



Metabolic syndrome in polycystic ovary syndrome

Zespół metaboliczny w zespole policystycznych jajników

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Abstract

Both metabolic syndrome (MS) and polycystic ovary syndrome (PCOS) are common among women. The exact prevalence of MS in women with PCOS is dependent upon the diagnostic criteria used for each. However, the frequent co-occurrence of both MS and PCOS in women is suggestive of a common aetiology. In this short review article we argue that insulin resistance, as a consequence of abdominal obesity, may represent such a common aetiology. We also review the literature on the prevalence of MS in women with PCOS and consider the impact that the particular criteria used to diagnose both MS and PCOS may have had on these estimates of prevalence.

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Key words: polycystic ovary syndrome, metabolic syndrome, obesity

Streszczenie

Zespół metaboliczny (MS, *metabolic syndrome*) i zespół policystycznych jajników (PCOS, *polycystic ovary syndrome*) są często rozpoznawanymi zaburzeniami u kobiet. Częstość występowania zespołu metabolicznego u kobiet z PCOS zależy od zastosowanych kryteriów diagnostycznych. W prezentowanej pracy autorzy rozważają tezę, że przyczyną obu zaburzeń może być insulinooporność, będąca następstwem otyłości brzusznej. Ponadto dokonują przeglądu literatury dotyczącej występowania MS u kobiet z PCOS oraz omawiają wpływ wyboru określonych kryteriów diagnostycznych MS i PCOS na oszacowanie częstości ich występowania.

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Słowa kluczowe: zespół policystycznych jajników, zespół metaboliczny, otyłość

Introduction

The metabolic syndrome (MS) is a constellation of interrelated abnormalities [1]. The importance of diagnosing MS in the general population lies in its association with a two-fold increased risk of cardiovascular disease and a five-fold increased risk of type 2 diabetes mellitus (T2D) [2]. Polycystic ovary syndrome (PCOS) is associated with a significantly higher odds ratio for the

development of various cardiovascular risk factors [3] and a significantly greater risk of MS when compared with controls [4]. However, it is not yet clear whether MS in women with PCOS is associated with the same degree of cardiovascular risk (and by implication, mortality) as MS in the general female population [5]. This is due, at least in part, to the difficulty of making an accurate retrospective diagnosis of PCOS in post-menopausal women.

Both PCOS and MS are common among women. PCOS affects between 6% and 10% of pre-menopausal women [6]. In a study of 4549 women (≥ 20 years of age), in the third National Health and Nutrition Examination Survey (NHANES III), the age-adjusted prevalence of MS using National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria was shown to be 23.4% [7]. (NHANES III is a cross-sec-

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tional health survey of a nationally representative sample of the non-institutionalised civilian US population). Similar prevalence rates of MS among women have been shown in other studies [8, 9]. In this short review article we discuss three aspects of the association between MS and PCOS:

1. The diagnostic criteria used for MS and PCOS;
2. The prevalence of MS in women with PCOS;
3. The role of insulin resistance and abdominal obesity as possible common aetiologies in the development of MS and PCOS.

Diagnostic criteria for metabolic syndrome and PCOS

Metabolic syndrome diagnostic criteria

In 1988 Reaven formed the hypothesis that insulin resistance is a common aetiological factor for several disorders that co-occur more frequently than would be expected by chance. "Syndrome X", the name Reaven used for this constellation of disorders, has since become

known as metabolic syndrome (MS) [10]. The precise composition, definition and meaning of MS have been controversial. Consequently, various diagnostic criteria for MS have been proposed (outlined in Table I). Perhaps the most practical clinical criteria for the diagnosis of MS are those proscribed by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [11, 12]. More recently, the International Diabetes Federation (IDF) has proposed a new definition for MS [13]. This definition includes central obesity (defined as a waist circumference ≥ 80 cm in European women) as a necessary prerequisite risk factor for the diagnosis of MS.

One consequence of these varying definitions of MS is that the prevalence of MS in any given population is likely to vary according to the particular diagnostic criteria used to define MS. As an example, Vural and colleagues studied the prevalence of MS in 43 women with PCOS compared with 43 age-matched controls. MS occurred in 11.6% of PCOS women using the WHO criteria, compared with 2.3% using the NCEP ATP III criteria [5, 14].

