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Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: A 2 year follow-up study

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ABSTRACT

Objective: Several studies indicate increased prevalence of metabolic syndrome (MetS) among patients with psychiatric disorders as well as among individuals with gender dysphoria (GD) treated by cross-sex hormonal treatment. However, the MetS prevalence among hormone treated GD individuals suffering from psychiatric problems has not been detected.
Methods: From a sample of 146 GD patients we selected 122 metabolically healthy individuals in order to investigate the prevalence of MetS after the beginning of the cross-sex hormonal treatment in a 2 year follow-up assessment. Furthermore, we assessed differences in MetS prevalence between hormone treated GD patients with and without concomitant psychiatric problems.
Results: When treated with hormone therapy, GD patients reported changes in several parameters which are clustered in MetS, with statistically significant differences compared to baseline. Glyco-insulinemic alterations were more pronounced in male to female patients (MtFs). However, weight gain, waist circumference increases, blood pressure increases, and lipid alterations were similar in MtFs and female to male patients (FtMs). 14.8% of the sample at year 1 and 17.2% at year 2 developed MetS. Among patients with concomitant psychiatric problems, 50% at year 1 and 55% at year 2 developed MetS against 8% at year 1 and 10% at year 2 of patients without concomitant psychiatric problems.
Conclusion: This study indicates that sex hormones induce MetS in a relatively low proportion of healthy GD individuals and especially during the first year of hormonal treatment. Most importantly, concomitant psychiatric problems are associated with considerably greater MetS prevalence in hormone treated GD individuals.

Introduction

The first formalized definition of metabolic syndrome (MetS) was proposed in 1998 by the World Health Organization (WHO), considering insulin resistance as the major underlying risk factor necessary for diagnosis [1]. MetS has gradually evolved over time with progressively changing definitions, but the core disturbances, consisting of glucose intolerance (hyperinsulinemia, insulin resistance), obesity (especially a visceral localization of body fat), hypertension (blood pressure ≥ 140/90 mm Hg), and dyslipidemia [high fasting triglycerides (TGs), low high density lipoprotein-cholesterol (HDL-C), small and dense low density lipoprotein-cholesterol (LDL-C)] remain the cornerstone of all diagnostic criteria. All these features predispose the affected individual to an increased risk of cardiovascular disease (CVD) [2–4].

Persons with gender dysphoria (GD) are preoccupied with their wish to live as members of the other gender and experience an incongruence between their assigned gender and their experienced gender [5]. Individuals with GD intensely desire to adopt the social role of the other sex or to acquire the physical appearance of the other sex through cross-sex hormonal treatment and sex reassignment surgery [5]. Men seeking transition to the female sex (MtFs) generally use estrogen and antiandrogens (cyproterone acetate, spironolactone). Women seeking

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transition to the male sex (FtMs) generally use testosterone. The complexity of this treatment is in balancing the psychological needs of patients and adverse effects. In fact, sex steroid hormones have been shown to play an important role in the appearance and development of MetS [6]. Studies on cross-sex hormone administration and sex-appropriate sex hormone administration in healthy subjects suggest that estrogen and testosterone directly affect glucose metabolism, inducing insulin resistance, and induce dyslipidemia and abdominal/visceral fat increases[7–11]. Consistently, studies indicate that sex hormone use in GD may be associated with potential adverse effects such as glyco-insulinemic metabolism disorders, atherosclerosis, dyslipidemia and CVD [12–15]. In particular, individuals with GD, especially MtFs, may experience decreased insulin sensitivity because of hormonal treatment [12,16,17]. Studies on lipid metabolism report an increased atherogenic profile, even during the first year of hormonal treatment [14,15,18–20], also indicating an association between the worsening of lipid parameters and the duration of hormone therapy, both in MtFs and FtMs [15]. Moreover, some studies report hypertension, weight gain and increased prevalence of type 2 diabetes after the beginning of hormone therapy [17,21–24]. Finally, recent studies suggest a higher prevalence of myocardial infarction, cerebrovascular disease, and venous thrombosis and an independent threefold increased risk of cardiovascular death in hormone treated MtFs, with some cases of venous thrombosis and/or pulmonary embolism during the first year of treatment [23–25]. In summary, many of the cardiovascular risk factors clustered in MetS are known to be affected by sex steroid administration in individuals with GD [17].

Recently, research has focused on medical co-morbidities in psychiatric disorders. MetS and CVD have emerged as a major cause of mortality in psychosis and affective disorders [26,27], suggesting the importance of assessing cardiovascular risk in patients with psychiatric disorders. The mechanism underlying the increased prevalence of MetS among patients with psychiatric disorders is not well understood. For both psychosis and depression, a number of explanations have been proposed, including lifestyle and dietary habits (i.e. sedentary behavior, sleep dysregulation, and increased appetite) [28,29], alterations of the hypothalamic–pituitary–adrenal axis (HPA) [30,31], vulnerability to a genotypic peculiar form of MetS [32–35] and direct action of antidepressant and antipsychotic drugs on lipid and carbohydrate metabolism [36–41].

