatic Model Assessment (HOMA-IR) is computed with the formula fasting plasma glucose (mg/dL) times fasting insulin (μIU/mL) divided by 405 [36].

Baseline blood sampling included HDL, triglycerides and fasting glucose values. After that subjects swallowed 75 g of dextrose dissolved water. Blood was drawn for the measurement of glucose concentration 2 h after the dextrose was ingested. Glucose tolerance was categorized according to American Diabetes Association guidelines (The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus*, 2003).

2.3. Statistical Analysis

The two matched groups were compared using the non-paired Student's *t*-test, or the χ^2 test for comparisons of proportions. Insulin resistance was evaluated with a non-parametric analysis due to lack of homogeneity in variances (*U* Mann-Whitney). Significance was defined as $P < 0.05$ for all statistical tests, and these were performed using SPSS version 19.0 for Windows.

3. Results

Eighty-four patients were included and assessed according to the IDF and the NCEP-ATP-III-A metabolic syndrome criteria. Ninety-eight matched controls by age, gender, BMI and smoking were used in the analysis (Table 2).

No statistical differences were found between patients and controls regarding any metabolic syndrome criteria (Table 3). No significant differences were found between patients and controls by gender (data not shown).

Table 2
Clinical and metabolic characteristics of the sample.

	Psychosis (n = 84)	Healthy Controls (n = 98)	Statistics, P
Age (years old)	28.8 [8.3]	27.5 [6.0]	0.318
Gender (Male)	65%	59%	0.383
Body Mass Index (kg/m^2)	22.4 [3.9]	23.2 [2.8]	0.149
Smoking (cigarettes per day)	7.7 [8.9]	5.9 [7.9]	0.236