Table I

Diagnostic criteria for metabolic syndrome in women

Tabela I

Kryteria diagnostyczne zespołu metabolicznego u kobiet

Organisation	Criteria for the diagnosis of metabolic syndrome
NCEP ATP III [11, 12]	Three or more of the following criteria are met: <ol style="list-style-type: none"> 1. Abdominal obesity: waist circumference > 88 cm in women 2. Elevated triglycerides (≥ 1.7 mmol/l) 3. Reduced HDL cholesterol (< 1.3 mmol/l in women) 4. Elevated blood pressure ($\geq 130/85$ mm Hg) 5. Elevated fasting glucose concentration (≥ 6.1 mmol/l)
WHO [15]	Requires the presence of diabetes, IFG, IGT or insulin resistance (on the basis of HOMA level). In addition, at least two of the following criteria are met: <ol style="list-style-type: none"> 1. Waist : hip ratio > 0.85 in women 2. Elevated triglycerides (≥ 150 mg/dl) 3. Reduced HDL cholesterol (< 39 mg/dl in women) 4. Urinary albumin excretion rate > 20 μg/minute 5. Elevated blood pressure ($\geq 140/90$ mm Hg)
IDF (2005) [13]	Requires the presence of central obesity (waist circumference ≥ 80 cm in European women). In addition, at least two of the following criteria are met: <ol style="list-style-type: none"> 1. Elevated triglycerides (≥ 1.7 mmol/l) 2. Reduced HDL cholesterol (< 1.29 mmol/l in women) 3. Specific treatment for lipid abnormalities 4. Elevated blood pressure (systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg) 5. Specific treatment of previously diagnosed hypertension 6. IFG (fasting plasma glucose ≥ 5.6 mmol/l) 7. Previously diagnosed T2D

NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HOMA, Homeostasis Model of Insulin Resistance; WHO, World Health Organisation; IDF, International Diabetes Federation; T2D, type 2 diabetes mellitus

Table II
Diagnostic criteria for PCOS

Tabela II
Kryteria diagnostyczne zespołu policystycznych jajników

Organisation	Criteria for the diagnosis of PCOS
NIH [18]	Both of the following criteria are required: 1. Hyperandrogenic features (defined biochemically and/or clinically) 2. Chronic anovulation (manifesting as menstrual disturbance)
ESHRE/ASRM (Rotterdam) [16, 17]	Two or more of the following criteria are required: 1. Polycystic ovarian (PCO) morphology on ultrasound scan 2. Hyperandrogenic features (defined biochemically and/or clinically) 3. Oligo-amenorrhoea (inter-menstrual interval greater than 42 days)

ESHRE, European Society for Human Reproduction and Embryology; ASRM, American Society for Reproductive Medicine; NIH, National Institutes of Health

PCOS diagnostic criteria

The main diagnostic criteria for PCOS are outlined in Table II. One of the main objectives behind the 2003 Rotterdam revised criteria [16, 17] was to accommodate the increasing evidence that the spectrum of clinical and biochemical features in women with polycystic ovaries was wider than that proscribed by the 1990 NIH criteria for diagnosis of PCOS [18]. According to these earlier criteria, a diagnosis of PCOS could be made without reference to ovarian morphology.

One consequence of the Rotterdam criteria [16, 17] is that four distinct phenotypic subgroups have been generated. These are designated as follows: (i) "PHO": women with PCO morphology (P), hyperandrogenic features (H) and oligomenorrhoea (O); (ii) "PH": women with PCO morphology, hyperandrogenic features and normal menses; (iii) "PO": women with PCO morphology, oligomenorrhoea and normoandrogenaemia; and (iv) "HO": women with hyperandrogenic features, oligomenorrhoea and normal ovarian morphology on ultrasound.

Several recent studies have shown that there is marked clinical heterogeneity between the PCOS subgroups with respect to metabolic risk profiles. These studies have focused particularly on two phenotypic subgroups ("PH" and "PO") which are new and would not have been classified as PCOS under the NIH criteria [18]. Dewailly and colleagues demonstrated in a study of 406 French women with PCOS that PCOS women with features similar to the "PO" subgroup had lower fasting insulin concentrations than other PCOS subgroups

[19]. On restricting their analysis to obese anovulatory women, Broekmans and colleagues showed that obese normoandrogenaemic women with PCOS had a milder metabolic phenotype than obese women with PCOS diagnosed according to the 1990 NIH criteria (a comparison of "PO" versus "PHO" + "HO" using the terminology outlined above) [20]. More recently, Welt and colleagues studied 418 women with PCOS recruited in Iceland and Boston, USA. They showed that BMI and fasting insulin concentrations were highest in the PCOS women with features similar to the "PHO" subgroup, compared with women in the other phenotypic subgroups (including the "PH" and "PO" subgroups) [21]. In a separate study Robinson and colleagues showed that PCOS women with regular menstrual cycles ("PH" subgroup) are relatively less insulin resistant than oligomenorrhoeic PCOS women ("PHO" subgroup) [22].

