Psychiatry Research 220 (2014) 71–75

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Phenotypic characteristics in metabolically healthy but obese patients with schizophrenia

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ARTICLE INFO

Article history:
Received 5 March 2014
Received in revised form
2 July 2014
Accepted 9 July 2014
Available online 16 July 2014

Keywords:
Schizophrenia
Metabolically healthy but obese
Insulin resistance
Lipoprotein

ABSTRACT

The purpose of this study was to characterize phenotypic characteristics of metabolically healthy but obese individuals with schizophrenia. Participants were non-diabetic outpatients 19 to 75 years old diagnosed with schizophrenia or schizoaffective disorder. Obese patients (body mass index (BMI) >30 kg/m^2) were included in the present analysis. Patients were further defined as metabolically healthy but obese or obese individuals with metabolic abnormalities based on a cut-off value of 2.5 using the homeostasis model assessment of insulin resistance (HOMA-IR). Fasting blood samples were collected to determine levels of various metabolic parameters. Lipoprotein subclass concentrations and sizes were analyzed using nuclear magnetic resonance (NMR) spectroscopy. Fourteen metabolically healthy but obese patients and 62 obese patients with metabolic abnormalities were identified from 206 patients with schizophrenia. After controlling for age, there were no significant differences between the two groups on anthropometric measures. However, the metabolically healthy but obese group had significantly lower levels of large VLDL particle, significantly higher levels of intermediate VLDL particle, and significantly smaller mean particle size in VLDL compared with the obese group with metabolic abnormalities (metabolically obese). A metabolically healthy but obese phenotype characterized by high levels of intermediate VLDL particle and low levels of large VLDL particle exists in obese, non-diabetic patients with schizophrenia.

1. Introduction

Patients with schizophrenia suffer from increased medical morbidity and mortality compared to the general population (Newman and Bland, 1991). They are reported to be twice as likely to die from cardiovascular disease as compared with those in the general population, with coronary heart disease being the leading cause of death (Casey, 2005; Hennekens et al., 2005). Another study reported that patients with schizophrenia had a 20% shorter life span compared to the general population (Casey et al., 2004).

Metabolic syndrome is a strong risk factor for cardiovascular disease and premature mortality (Janssen, 2005; Sattar et al., 2003). Major components of metabolic syndrome include abdominal obesity, alteration in glucose homeostasis, blood pressure elevation, and dyslipidemia. Patients with schizophrenia are at a much higher risk to develop metabolic syndrome compared to the general population (Grundy et al., 2004; Saari et al., 2005). Previous studies have indicated that insulin resistance plays a central role in the development of diabetes and other metabolic disturbances (Antuna-Puente et al., 2011).

Obesity is more common in patients with schizophrenia compared to the general population. The increased risk for obesity in this patient population is probably caused by multiple factors including sedentary life style, poor dietary habits, alcohol and substance abuse, and the use of antipsychotic medications (Barnett et al., 2007; Fan et al., 2013). The health consequences of obesity have been well established. However, there is increasing evidence that specific phenotypes of obesity exist that appear to deviate from the linear relationship between increased BMI and its adverse clinical outcomes (Brochu et al., 2001; Karelis et al., 2004a, 2004b; Sims, 2001). A group of individuals termed metabolically healthy but obese has been identified in the general population. Those individuals, despite having a high BMI, are relatively insulin sensitive, and have a favorable cardiometabolic profile (Iacobellis et al., 2005; Karelis et al., 2005; Prince et al., 2014; Succurro et al., 2008).

There is no consensus on the definition of metabolically healthy but obese individuals. In some studies, metabolically healthy but obese subjects were classified based on various cut-off values for

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http://dx.doi.org/10.1016/j.psychres.2014.07.015
0165-1781/

insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp technique (Brochu et al., 2001; Karelis et al., 2005). In another study, an arbitrary cut-off value of 1.95 for insulin resistance based on the homeostasis model assessment of insulin resistance (HOMA-IR) was used (Karelis et al., 2004a), while other studies have used a cut-off value of 2.5 (Kuk and Ardern, 2009).

The present study examined phenotypic characteristics of metabolically healthy but obese individuals in a sample of obese, non-diabetic patients with schizophrenia. The study sample was extracted from a multi-center, cross-sectional study originally designed to assess metabolic health in non-diabetic patients with schizophrenia or schizoaffective disorder (Hardy et al., 2006).

2. Methods

2.1. Subjects

Outpatients 18 to 75 years old diagnosed with schizophrenia or schizoaffective disorder were recruited from 28 study sites in the United States. Patients were psychiatrically stable, with no hospitalizations within the previous 3 months. Patients had been receiving olanzapine, risperidone or typical antipsychotic agents continuously for at least 1 year and as monotherapy for the 3 months preceding enrollment. Exclusion criteria included serious and unstable medical illnesses, pregnancy, substance dependence within the previous 3 months, known medical conditions which might affect changes in metabolic parameters, known history of diabetes or lipid disorder, use of glucose-lowering or lipid-lowering therapy or special diets to lower glucose or lipid levels, and use of anti-inflammatory agents.

The metabolically healthy but obese group was defined by BMI >30 kg/m^2 and an insulin resistance value less than 2.5 as calculated by HOMA-IR. The cut-off value of 2.5 was used in a previous study based on a large study sample from the Third National Health and Nutrition Examination Survey (NHANES III) (Kuk and Ardern, 2009). The metabolically obese group was defined as BMI >30 kg/m^2 and HOMA-IR ≥ 2.5.

