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Metabolic syndrome in drug-naïve and drug-free patients with schizophrenia and in their siblings

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ABSTRACT

Objectives: We tested the hypothesis that metabolic disturbances in people with schizophrenia exist as a part of the schizophrenic syndrome, even when the antipsychotic drug effect is eliminated. We aimed to determine the prevalence of metabolic syndrome among patients with schizophrenia who were antipsychotic drug-naive or drug-free and their siblings for comparison with healthy controls.
Methods: One-hundred-two patients with schizophrenia (drug-naïve or drug-free), 64 siblings and 70 age-matched healthy subjects were recruited for this case–control study. Metabolic syndrome was assessed based on Adult Treatment Panel (ATP) III, adapted ATP III and International Diabetes Federation criteria. Student's *t*-tests, chi-squared tests, Kruskal–Wallis tests and Bonferroni corrections were used as appropriate.
Results: The diagnoses of metabolic syndrome and metabolic disturbances as a subsyndromal state were found to be significantly more frequent in patients and their siblings than in the controls. Low levels of high-density lipoprotein cholesterol and disturbances in blood pressure put the patient group at risk for metabolic syndrome even before they were exposed to antipsychotic drugs.
Conclusions: Although antipsychotic drugs have consistently been related to disturbances of glucose and lipid metabolism in patients with schizophrenia, this study showed that patients with schizophrenia and their siblings are already at a high risk for metabolic syndrome independent of any antipsychotic effects. These individuals should be monitored regularly following a diagnosis of schizophrenia.

1. Introduction

Patients with schizophrenia have a mortality rate that is nearly 2–3 times higher than that of the general population (Black and Fisher, 1992). Although unnatural causes of death, such as accidents and suicide, are common among this population, similar to the general population, the most common causes of death for patients with schizophrenia are natural causes, including cardiovascular diseases and cancer (Brown, 1997; Brown et al., 2000; Osby et al., 2000).

Metabolic syndrome, including abnormalities in glucose and lipid metabolism and obesity, is a well-known risk factor for cardiovascular diseases (Curkendall et al., 2004). Both metabolic syndrome itself and its components have been shown to be more prevalent in patients with schizophrenia than in the general population (Kato et al., 2004). Most of the relevant studies have recruited patients with schizophrenia who are already receiving treatment (Arango et al., 2008; Baptista et al., 2007; Correll et al., 2007; De Hert et al., 2010). Few studies have focused on metabolic disturbances in drug-free and drug-naive patients with schizophrenia (Grover et al., 2012; Pallava et al., 2012; Baptista et al., 2007). In cross-sectional evaluations, the prevalence of metabolic syndrome has been reported to vary from 11–69% among medicated patients and 4–26% among drug-naive patients with schizophrenia (Malhotra et al., 2013). A recent meta-analysis demonstrated that nearly one-third of patients with schizophrenia meet the criteria for metabolic syndrome, nearly half of the patients are overweight, almost 20% of them have hyperglycemia, and 40% have abnormalities in lipid metabolism (Mitchell et al., 2013).

The possible causes for the high prevalence of metabolic disturbances in patients with schizophrenia include poor lifestyle choices, such as a sedentary lifestyle, smoking, poor diet, prolonged stress, antipsychotic drugs and genetic liability (De Hert et al., 2009). It has been hypothesized that the metabolic disturbances that are observed in the course of the illness may be related to schizophrenia itself or may share a common genetic origin with schizophrenia (Verma et al., 2009).

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In this study, we tested the hypothesis that metabolic disturbances among patients with schizophrenia exist as a part of the schizophrenic syndrome even when the antipsychotic drug effect is eliminated. We determined the prevalence of metabolic syndrome among patients with schizophrenia who were antipsychotic drug-naive or drug-free. We also investigated the prevalence of the disease among their first-degree relatives for comparison with healthy controls.

2. Materials and methods

2.1. Subjects

This study took place in the Department of Psychiatry at Ankara Numune Training and Research Hospital, Turkey, between December 2009 and April 2010. All participants (patients, siblings and controls) were evaluated with the SCID-I for the psychiatric diagnoses. All participants were questioned by a researcher regarding whether they had any diagnosis of a medical illness and whether they had used any prescription for a period longer than 3 months for a medical disease. Individuals with known medical diagnoses and those using prescriptions for these illnesses, those with alcohol or substance use disorders other than nicotine, and those with any other psychiatric comorbidities as well as siblings and controls with any psychiatric diagnoses were excluded.