To summarise, one consequence of the Rotterdam criteria for PCOS [16, 17] is the inclusion of women with less severe departures from a normal metabolic profile ("PH" and "PO" subgroups). Consequently, the overall prevalence of MS and the components of MS in women with PCOS diagnosed on the basis of the Rotterdam criteria [16, 17] is likely to be lower than that in PCOS women diagnosed on the basis of the NIH criteria [18]. The data reviewed here and in the previous section highlight the impact that the diagnostic criteria used for both MS and PCOS may have on estimations of the prevalence of MS in women with PCOS.

Prevalence of metabolic syndrome in women with PCOS

Most previous studies on the prevalence of MS in women with PCOS (and all of those described below) have been performed on women from the USA and have defined MS and PCOS on the basis of the NCEP ATP III and NIH criteria respectively [4, 23–25]. The consistency of diagnostic criteria used in these studies has enabled a direct comparison to be made of MS prevalence between studies. Estimations of the prevalence of MS in women with PCOS derived from these studies vary between 34% and 46%, as outlined below.

Ehrmann and colleagues studied the prevalence of MS in 394 (mostly white) women with PCOS. Although none of the PCOS women with a BMI less than or equal to 27.0 kgm⁻² had MS, 40% of those PCOS women with a BMI greater than 27 kgm⁻² had MS [23]. Dokras and colleagues compared the prevalence of MS among 129 women with PCOS compared with 177 female controls. Overall, 93% of the participants were white. The prevalence of MS in the PCOS women was 34.9% (47.3% adjusted for age), compared with 6.8% (4.3% adjusted for age) in controls ($P < 0.001$). Those PCOS women

who were below 30 years were at particular risk of MS [4].

In a further study Glueck and colleagues showed the prevalence of MS among 138 white women with PCOS to be 46% [24]. Apridonidze and colleagues reported a similar 43% prevalence of MS among 106 (mostly white) women with PCOS [25]. This compares with a 6% (ages 20–29 years) and 15% (ages 30–39 years) prevalence of MS among women in the USA general population from the NHANES III. Apridonidze and colleagues concluded that the major predictors of MS in PCOS women were elevated serum free testosterone and reduced serum SHBG levels [25]. Consistent with these results, a significant ($P = 0.003$) inverse relationship between SHBG level and the occurrence of MS in women with PCOS was also shown in a recent study by Chen and colleagues [26], although BMI is likely to play an important role in the inverse correlation between SHBG and MS in women with PCOS.

The studies outlined above suggest that the prevalence of MS in women in the USA with PCOS (using NCEP ATP III and NIH criteria for the diagnosis of MS and PCOS respectively) is at least twice that in age-matched control women. The association of MS with PCOS appears to be particularly strong in those PCOS women who are young (below 30 years) and, as expected, overweight or obese ($BMI > 27 \text{ kgm}^{-2}$) [4, 23]. However, a limitation of the studies outlined above is that they only relate to women from the USA and that they only used one set of diagnostic criteria for MS and PCOS (NCEP ATP III and NIH respectively). Owing to the association of PCOS with obesity, a further limitation is the lack of an appropriate age- and BMI-matched female control group for comparison, necessitating adjustments for these factors in the analyses.

Application of different diagnostic criteria for MS and PCOS (specifically, the IDF and Rotterdam criteria respectively) may have resulted in differences in the prevalence of MS among PCOS women. One may speculate that application of the Rotterdam criteria (as opposed to the NIH criteria) to diagnose PCOS would have resulted in significantly lower estimates of prevalence of MS among women with PCOS in the studies outlined above as a result of the inclusion of additional phenotypic subgroups of PCOS women. These new subgroups, not included using the NIH criteria, show less severe departures from a normal metabolic profile. Data to support this notion comes from a study on 418 women with PCOS (Rotterdam criteria) recruited in Iceland and Boston, USA [21]. With the use of NCEP ATP III criteria to diagnose MS it was shown that the prevalence of MS among the new "PH" and "PO" subgroups of PCOS women (using the terminology described

above) in 20–29 or 30–39 year groups was not different from that in the NHANES III subjects, regardless of BMI.

Insulin resistance and abdominal obesity as common aetiologies in the development of metabolic syndrome and PCOS

Sam and colleagues showed that the prevalence of MS in 215 non-Hispanic white mothers of women with PCOS is significantly higher than that in non-Hispanic white women from the NHANES III (47% versus 32% in PCOS mothers and NHANES III women respectively, $P < 0.001$) [27]. In a further study it was also shown that the prevalence of MS is increased in affected sisters of women with PCOS [28]. It is likely, therefore, that the metabolic features of PCOS are heritable traits. Given the heritability of metabolic traits in PCOS and the frequent co-occurrence of MS and PCOS, it is likely that these two disorders share one or more common aetiological factors.

