Metabolic inflexibility in women with polycystic ovary syndrome: A systematic review

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Short Title: Metabolic inflexibility in PCOS

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Abstract:

Context: Polycystic ovary syndrome (PCOS) is a risk factor for dysglycemia, insulin resistance, and type 2 Diabetes Mellitus (T2DM). Inefficient energy oxidation, metabolic inflexibility, is a marker of blunted metabolism. We conducted a systematic review on metabolic inflexibility in women with PCOS.

Evidence Acquisition: We searched MEDLINE, EMBASE and Cochrane central (inception-October 2018) for studies evaluating metabolic inflexibility and reporting on changes in Respiratory Quotient (ΔRQ). We extracted data and assessed quality using The Newcastle-Ottawa Scale.

Evidence Synthesis: We included five prospective cohort studies (461 women). Three compared PCOS women to unaffected subjects, one to women with obesity or T2DM, and one to adolescent girls; all had medium quality. Three studies showed higher metabolic inflexibility in women with PCOS (ΔRQ range 0.05-0.098) compared to unaffected subjects. Women with PCOS had similar metabolic inflexibility compared to those with T2DM (ΔRQ 0.05±0.03 vs 0.06±0.04, p=0.98) and obesity (p=0.06). Inflexibility was higher in hyperandrogenemic women with PCOS (ΔRQ 0.091±0.060 vs 0.120±0.010, p=0.014). ΔRQ was lower in PCOS women with insulin resistance vs those with normal insulin sensitivity (0.04±0.02 vs. 0.07±0.04, p=0.007).

Conclusions: Women with polycystic ovary syndrome appear to have higher metabolic inflexibility associated with hyperandrogenemia and insulin resistance.

Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrine disorder affecting women of reproductive age with an estimated prevalence between 8–13% [1]. It is a known risk factor for dysglycemia; 75% to 95% of women with PCOS demonstrate insulin resistance, with a four-fold increased risk for developing gestational and type 2 diabetes mellitus (T2DM) [2,3].

Impaired glucose metabolism could be attributed to the increased insulin resistance, inadequate glucose uptake in target tissues, impaired glycogen synthesis and inefficient switching from lipids to glucose oxidation in affected subjects[4]. Additionally, the reduced metabolic capability to switch from lipid oxidation in fasting conditions to lipid availability in glucose rich conditions, termed metabolic inflexibility, leads to lipids accumulation in ectopic tissues (e.g skeletal muscles) inducing lipotoxicity with worsening insulin resistance [5]. Thus a vicious cycle of hyperinsulinemia, ectopic fat storage in peripheral tissues and inefficient metabolism develops [6].

Evidence of metabolic inflexibility is well documented in obese and diabetic subjects suggesting an association with insulin resistance [5]. Hypothesising a common pathway, women with PCOS might have a disposition for both insulin resistance and metabolic inflexibility. We conducted a systematic review of the literature to evaluate the available evidence on metabolic inflexibility in women with PCOS.

Methods:

We undertook a systematic review using a prospectively registered protocol (CRD42018116809) and reported in line with the PRISMA guidelines [7].

Literature search

We searched major electronic databases (MEDLINE, EMBASE and Cochrane central) for all primary studies evaluating metabolic inflexibility in women with PCOS from inception until October 2018. We combined the following Mesh search terms using the Boolean operators AND/OR to screen for relevant articles (polycystic ovary, polycystic ovaries, PCO, polycystic ovarian syndrome, ovary, inflexibility, flexibility, metabolic, metabolism, lipids, carbohydrate, clamp, oxidation) (Appendix 1). We did not employ any search filters or language restrictions. We manually searched the bibliographies of relevant articles to identify studies not captured by our electronic search. We contacted the authors of relevant studies to obtain any missing additional data.

Study selection and inclusion

Two independent reviews (MR and BW) completed the study selection and inclusion process in two stages, any discrepancies were resolved in consensus with a third reviewer (ST). First, we screened titles and abstracts to identify potentially relevant articles; then we reviewed full copies of relevant articles against our inclusion criteria. We included all primary studies of any design reporting on the metabolic inflexibility (or flexibility) between women with and without PCOS using respiratory exchange ratio or respiratory quotient (RQ) as surrogate markers to evaluate metabolic inflexibility. We excluded studies on animals, case reports, case series, and studies with no appropriately matched comparison groups.

