



Male PCOS equivalent and nutritional restriction: Are we stepping forward?

Federica Di Guardo^{a,*}, Maria Cecilia Cerana^b, Gisella D'urso^a, Fortunato Genovese^a,
Marco Palumbo^a

^a Department of Medical Surgical Specialties, University of Catania, Via Tindari 2, 95124 Catania, Italy

^b Department of Internal Medicine, The University of Connecticut, 263 Farmington Ave, Farmington, CT 06030, United States



ABSTRACT

Polycystic ovarian syndrome (PCOS) is an endocrine disorder characterized by alteration of menses, polycystic ovaries, clinical and or biochemical signs of hyperandrogenism in the context of metabolic abnormalities such as obesity and insulin resistance that play a fundamental role in pathogenesis of the disease as well as in development of long-term complications including cardiovascular disease (CVD) and type II diabetes mellitus (DM II). Latest evidence supports the hypothesis of a genetic component in the aetiology of PCOS that seems to be inherited through an oligo-genic mechanism and cluster in families. Recent studies identified the existence of a male PCOS correspondent syndrome in which the genes responsible for PCOS susceptibility in women may be inherited by male relatives of women with PCOS. The same hormonal, clinical and metabolic alterations of women with PCOS have been found in their male relatives suggesting a relation between the syndrome in its male equivalent.

Considering clinical manifestations of male PCOS equivalent, the early onset androgenetic alopecia (AGA) is considered a clinical marker of insulin resistance, supported by the findings of a case-control study that reported an increased prevalence of hyperinsulinemia and insulin-resistance-associated disorders such as dyslipidaemia, hypertension and obesity, in men with early onset of alopecia (< 35), compared with age-matched controls. Moreover, AGA and insulin resistance show higher levels of active androgens, highlighting that low SHBG levels occur in both the diseases and that the two conditions may concur to a worsening of the disease. With regards to the existence of a male PCOS equivalent syndrome, in particular with refer to its phenotypic hallmark of early onset AGA, our hypothesis supposes a beneficial effect of diet restriction used for PCOS as therapy for male patients affected by PCOS equivalent syndrome. Several observational studies and some randomized trials reported that modest reductions of body weight decrease the risk of development of many diseases, including diabetes and cardiovascular disease and contributes to increase insulin sensitivity in PCOS women. Weight reduction may be adopted for men affected by PCOS equivalent syndrome in order to reduce both levels of circulating androgens, insulin resistance and related-complications such as CVD and DM II.

Introduction

Polycystic ovarian syndrome (PCOS) is an endocrine disorder characterized by alteration of menses, polycystic ovaries, clinical and or biochemical signs of hyper-androgenism [1]. Although the previous elements represent the definition of the syndrome, metabolic abnormalities such as obesity, Vitamin D deficiency and insulin resistance play a fundamental role in pathogenesis of the disease as well as in the development of long-term complications including cardiovascular diseases (CVD) and type II diabetes mellitus (DM II) [2]. Moreover, a more complex theory involving the peroxisome proliferator-activated receptors (PPARs), has been reported to explain the pathogenesis of the previous cited complications; it seems that this family of ligand-activated transcription factors, are responsible for the modulation of the expression of many genes implicated in glucose and lipid metabolism balance [3–5]. Latest evidence supports the hypothesis of a genetic component in the aetiology of PCOS that seems to be inherited through an oligo genic mechanism and cluster in families 3 [6]. Recent studies

identified the existence of a male PCOS correspondent syndrome in which the genes responsible for PCOS susceptibility in women may be inherited by male relatives of women with PCOS. Several hormonal, clinical and metabolic evidences have been found in male relatives of women with PCOS supposing a relation between the syndrome and its male equivalent. With regard to the hormonal pattern, higher levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and antimüllerian hormone (AMH) were found in male relatives of women with PCOS [7]. Interestingly, an increased response to gonadotropin releasing hormone (GnRH) analog in terms of elevation of FSH and LH levels was described in brothers of women with PCOS compared to controls, supporting the fact that an abnormal neuroendocrine regulation of gonadotropin secretion may exist in these men [8]. Considering clinical manifestations of PCOS, some authors reported data in support of the early onset androgenetic alopecia (AGA) that may represent a clinical sign of the male PCOS equivalent [9,10]. This type of alopecia occurs before 35 years of age, and includes pronounced hypertrichosis, insulin resistance, biochemical as well as hormonal abnormalities [11],

* Corresponding author at: Department of Medical Surgical Specialties, Gynecology and Obstetrics Section, University of Catania, Via Tindari 2, 95124 Catania, Italy.

E-mail addresses: fediguardo@gmail.com, diguardo.federica@studium.unict.it (F. Di Guardo).

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was found to develop in male members of families with a considerable family history for PCOS [12]. Among hormonal and metabolic abnormalities, siblings of patients with PCOS, reported higher prevalence of hyperinsulinemia and hypertriglyceridemia as well as early onset AGA [13]. Moreover, insulin resistance, hypertension and dyslipidaemia occurs frequently in brothers of women with PCOS [14]. Accordingly, first degree male and female relatives of women with PCOS showed an increased prevalence of early onset AGA as well as metabolic disorders such insulin resistance and obesity, resulting then in a higher prevalence of DM II and CVD that was also found in these subjects [15,16].