Insulin resistance in MS and PCOS

Insulin resistance and compensatory hyperinsulinaemia are common in PCOS and MS. Insulin resistance is believed to be the major underlying metabolic abnormality in the development of MS [29]. Consistent with this hypothesis is the observation of a significant ($P < 0.0001$) increasing trend in the proportion of PCOS women with MS in relation to fasting insulin concentration in a study on 394 PCOS women [23]. Insulin resistance also plays an important role in the aetiology of PCOS, as outlined below.

The association between insulin resistance and PCOS was first established in 1980 [30]. Between 50% and 90% of women with PCOS (depending on the diagnostic criteria used) have insulin resistance to a significantly greater extent than in age and BMI-matched control women, this disparity being more marked in obese women [31–33]. Insulin sensitising drugs and weight loss in women with PCOS significantly improve the metabolic and endocrine abnormalities, including ovulatory function, menstrual cyclicity and fertility rates [34–37]. These observations suggest that insulin resistance (and the associated hyperinsulinaemia) plays an important role in the aetiology of PCOS.

In women with PCOS insulin interacts synergistically with luteinising hormone (LH) within the theca cells of polycystic ovaries (in which theca cell hyperplasia is usually present) to cause activation of the enzyme P450c17 α , the key enzyme in the biosynthesis of ovarian androgens such as testosterone [38–40]. Insulin is also implicated in abnormal granulosa cell function and the arrest of ovarian follicle development in women with PCOS (thereby contributing towards ano-

vation) [22, 41]. Hyperinsulinaemia may also have adverse effects at non-ovarian sites, including enhancement of pituitary LH pulse amplitude (at least in rodent models) [32, 42], suppression of the hepatic synthesis of sex hormone binding globulin (SHBG) [43, 44] and stimulation of adrenal P450c17 α activity (increasing adrenal androgen production) [45].

These putative stimulatory effects of insulin in women with PCOS may, in the context of peripheral insulin resistance, appear paradoxical but can be explained, in principle, by tissue-specific differences in insulin sensitivity. It has been demonstrated in T2D subjects that physiological insulin resistance (which is largely determined by glucose disposal into skeletal muscle) at the molecular level is associated with a specific impairment in the phosphatidylinositol 3-kinase (PI3-kinase) mediated insulin signal transduction pathway. Signalling through the alternative mitogen-activated protein kinase (MAP kinase) pathway (which typically mediates the effects of insulin on cell growth) is preserved [46]. As PCOS, T2D and MS closely overlap, it is probable that similar effects obtain in PCOS. If so, this would explain the differential resistance to the metabolic and steroidogenic effects of insulin in the ovaries of women with PCOS [47]. Therefore the consequence of peripheral insulin resistance (and consequent hyperinsulinaemia) may actually be increased insulin signalling in the ovary, leading to enhanced ovarian steroidogenesis.

As discussed above, insulin resistance plays a key role in the aetiology of both MS and PCOS. An obvious question is whether there are any features common to women with MS and PCOS that may be responsible for the development of insulin resistance in both. Abdominal obesity may be one such feature, and its role in this process is discussed in the next section.

Abdominal obesity in MS and PCOS

Insulin resistance is closely associated with abdominal obesity both in normal women [48] and in women with PCOS [49]. Perhaps as a reflection of the belief that insulin resistance underlies the MS [29], abdominal obesity (defined as a waist circumference \geq 80 cm in European women) is required for a diagnosis of MS, at least within the recent IDF criteria [13]. For any given BMI, women who have gynoid BFD (fat distributed mainly on the hips and thighs) are therefore less likely to fulfil IDF diagnostic criteria for MS compared with women who have android BFD (fat distributed mainly in visceral and abdominal subcutaneous depots), as a result of differences in waist circumference. It follows that abdominal obesity and body fat distribution (BFD) are relevant to the diagnosis of MS.

Abdominally obese women are also more likely to fulfil the other IDF-proscribed criteria for MS; it is well

established that abdominal obesity in women (specifically visceral adiposity), is a much better marker of insulin resistance and metabolic disturbance than gynoid-distributed adipose tissue [31, 32, 37, 49, 50]. Visceral fat was also shown to be the most significant variable correlating with metabolic disturbance in women with PCOS ($P < 0.001$) [51]. By definition, women with MS are abdominally obese, and therefore more likely to have android BFD. Among women with PCOS this has also been shown to be the case, as outlined below.