Quality assessment of the included studies

We used the Newcastle-Ottawa Scale (NOS) [8] to assess the quality of the included studies in duplicate by two reviewers (MR) and (BW). Studies were awarded a maximum of four stars for selection, two for comparability and three for assessment of outcomes. Those

which scored four stars for selection, two stars of comparability and three stars for assessment of outcomes were considered to be of high quality. Scores of one star or less for selection, comparability or outcome assessment were considered to be of low quality. Any other score combinations were considered of medium quality.

Data extraction and analysis

Two reviewers (MR and BW) extracted data in duplicate using a piloted electronic data extraction tool on the study design, number of included participants, inclusion and exclusion criteria of each study, protocols of the used euglycemic clamp and calorimetry studies, journal of publication and year of publication. We extracted data on the reported outcomes including insulin sensitivity, substrate oxidation (carbohydrate and protein), levels of testosterone, free testosterone, sex hormone binding globulin, free androgen index. luteinizing hormone, body mass index, fat mass, and free fat mass. We reported the findings narratively using natural frequencies and percentages. All analyses were conducted in Microsoft Excel 2013 (Microsoft Inc, Washington 2013).

Results

Characteristics of included studies

Our electronic search revealed 17 potentially relevant citations, we removed three duplicates and assessed 14 articles in full against our inclusion criteria. We included five prospective cohort studies reporting on 461 women (Figure 1). Two were carried out in the United States of America, two in Poland and one in Italy. All were published in specialist journals on endocrinology, nutrition, or metabolism.

All studies were relatively small with a median sample size of 98 (range 42-122). Three compared women with PCOS to unaffected women with normal weight, one to overweight or obese women and women with T2DM, and one study compared adolescent girls with PCOS to unaffected subjects (Table 1). All included women were diagnosed with PCOS based on the National Institute of Health or Rotterdam criteria [9]. All studies evaluated metabolic inflexibility by calculating the difference between the mean RQ in the fasting state and the mean RQ in the insulin rich state. Metabolic inflexibility was diagnosed in the group with a significantly lower mean difference (ΔRQ). All studies employed a calometric breath analysis to evaluate lipid oxidation and used euglycemic clamp studies to evaluate carbohydrate oxidation between fasting and insulin rich status (Table 1).

Quality of included studies

Overall, the quality of included studies was medium; three studies scored highly for the selection process, and two were of low quality. The majority of studies (80%, 4/5) had a medium quality for comparability, primarily due to small sample size with a limited variation in the comparison cohorts in view of the varied phenotype of PCOS in the general population. Most studies (60%, 3/5) had an adequate assessment of outcomes and follow up process. (Figure 2) (Appendix 2).

Metabolic flexibility

Three of the included studies showed evidence of metabolic inflexibility in women with PCOS compared to healthy, overweight or obese unaffected women [10,11] (Table 2), or to healthy adolescents (ΔRQ 0.05 ±0.01 vs 0.095 ±0.009, p=0.004) [12]. Hyperandrogenemic women with PCOS had worse metabolic inflexibility compared to those with normal

androgen profile (ΔRQ 0.091±0.060 vs 0.120±0.010, p=0.014) [11]. Women with PCOS demonstrated similar metabolic inflexibility to unaffected women with T2DM (ΔRQ 0.05±0.03 vs. 0.06±0.04, p=0.98) [10].

In contrast, two studies from the same research group suggested no difference in metabolic flexibility between women with PCOS and healthy adults [13,14]. Both studies had a high risk of bias for cohort selection (Appendix 2). Due to variations in the included controls and selective outcomes reporting, a quantitative pooling of data was not possible (Table 2).

Metabolic and endocrine outcomes

All included studies reported higher insulin resistance in women with PCOS compared to unaffected subjects [10–12], with similar levels compared to unaffected obese women and those with T2DM [10,13,14].

Fasting glucose levels were higher in women with PCOS [10,11], but this was not consistent across all included cohorts [12,14]. There was mixed evidence on the efficiency of glucose and lipid oxidation in women with PCOS with some studies reporting significantly higher glucose oxidation before the CLAMP study and reduced lipid oxidation before and during the CLAMP study [12]. A clear conclusion could not be reached, due to variations in reporting across studies.

