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Review

Adipocyte biology in polycystic ovary syndrome

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrinopathy that is associated with an adverse metabolic profile including insulin resistance. There is a clear association between obesity, the development of PCOS and the severity of its phenotypic, biochemical and metabolic features. Evidence to support this link includes data from epidemiological, pathophysiological and genetic studies. Given the importance of obesity in the development and manifestation of PCOS, ongoing research into the many facets of adipocyte biology in women with the condition is important and should continue to be a priority. In this review article, we discuss the existing literature on fat distribution, adipokines, adipocyte hypertrophy and adipocyte steroid metabolism in women with PCOS.

Contents

1. Introduction

Although not part of the diagnostic criteria for PCOS (2004a,b), it is well-established that metabolic dysfunction, including insulin resistance, is associated with PCOS and forms part of its phenotype (Talbott et al., 1998; Legro et al., 2001; Berneis et al., 2006; Dunaif et al., 1989; Dunaif, 1997; Venkatesan et al., 2001; Ehrmann et al., 2006; Dokras et al., 2005; Glueck et al., 2003; Apridonidze et al., 2005). There is a high prevalence of metabolic syndrome in women with PCOS, estimated to be between 34% and 46%, based on studies of white women with PCOS from the US using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria (Ehrmann et al., 2006; Dokras et al., 2005; Glueck et al., 2003; Apridonidze et al., 2005). Although the risk of developing

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Type 2 Diabetes Mellitus (T2D) and other cardio-metabolic risk factors is higher in PCOS than in the general female population (Wild et al., 2000), the translation of this risk into higher rates of cardiovascular *events* and mortality has not been demonstrated convincingly in any long-term prospectively designed study in PCOS to date. (The design and execution of such a study should be a priority within this field.) However, it is clear that pathways implicated in metabolic dysfunction that are influenced by obesity also impact on the manifestations of the reproductive and hyperandrogenic features of PCOS, and probably play important roles in its aetiology (Barber et al., 2006; Legro, 2000; Balen et al., 1995; Franks et al., 2000; Robinson et al., 1993; Dunaif, 1997; Morin-Papunen et al., 2000). Although there is a clear association between fat mass and the presentation of PCOS, including the severity of its clinical, biochemical and metabolic features, the actual mechanisms involved are incompletely understood.

The association of PCOS with metabolic dysfunction and obesity, and the role of weight gain in the manifestation of PCOS in many women with the condition, encourages the study of adipocyte biology in PCOS as an important research topic. Within the last decade, there has been much interest in this field and a large number of published articles. Whilst it is beyond the scope of this review article to provide an exhaustive discussion of all aspects of this field, we have focused on the main elements and selected studies of high importance. Following a brief discussion of the role of adiposity in the development of PCOS, we focus on four main areas: (i) fat distribution in PCOS; (ii) adipokines in PCOS; (iii) adipocyte hypertrophy and lipolysis in PCOS; and (iv) adipocyte steroid metabolism in PCOS.

2. Adiposity and the development of PCOS

The clinical and biochemical presentation of PCOS is profoundly affected by obesity (Barber et al., 2006). Although studies have shown that between 38% and 88% of women with PCOS are either overweight or obese (Legro, 2000; Balen et al., 1995), the actual prevalence of obesity in PCOS is difficult to determine. The wide-ranging prevalence of obesity in women with PCOS quoted in the literature (38–88%, Legro, 2000; Balen et al., 1995) is likely to reflect geographical and racial variability of Body Mass Index (BMI) between studies (Villa and Pratley, 2011). Furthermore, PCOS may remain undiagnosed in many women with the condition, adding further uncertainty (March et al., 2010). The epidemiological link between obesity and PCOS outlined above, is supported by genetic studies by our own group, by demonstration of association between variants in the fat mass and obesity gene (*FTO*) and susceptibility to the development of PCOS in a large UK-based case-control study (Barber et al., 2008a). This was the first study to demonstrate an association of the *FTO* gene with development of PCOS (Barber et al., 2008a), and has since been supported by the results of other case-control and family-based studies (Attaoua et al., 2008; Wehr et al., 2010; Tan et al., 2010; Ewens et al., 2011). It is likely that other obesity-related gene variants are also associated with susceptibility to PCOS, for example those in the *MC4R* gene as described by Ewens et al., 2011.