2.1.1. Patients

During the period of the study, 1241 patients meeting the criteria for schizophrenia of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM IV-TR) were admitted to the department. Among these patients, 116 were drug naive ($n = 42$) or drug free ($n = 74$) for at least 8 weeks regarding oral antipsychotics and for 12 weeks regarding long-acting or depot antipsychotics prior to the study. The drug-naive and drug-free patients with diagnoses of schizophrenia were evaluated, and 14 patients with histories of alcohol or substance use disorders or severe medical illnesses (hypertension, diabetes mellitus, or hypothyroidism) and those who refused to participate in the study were excluded. Ultimately, 40 drug-naive and 62 drug-free patients with schizophrenia participated in the study.

2.1.2. Siblings

The siblings of the patients with schizophrenia who were admitted to the department during in the period of the study were invited to participate. Among the 101 siblings, 37 were excluded due to diagnoses of psychiatric or medical illnesses. Sixty-four siblings were enrolled in the study.

2.1.3. Controls

In the hospital in which the study took place, all caregivers and secretaries ($n = 322$) were invited by e-mail to contact their family members to participate in this study as controls. Ninety-eight family members of the respondents were evaluated, and 28 were excluded due to histories of medical or psychiatric illnesses or histories of having a first degree relative with schizophrenia. Thus, the control group consisted of 70 healthy subjects who were relatives of the clinical staff and had no histories of medical or psychiatric diagnoses or familial histories of schizophrenia.

2.2. Measurements

Sociodemographic data were obtained from all participants using a clinician-administered questionnaire. The questions focused on efforts to control weight, regular exercise, nicotine use and sociodemographic data. Regular exercise was defined as at least 30 min of daily physical training 3 days per week. Diet and regular exercise were determined in an effort to control for weight on this questionnaire.

Anthropometric measurements were obtained by the same physician using standard protocols and techniques. Blood pressure was measured using a manual sphygmomanometer and a stethoscope after 15 min of resting in a sitting position. Waist circumference was measured at the level of the umbilicus in a standing position. All blood samples were obtained in the morning after a 12-hour overnight fast, and all samples were analyzed in the same laboratory.

The presence of metabolic syndrome was assessed using the National Cholesterol Education Program, Adult Treatment Panel III (ATP-III) criteria (NCEP, 2001), the adapted ATP-III criteria (Grundy et al., 2004) and the International Diabetes Federation (IDF) criteria (11) (Table 1). Subsyndromal state terms were used to define the states that matched at least two of the criteria of each diagnostic tool.

The homeostasis model assessment (HOMA) index was used as a marker of insulin resistance and was calculated using the following algorithm derived from fasting glucose and insulin concentrations: {[glucose (mg/dl)/18] × insulin (μU/mL)} / 22.5 (Matthews et al., 1985).

2.3. Data analysis

Descriptive statistics were computed for the basic demographic and clinic variables and the variables relevant to metabolic abnormalities. The Statistical Package for Social Science (SPSS) version 15.0 was used to conduct ANOVA and chi-squared tests and the Kruskal–Wallis tests and Mann–Whitney *U* tests that were used as appropriate. Significance was determined at the 0.05 level, and the Bonferroni correction was used when needed.

2.4. Ethical issues

The study was approved by the 4th Ethical Committee of Ankara, which is a regional body composed of medical professionals from the Training and Research Hospitals of the Turkish Ministry of Health in 2009. Written informed consent was obtained from all participants. The study was conducted in compliance with the principles of the Declaration of Helsinki and Good Clinical Practices.

3. Results

3.1. Group characteristics

The sociodemographic and clinical characteristics of the study sample are listed in Table 2. Two-hundred-thirty-six subjects were enrolled in the study. All four groups were matched in terms of age. The patient groups were predominantly male. The patients with schizophrenia and their siblings were significantly more frequently single and unemployed than the controls. The subjects in these three groups exerted significantly less effort to control their weight and to perform regular exercise than the healthy subjects. The level of education was significantly lower in the patient group than in the sibling and healthy control groups ($p < 0.01$). The prevalence of smoking in the four groups did not significantly differ.

The mean age at the onset of schizophrenia in the drug-naive group was 31.8 ± 10.3 years, and the duration of illness was 1.7 ± 1.2 years. The corresponding numbers were 24.6 ± 6.9 years and 3.7 ± 1.2 years in the drug-free group.

Forty of the patients had never been treated with antipsychotics. Sixty-two of the patients had been treated with antipsychotics for longer than at least 8 weeks. The mean untreated time was 68.07 ± 109.33 weeks (minimum: 8 weeks; maximum: 624 weeks). The prevalence of atypical antipsychotic exposure in this group was 64.5%, and 37.3% of the treated patients had been exposed to two or more atypical antipsychotic treatments at the same time (i.e., polypharmacy).

3.2. Metabolic measurements

The high-density lipoprotein (HDL) cholesterol levels were the lowest in the patients who were both drug naive and drug free. The HDL