The hypothesis

Metabolic abnormalities such as obesity and insulin resistance have a key point in PCOS pathogenesis and contribute to development of long-term complications including CVD and DM II [2]. To date widely accepted evidence highlights the importance of early nutritional interventions in terms of weight loss to reduce the risk of life-threatening complications, such as DM II and CVD in women with PCOS [17]. With regards to the existence of a male with PCOS equivalent syndrome, in particular with its phenotypic hallmark of early onset AGA, our hypothesis supposes a beneficial effect of diet restrictions for male patients affected by PCOS equivalent syndrome.

Discussion of the hypothesis

It has been proven that early AGA are associated with risk of serious cardiovascular events as well as glucose metabolism disorders [18–22]. Similarly, to PCOS, it should be pointed out that the occurrence of AGA, especially before 35 years of age, may be considered as a marker of increased risks of several metabolic diseases in later age. Moreover, the hypothesis that early AGA could be a clinical marker of insulin resistance is supported by the findings of a case-control study that reported an increased prevalence of hyperinsulinemia and insulin-resistance-associated disorders such as dyslipidemia, hypertension and obesity, in men with early onset of alopecia (< 35), compared with age-matched controls [23]. To date several observational studies investigated the possibility of a link between the insulin resistance and the development of AGA [24,25]. Although, this correlation is not yet clear, it is well known that, both the conditions reported a higher proportion of free to bound androgens. The serum androgens are usually bound with sex hormone binding globulin (SHBG) [26–28]: AGA and insulin resistance show higher levels of active androgens, highlighting, thus, that low SHBGs levels occur in both the diseases [27–29]. However, although it is not accepted universally that insulin resistance is involved in the pathogenesis of AGA, insulin resistance may amplify the free androgen proportion leading to reduction in SHBG levels and thus, to a worsening of the AGA. Accordingly, PCOS women show the same condition of increased of circulating androgens in which hyperinsulinemia decreases SHBG production [30]. Nevertheless, a positive effect in the context of insulin resistance and AGA may be expected when therapies and nutritional interventions with the aim to decrease SHBG to within normal range is applied. As widely demonstrated for women with PCOS, weight loss gained by adequate dietary regimen and exercise are associated with increased SHBG concentration, reducing testosterone level [31,32]. High-protein diets are considered more effective than high-carbohydrate diets [33,34] and it's important to avoid acute weight loss as the goal should be a long-term weight loss and maintenance. Several observational studies and some randomized trials [35,36] reported that a reduction > 5% of body weight decreases the risk of development of many diseases, including diabetes and cardiovascular disease and contributes to an increase in insulin sensitivity in women with PCOS [37]. Weight reduction may be adopted for men affected by PCOS equivalent syndrome in order to reduce both the levels of circulating androgens, insulin resistance and

related-complications. A correlation between insulin signalling pathways and fasting have been found. Fasting seems to act through epigenetic modulation of key regulation genes of the metabolism [38] determining beneficial effects in PCOS women such as the reduction of IGF-1, IGFBP1, glucose and insulin levels in the medium and long-term [39]. In this view, fasting may be adopted as therapy in male correspondent PCOS syndrome. Regarding intermittent fasting, also called, “alternate-day fasting” and “5:2 diet” [40], the effect on insulin resistance was studied in animal models and showed equal or higher efficacy than isoenergetic continuous energy restriction in improving insulin sensitivity [41]. Periodic fasting, indeed, was considered more effective in restoring multiple features of the metabolic syndrome in humans, increasing insulin sensitivity, stimulating lipolysis and reducing blood pressure [42]. Taking into account, diet regimes in combination with nutraceuticals such as Inositols, their positive effects in PCOS women are clearly reported in literature [43,44]; in particular Myo-inositol (MI) and D-chiro-inositol (DCI), considering their insulin sensitizing action, showed to be effective both in overweight and normal weight PCOS women, suggesting that the typical insulin resistance of this kind of patients plays a crucial role not only in the case of high BMI [45,46]. Last but not least, a pivotal role in the pathogenesis of PCOS insulin resistance have been supposed also for Vitamin D; more in deep, the alteration of the Vitamin D receptor (VDR) signalling pathway and the Vitamin D deficiency, may be in part responsible of this typical metabolic characteristic. In this view diet supplementation with Inositol and/or Vitamin D should be auspicated also in male PCOS equivalent patients [47,48].

Consequences of the hypothesis and discussion

To the best of our knowledge, although a certain role of insulin resistance in the pathogenesis of male PCOS equivalent has not been yet established, data about the correlation of early AGA and risk of metabolic diseases as well as cardiovascular events are well documented. However, the adoption of the nutritional interventions commonly used for PCOS, has not yet been considered a strategy to stop the progression of the male PCOS equivalent syndrome and to avoid long terms complications.

In this view, we welcome future observational studies, investigating the potential effect of the nutritional restriction in the prevention of worsening male equivalent PCOS syndrome and its complications. Finally, it would be interesting to compare the application of various diets as well as fasting practices in order to understand which is the most effective in the treatment of this syndrome.

Conflict of interest

The authors declare no conflict of interest in relation to this article. The authors alone are responsible for the content and writing of the paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.03.003>.

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