Based on previous research and on our clinical experience, we hypothesized that patients with GD suffering from psychiatric disorders may have metabolic alterations, which could then further be worsened by the subsequent administration of cross-sex hormonal treatment. To our knowledge only one study has comprehensively investigated hormonal treatment induced MetS in a small group of metabolically healthy individuals with GD [17]. In addition, no previous study has investigated the role of concomitant psychiatric problems in the development of MetS in hormone treated GD patients.

This study had two aims: the first was to assess longitudinally the prevalence of MetS after the beginning of the cross-sex hormonal treatment in metabolically healthy subjects with GD without personal or family history of metabolic alterations. The second aim was to compare differences in the prevalence of MetS between GD patients with and without concomitant psychiatric problems.

Materials and methods

Study design and sample

This is a 2 year follow-up study and was conducted at the Gender Identity Unit of Bari University Psychiatric Department as part of a larger research on gender dysphoria patients' psychobiological and mental distress [42–44]. A consecutive series of 146 patients was evaluated for GD from 2008 to 2013. Each patient has been visited by 2 psychiatrists with a special interest in this topic. Each patient has received psychological counseling and has been interviewed according to the semi-structured interview SCID I for psychiatric disorders. All participants met the diagnostic criteria for gender identity disorder in adults according to DSM-IV-TR [45].

Clinical history was obtained from all subjects, including age, sex, personal and family medical history, intake of drugs, smoking and alcohol consumption, levels of physical exercise, previous history of high blood pressure or diabetes, and symptoms of coronary heart disease, ischemic stroke, or peripheral vascular disease. The following inclusion criteria were used in this study: fasting blood glucose (FG) < 100 mg/dl (5.6 mmol/l); triglycerides (TGs) < 150 mg/dl (1.7 mmol/l); total cholesterol (TC) < 240 mg/dl (6.2 mmol/l); body mass index (BMI) < 25 kg/m^2; waist circumference <102 cm for men and <88 cm for women (according to the biological sex), according to the American Diabetes Association (ADA) criteria for MetS [4]; general analytical evaluation (hepatic, renal, and thyroid function, complete blood count, uric acid, and standard urine analysis) within normal limits; no use of medical/recreational drugs for six months prior to the study; alcohol consumption < 35 g per day; and physical activity habits stable for 3 months preceding the enrollment. The following exclusion criteria were used in this study: hypertension (blood pressure ≥ 140/90 mm Hg); consumption of a hypocaloric diet; weight gain or loss > 10% in the 3 months preceding the study; presence of any neurologic or previous treated psychiatric pathology; and presence of any endocrinological or intersexual pathology (as diagnosed by an endocrinologist, and accompanied by hematologic and chromosome profile evaluations).

After clinical screening (medical history, physical examination, and laboratory tests), only healthy subjects with the inclusion criteria were enrolled into the study. A total of 122 subjects [79 (65%) MtFs] were studied; they underwent metabolic parameter evaluation once before the onset of hormone therapy (baseline), once after about 12 months (52.14 weeks ± 17.1 days) of hormone therapy (at year 1) and once after about 24 months (107.75 weeks ± 18.9 days) of hormone therapy (at year 2). The remaining 24 patients (16.4%) were excluded because of their metabolic alterations ($n = 14$, 9.6%) and/or because of their positive family history of metabolic alterations ($n = 18$, 12.3%) which were a potential bias in studying the metabolic risks of hormone therapy. Among the excluded 24 patients with personal/family history of metabolic alterations, 8 had also a previous treated psychiatric pathology ($n = 8$, 5.5%).

Hormonal treatment for MtF patients consisted of transdermal estradiol gel (2.12 ± 0.57 mg/day), in association with oral cyproterone acetate (100 mg/day). The androgen administration schedule in female to male (FtM) patients consisted of testosterone administered as intramuscular injections of a testosterone ester depot (250 mg every 21.16 ± 3.17 days). All the patients in this study received hormonal therapy. The unit has adopted the standards of care guidelines of the World Professional Association for Transgender Health (WPATH) [46]. No patient had undergone any type of surgical intervention during the 2 year follow-up study.

Metabolic parameter evaluation

Blood sample collection

Blood samples were collected after a 12-h overnight fast, 1 h after waking up. Blood samples were deposited in dry tubes with EDTA. The plasma was separated immediately using refrigerated centrifugation at 2500–3000 rpm for a period of 10 min. The samples were processed either immediately or during the first week after conservation at −20 °C. These evaluations were performed on all patients. Blood sampling in FtM patients was performed during the early follicular phase (cycle day 2, 3, 4 or 5) at baseline and halfway between two testosterone administrations at year 1 and at year 2. All tests were performed in accordance with standard procedures [47].