The epidemiological, genetic and pathophysiological evidence outlined above strongly implicate the importance of obesity in the expression of PCOS in many women with this condition, and provide the rationale for research on adipocyte biology in PCOS. The development of PCOS in a minority of lean women does suggest that factors independent of obesity are important for the pathogenesis of PCOS in this sub-group (Barber et al., 2006). It is well described that obesity plays an important pathogenic role in the majority of women with PCOS, and that dietary treatment improves outcome (Barber et al., 2006). However, there is uncertainty regarding the actual prevalence of obesity in women with PCOS. It is well-established that weight loss of even 5%, results in significant improvements of ovulatory function, menstrual cyclicity, hyperandrogenic features, insulin sensitivity and metabolic function (Kiddy et al., 1992; Barber et al., 2006). These data provide evidence to support weight loss (through dietary and other means) as a key component in the management of obese and overweight women with PCOS, which remains the mainstay of treatment for many obese women with PCOS.

3. Fat distribution in PCOS

It is well-established that PCOS is associated with insulin resistance and metabolic dysfunction (Barber et al., 2007b, 2006). Although obesity *per se* is also associated with insulin resistance and metabolic dysfunction, the *co-occurrence* of PCOS and obesity seems to augment this link (Barber et al., 2006): obese women with PCOS demonstrate higher odds ratios for cardio-metabolic risk factors such as insulin resistance and raised cholesterol compared with control women *following adjustments for differences in age and BMI between the two groups* (Wild et al., 2000). The question therefore arises whether differences in body fat *distribution* (BFD) between obese women with PCOS and obese control women may explain the observed differences in insulin sensitivity and metabolic profiles between these two groups. Differences in BFD between lean women with PCOS and lean control women is also of interest given that lean women with PCOS also appear to be insulin resistant (Barber et al., 2006). It is well-known that abdominal (*visceral*) adipose tissue is associated with an adverse metabolic profile (including insulin resistance) compared with adipose tissue located in subcutaneous depots (Banerji et al., 1999; Marks et al., 1996). Mechanisms include differences in adipokine release and hepatic effects of free fatty acids (Zhuang et al., 2009). The *location* or *distribution* of adipose tissue is therefore relevant to metabolic health and perhaps even more pertinent than BMI *per se*.

It has been suggested that obese women with PCOS are more likely to demonstrate a preponderance of adipose tissue within abdominal/visceral depots compared with obese control women (Escobar-Morreale and San Millan, 2007). This hypothesis has been widely-accepted and offers a possible explanation for the association of obesity and PCOS with 'abnormal' insulin resistance. Furthermore, this hypothesis seemed to have been supported by data from previous studies that employed a variety of imaging techniques for the assessment of BFD. These techniques include ultrasound (Yildirim et al., 2003), lipometer (Horejsi et al., 2004) and dual-energy X-ray absorptiometry (DEXA) (Kirchengast and Huber, 2001; Puder et al., 2005). However, there are problems inherent with each of these techniques including high operator-dependence (especially use of ultrasound in the assessment of the thickness of a fat depot), sub-optimal image resolution and lack of discernability between abdominal visceral and subcutaneous fat depots. Furthermore, differences in BMI between PCOS cases and controls in some studies may have adversely affected the results obtained.

Recently, the dogma that obese women with PCOS have preponderant abdominal/visceral fat has been challenged by data from studies employing the technique of Magnetic Resonance Imaging (MRI) for measurement of BFD. Advantages of MRI include minimal operator-dependence and the generation of highly-resolved images with well-delineated abdominal visceral and subcutaneous fat depots (Barber et al., 2007a). We compared 22 BMI/fat mass-matched pairs of PCOS cases and controls (whole-group comparisons were based on 50 PCOS cases versus 28 female controls), with measurements of cross-sectional areas of fat depots derived from axial MRI images taken at anatomically pre-defined sites (including the