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Sex steroids, insulin sensitivity and sympathetic nerve activity in relation to affective symptoms in women with polycystic ovary syndrome

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Summary
Context: Affective symptoms are poorly understood in polycystic ovary syndrome (PCOS). Clinical signs of hyperandrogenism and high serum androgens are key features in PCOS, and women with PCOS are more likely to be overweight or obese, as well as insulin resistant. Further, PCOS is associated with high sympathetic nerve activity.
Objective: To elucidate if self-reported hirsutism, body mass index (BMI) and waistline, circulating sex steroids, sex hormone-binding globulin (SHBG), insulin sensitivity and sympathetic nerve activity are associated with depression and anxiety-related symptoms in women with PCOS.
Design and methods: Seventy-two women with PCOS, aged 21—37 years, were recruited from the community. Hirsutism was self-reported using the Ferriman—Gallway score. Serum estrogens, sex steroid precursors, androgens and glucuronidated androgen metabolites were analyzed by gas and

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liquid chromatography/mass spectroscopy (GC—MS/LC—MS/MS) and SHBG by chemiluminiscent microparticle immunoassay (CMIA). Insulin sensitivity was measured with euglycemic hyperinsulinemic clamp. Sympathetic nerve activity was measured with microneurography. Symptoms of depression and anxiety were self-reported using the Montgomery Åsberg Depression Rating Scale (MADRS-S) and the Brief Scale for Anxiety (BSA-S).

Results: Circulating concentrations of testosterone (T) ($P = 0.026$), free T (FT) ($P = 0.025$), and androstane-3α 17β-diol-3glucuronide (3G) ($P = 0.029$) were lower in women with depression symptoms of potential clinical relevance (MADR-S $\geq$ 11). The odds of having a MADRS-S score $\geq$11 were higher with lower FT and 3G. No associations with BSA-S were noted.

Conclusion: Lower circulating FT and 3G were associated with worse self-reported depression symptoms. The relationship between mental health, sex steroids and corresponding metabolites in PCOS requires further investigation.

1. Introduction

Affective symptoms are prevalent but poorly understood in women with polycystic ovary syndrome (PCOS), a common premenopausal endocrine disorder (Deeks et al., 2010; Jedel et al., 2010). PCOS is characterized by higher serum concentrations of estrogens, sex steroid precursors, androgens and glucuronidated androgen metabolites (Stener-Victorin et al., 2010). In addition, women with PCOS are more likely to be overweight or obese, as well as insulin resistant (Manneras-Holm et al., 2011). Hyperandrogenism and insulin resistance are two important factors in the pathophysiology of PCOS (Schuring et al., 2008). However, the temporal relationship between these factors is unclear. For example, obesity may lead to insulin resistance; and insulin resistance and compensatory hyperinsulinemia may augment androgen levels (Glintborg and Andersen, 2010; Schuring et al., 2008). Given the global obesity epidemic, potential repercussions in women with PCOS are severe (Teede et al., 2010). PCOS is also associated with high sympathetic nerve activity and it has been proposed to contribute to the etiology of PCOS (Sverrisdottir et al., 2008). Interestingly, high circulating testosterone is associated with high sympathetic nerve activity (Sverrisdottir et al., 2008).

Adverse correlates of PCOS are both psychological and physical. Women with comorbid PCOS and depression have been observed to have higher body mass index (BMI) and insulin resistance compared to women with PCOS without depression (Hollinrake et al., 2007). Medication use may play an important role in this observation, as women on psychotropic medication are more likely to experience weight gain (Tschoner et al., 2007).

Several studies of mood and related factors have been conducted among women with PCOS (Adali et al., 2008; Mansson et al., 2008; Moran et al., 2010). In these studies, higher BMI has been related to symptoms of depression and anxiety (yet without diagnosed affective disorder) (Adali et al., 2008; Moran et al., 2010); higher emotional distress (Adali et al., 2008); and lower health-related quality of life (Moran et al., 2010). Women with PCOS may also be more likely to fear future health consequences related to weight gain compared with controls (Moran et al., 2010). Despite this, reports from our study suggest that BMI is not related to depression and anxiety-related symptoms in women with PCOS (Jedel et al., 2010).

It is unclear whether biochemical hyperandrogenism is associated with depression and anxiety symptoms in women with PCOS (Adali et al., 2008; Weiner et al., 2004). Exploratory analyses of a pooled PCOS case-control study observed a curvilinear relationship between free testosterone (FT) and negative mood, such that the most depressed women were those with FT concentrations exceeding the upper and lower reference values (Weiner et al., 2004). However, within a smaller sample of 42 women with PCOS, there were no correlations observed between testosterone (T), dehydroepiandrosterone sulfate (DHEAS) and depression scores (Adali et al., 2008). Nor were correlations observed between the homeostasis model assessment of insulin resistance (HOMA-IR) and depression scores (Adali et al., 2008). Further, higher free androgen index has been observed in women with PCOS and social phobia (Mansson et al., 2008).

Single unit nerve recordings of muscle sympathetic nerve activity (MSNA) show higher incidence of sympathetic nerve single-fiber multiple firing in patients with high degree of psychological distress and panic disorder (Lambert et al., 2006), major depressive disorder (Lambert et al., 2008) and anxiety (Lambert et al., 2010). Thus, high sympathetic activity, as observed in women with PCOS (Sverrisdottir et al., 2008), may contribute to their affective symptoms.

Affective symptoms require further exploration in women with PCOS, including examination in relation to specific features of the syndrome. In this study we sought to determine whether depression and anxiety-related symptoms in drug-naïve women with PCOS is associated with their previously reported hyperandrogenism (hirsutism and circulating sex steroids), insulin resistance and/or high sympathetic nerve activity.

2. Materials and methods

2.1. Participants

This cross-sectional study was conducted at the Sahlgrenska Academy, University of Gothenburg, Sweden. Potential participants were recruited from the community between November 2005 and September 2008 by advertising for women aged 18—37 years. Polycystic ovarian morphology was part of the PCOS diagnostic inclusion criteria, and women were included in the current study if the following criteria were fulfilled: 12 or more 2—9 mm ovarian follicles and/or