Most women with PCOS (between 38% and 88%) are overweight or obese [52, 53]. A likely explanation for the mechanisms underlying the development of obesity in PCOS women is the combined effect of a genetic predisposition to obesity in the context of an obesogenic environment (poor diet and reduced exercise). In addition to obesity, android BFD also occurs in the majority of women with PCOS (between 50% and 60%), regardless of BMI. This estimation is derived from a variety of studies that used a diverse array of methods to assess BFD, including lipometry, ultrasound and dual-energy X-ray absorptiometry (DEXA) [54, 55]. In some PCOS women android BFD may have resulted from exposure to relatively high concentrations of testosterone during early development (as occurs in the pre-natally androgenised female Rhesus monkey) [56]. Alternatively, android BFD may also develop following exposure of adipose tissue depots to hyperandrogenaemia during adulthood [57]. Android BFD may, in turn, contribute to worsening hyperandrogenaemia through its adverse effects on insulin sensitivity and the consequent co-gonadotrophic effects of hyperinsulinaemia on the ovaries.

What is the mechanism by which abdominal obesity in women with PCOS is associated with insulin resistance? Ek and colleagues showed that there is a marked (approximately two-fold) increase in catecholamine-induced lipolysis within visceral adipocytes isolated from non-obese women with PCOS compared with BMI-matched control women [58]. This process may be facilitated by testosterone [59, 60]. Enhanced visceral adipocyte lipolysis, by increasing the concentration of portal (and systemic) NEFA, may enhance hepatic gluconeogenesis, reduce hepatic insulin extraction and reduce peripheral glucose uptake. Consequently, there is increased insulin resistance and the development of an adverse metabolic profile [58, 61].

The association of PCOS with abdominal obesity at least partly explains the association of PCOS with insulin resistance and, by implication, MS. This hypothesis is supported by the results of a comparison between women with PCOS and control women matched for abdominal adiposity, which showed that the difference in insulin resistance between the two groups was

much less marked than if the two groups were matched for BMI [49]. Therefore abdominal obesity and consequent insulin resistance are likely to be important aetiological factors, common to both women with MS and women with PCOS. As most women with PCOS have abdominal obesity, this may explain the frequent co-occurrence of MS and PCOS in women.

Conclusions

Whichever diagnostic criteria are applied, it is clear that the prevalence of MS in women with PCOS is significantly greater than that in normal women. If one accepts that insulin resistance (as a consequence of abdominal obesity) plays an important role in the aetiology of each disorder, then it follows that reduction of abdominal fat is a logical way to treat both disorders. This is currently achieved through modification of lifestyle (particularly diet). However, reduction of abdominal fat in these women should also be a drug target for the future, particularly in those women who suffer from both MS and PCOS. A reduction of abdominal fat in women with PCOS would improve not only their metabolic profile but also their menstrual cyclicity and fertility.

Although the prevalence of MS is high in women with PCOS, evidence for an increased incidence of cardiovascular disease and for increased severity of long-term cardiovascular sequelae of MS in these women is lacking. Wild and colleagues showed that although women with PCOS had higher levels of several cardiovascular risk factors, a history of coronary heart disease was not significantly more common in these women [3]. Furthermore, all-cause and cardiovascular mortality in women with PCOS was reported to be similar to women in the general population. This study by Wild et al. was a retrospective cohort study of 345 women with a history of PCOS (diagnosed primarily from ovarian morphology), compared with 1060 age-matched control women. In further research on the Nurses' Health study, involving 82,439 women, Solomon and colleagues reported that those with a history of menstrual irregularity or chronic anovulation had an increased relative risk of fatal and non-fatal coronary heart disease after a 14-year follow-up [62]. One limitation of the study reported by Solomon et al. is that a definitive diagnosis of PCOS was not used. Furthermore, the increased risk of coronary heart disease in the women with menstrual irregularity was diminished after adjusting for BMI.

As regards the direction of future research, there is clearly a need for more prospective long-term follow-up studies of large numbers of women with both MS and PCOS (with accurate and definitive diagnoses of

each) compared with an appropriate age- and BMI-matched control group. On the basis of our current understanding there is no reason to believe that the cardiovascular consequences of MS in women with PCOS should be any less serious than those in normal women. However, evidence for this hypothesis is lacking. The development of a good evidence-base in this area will help to motivate health-care professionals to be more vigilant for the emergence of MS in women with PCOS, and to manage its components early and aggressively. It will also help to motivate PCOS women with MS to lose weight.

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