Three studies reported lower levels of sex hormone binding globulin in women with PCOS compared to matched controls [10–12]. This was associated with an increase in both

total [11,12] and free testosterone [10–12]. Similarly, free androgen index was higher in women with PCOS compared to unaffected lean and obese women [10,14] (Table 2).

Discussion

The findings of our review support an overall association between PCOS and metabolic inflexibility, however, this was not consistent in all studies included. Inflexibility was reported in both adult and adolescent women with PCOS suggesting an association independent to age. It was more pronounced with high BMI, hyperandrogenemia, and worsening insulin resistance, signifying an impaired metabolism with worsening features of PCOS. Insulin resistance and blunted carbohydrates oxidation were common features in all included women, thus a common pathway of inappropriate energy oxidation, metabolic inflexibility and response to insulin in women with PCOS is apparent.

Strengths and limitations

To our knowledge, our review is the first to synthesis evidence on the prospect of metabolic inflexibility in women with PCOS. We used a prospective protocol following a standardised methodology and a comprehensive search strategy. We included all studies reporting on elements of metabolic inflexibility and reported on all relevant outcomes across included studies. We assessed the quality of in included studies and extracted data in duplicate. The main limitation of this review was the small number of included studies and the limited number of women included. PCOS has varied phenotypes and thus, the population reported on in this review might not fully represent all women with PCOS. There was variation in the reported outcomes with few studies reporting primary quantitative endpoints in a standardised manner which limited our ability to pool data quantitatively.

Wider implications

Women presenting with symptoms and signs of PCOS often suffer from delayed diagnosis and fragmented care [15]. The associated metabolic risk factors are seldom discussed or evaluated at diagnosis, driven by a heterogeneous care provision for women with PCOS across disciplines. Our findings help to define the metabolic risks associated with a diagnosis of PCOS, aligned with the known increased insulin resistance, T2DM and cardiovascular risk factors. The majority of included studies reported worsening metabolic inflexibility with higher BMI, and hyperandrogenemia, thus, establishing those risk factors at the time of diagnosis could facilitate a more targeted management plan and better response to treatment.

The use of CLAMP studies is cumbersome, expensive and invasive; other measures of insulin resistance lack accuracy as noted in the recent international evidence based guideline on PCOS management [15]. There is a need to establish more efficient surrogate markers of metabolic inflexibility for use in everyday clinical practice. Kim et al [12] suggested a clinical model to evaluate metabolic inflexibility based on fasting insulin, triglycerides, and adiponectin levels which explained 62% of the variance in metabolic inflexibility in the study participants. Developing predictive models with standardised and easy to record metabolic predictors could help to determine individual metabolic risk factors in women newly diagnosed with PCOS [16]. Other methods could also be employed to further evaluate the metabolic inflexibility in women with PCOS such as the measuring lactate and fat to carbohydrate oxidation in exercise settings [17]. More studies are needed to investigate the metabolic response to high-fat diets in women with PCOS as well as the

role of glucose disposal rate, adipose tissue lipid storage, and mitochondrial function on metabolic inflexibility [5].

Weight loss, lifestyle and exercise interventions were shown to improve the metabolic inflexibility in individuals with obesity and T2DM [4]. Losing 10% of body weight with lifestyle interventions [18] or 30% with bariatric surgery also improved the metabolic performance and the associated insulin resistance in obese patients [19]. There is a need to evaluate such interventions in women with PCOS to establish their feasibility and effectiveness in alleviating the established risk factors associated with this condition. To date, evidence on the benefit of lifestyle interventions in PCOS is varied and limited to a specific range of outcomes [20]. Adjusting lifestyle interventions to the individualised metabolic characteristics of women with PCOS could increase their effectiveness and improve compliance. Combining lifestyle interventions with insulin sensitising drugs such as metformin or myoinositol could help to reduce the associated insulin resistance, promote weight loss and stabilise the metabolic status in women with PCOS [21,22].

Our study summaries current evidence on metabolic inflexibility in women with PCOS. However, larger cohorts with better adjustment for confounding factors (age, ethnicity, BMI, baseline diet, and phenotype), more standardised reporting of relevant outcomes are needed [23].

Conclusion

Women with polycystic ovary syndrome appear to have higher metabolic inflexibility compared to unaffected women associated with hyperandrogenemia and insulin resistance. More research is needed to investigate this metabolic feature among all PCOS phenotypes.

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