2.2. Procedures

After providing written informed consent, each subject underwent a physical examination and a psychiatric diagnostic evaluation. Eligible subjects were admitted to an inpatient facility where they received a low-fat meal and were not allowed to ingest alcoholic beverages. Subjects were allowed to drink water during the fasting period. Anthropometric measures including weight, height, umbilicus waist circumference and hip circumference were obtained in the beginning of the inpatient stay. Blood samples were obtained 11 h (± 1 h) after the completion of the meal the night before.

2.3. Blood analyses

Blood analyses were performed at the Covance Laboratories (Princeton, NJ). Fasting serum levels of glucose, total cholesterol, uric acid, HDL and triglycerides were analyzed using standard enzymatic methods and an automated analyzer (Roche Modular Analyzer, Roche Diagnostics, Indianapolis, IN). LDL levels were determined by the Direct LDL reagents (Roche Diagnostics, Indianapolis, IN). Fasting serum insulin levels were analyzed using IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, CA). Fasting plasma glucose and serum insulin levels were averaged from samples drawn 15 min apart. The HOMA-IR was calculated by the following formula: [fasting serum insulin concentration (μIU/mL) $\times$ fasting plasma glucose concentration(mmol/L)/22.5 (Hermans et al., 1999). Serum leptin levels were determined using the Quantikine Leptin EIA (R & D Systems, Minneapolis, MN). Levels of free fatty acid were determined using the WAKO enzymatic non-esterified fatty acid method. The Apolipoprotein B assay was performed by immunonephelometry using the Dade Behring Nephelometer II (Newark, DE).

Lipoprotein subclass concentration and size were determined using nuclear magnetic resonance spectroscopy (NMR, LipoScience, Raleigh, NC) (Otvos, 2002; Otvos et al., 1992). NMR capitalizes on the fact that each lipoprotein subclass particle of a given size emits its own characteristic signal. Conversion factors relating signal amplitudes to subclass concentrations expressed in particle concentration units or in lipid mass concentration units are then applied. In the present study, the lipoprotein subclasses were grouped into the following categories: very low density lipoprotein (VLDL) subclasses (large, intermediate and small), low density lipoprotein (LDL) subclasses (large, intermediate and small), high density lipoprotein (HDL) subclasses (large and small) and intermediate density lipoprotein (IDL).

2.4. Statistical analysis

The data were analyzed using SPSS (version 20.0; SPSS Inc., Chicago, IL). Demographics, clinical measures and laboratory values were reported using descriptive statistics. Group comparisons were performed using student t test, χ^2 test or Fisher's exact test, or analysis of covariance (ANCOVA) controlling for potential confounding variables. For all statistical analyses, a p value of less than 0.05 (2-tailed) was used to test for statistical significance.

3. Results

Two hundred and fifty-two patients enrolled in the original study. Thirty-seven patients were missing fasting plasma glucose levels. Nine patients had fasting plasma glucose ≥ 126 mg/dL suggesting undiagnosed diabetes and were excluded from the analysis as per a priori decision (Genuth et al., 2003). For the remaining 206 patients, 76 had BMI >30. Within these 76 patients, 14 patients were identified as metabolically healthy but obese, and the remaining 62 patients were identified as obese with signs of metabolic abnormalities (metabolically obese). The percentage of metabolically healthy but obese individuals among obese patients was 18.4%.

The metabolically healthy but obese group tended to be younger than the metabolically obese group (37.3 ± 7.6 versus 42.8 ± 10.0 years old, $p=0.060$). However, there were no significant differences between the two groups on disease duration, BPRS total scores, gender, race, family history of diabetes, the use of antipsychotic agents, anti-depressive agents and mood stabilizers (p's >0.100, Table 1).

Further analyses were performed to compare metabolic characteristics between the two groups using analysis of covariance (ANCOVA) controlling for age (Table 2). There were no significant differences on anthropometric measures (weight, BMI, waist circumference, hip circumference and waist/hip ratio, p's >0.140). In addition, there were no significant differences on fasting total cholesterol, HDL, LDL, triglyceride, triglyceride/HDL ratio, leptin, free fatty acid, Apolipoprotein B, and uric acid (p's >0.140).

For the NMR lipoprotein subclasses, the metabolically healthy but obese group had significantly lower levels of large VLDL particle ($p=0.031$), significantly higher levels of intermediate VLDL particle ($p=0.020$), and significantly smaller mean particle size in VLDL ($p=0.017$) compared to the metabolically obese group. There were no significant differences on other NMR lipoprotein subclasses between two groups (p's >0.180).

4. Discussion

This study was the first to characterize metabolically healthy but obese individuals in patients with schizophrenia. The percentage of metabolically healthy but obese individuals (18.4%) among obese schizophrenia patients in our study is consistent with the percentages (11–30%) previously reported among obese individuals in other populations (Karelis et al., 2004b; Pajunen et al., 2011; Wildman et al., 2008).

VLDL is one of the five major groups of lipoproteins (chylomicrons, VLDL, LDL, IDL, and HDL). VLDL enables fats and cholesterols to move within the water-based solution of the bloodstream. It is assembled in the liver from triglycerides, cholesterols, and apolipoproteins. Among various types of lipoprotein, VLDL contains the highest amount of triglycerides. VLDL is converted to LDL in the bloodstream.

Our study found that metabolically healthy but obese schizophrenia patients had lower levels of large VLDL particle compared to metabolically obese schizophrenia patients. In an insulin resistant state, there is hepatic overproduction of VLDL; in addition, the