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Targets to treat metabolic syndrome in polycystic ovary syndrome

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Abstract

Introduction—Metabolic syndrome is comprised of a combination of the following states: increased insulin resistance, dyslipidemia, cardiovascular disease, and increased abdominal obesity. Women with polycystic ovary syndrome (PCOS) have an increased risk of developing metabolic syndrome over the course of their lives. Metabolic syndrome increases risk of major cardiovascular events, morbidity, quality of life, and overall health care costs. Though metabolic syndrome in women with PCOS is an area of great concern, there is no effective individual medical therapeutic to adequately treat this issue.

Areas Covered—This article will review key aspects of metabolic syndrome in PCOS. We will discuss classic and novel therapeutics to address metabolic syndrome in women with PCOS. We will conclude with the importance of developing strategic interventions to increase the compliance to lifestyle and dietary modification, in addition to appreciation of the emerging pharmaceutical therapeutics available.

Expert Opinion—Innovation in lifestyle modification, including diet, exercise, with and without dedicated stress reduction techniques is the future in treatment of metabolic syndrome in PCOS. Application of novel interventions, such as group medical care, may improve future adherence to lifestyle modification recommendations, in addition to or in combination with pharmaceutical therapeutics.

Keywords

group care; lifestyle modification; metabolic syndrome; polycystic ovary syndrome

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1. Introduction

Polycystic ovary syndrome (PCOS) affects up to 10% of reproductive age women and is one of the most common endocrine disorders in this age group.[1–5] PCOS is a heterogeneous disease with neuroendocrine findings and metabolic sequelae characterized by menstrual irregularity and hyperandrogenism, with or without presence of polycystic ovarian morphology. PCOS presents with a broad spectrum of phenotypes. Insulin resistance is not universal in PCOS. However, certain phenotypes are associated with insulin resistance and an increased long-term risk of developing diabetes,[6,7] metabolic syndrome (MBS),[8,9] and cardiovascular disease,[10,11] which are compounded by concurrent obesity.[12,13]

1.1. Polycystic ovary syndrome

The studies on the prevalence of the disorder depend on the criteria used, with estimates ranging from 6 to 12%.[1,4,14] There is debate on what constitutes the required diagnostic criteria for PCOS. There are three main diagnostic criteria for PCOS reported by the National Institutes of Health, the Androgen Excess Society and the Rotterdam criteria.[15,16] The most commonly used criteria in clinical practice is the Rotterdam criteria, which requires two out of three of the following: oligo-ovulation or anovulation, clinical or biochemical evidence of androgen excess and ultrasonographic evidence of polycystic ovary morphology.[17] Evidence of biochemical or clinical hyperandrogenism is a key finding linked to PCOS and is related to its multiple metabolic sequelae.[18,19]

1.2. Metabolic syndrome

MBS is defined as a combination of abnormal glucose metabolism, elevated blood pressure, abnormal lipid profile and abdominal obesity. MBS is defined by distinct, diagnostic criteria set forth by several groups. The most commonly utilized criteria are the guidelines set by the National Cholesterol Education Program Adult Treatment Program III (ATP 3) in 2005. In the United States, these criteria state that three or more of the following abnormalities are required for the diagnosis of MBS in women: fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose; serum high-density lipoprotein (HDL) < 1.3 mmol/L (50 mg/dL women) or drug treatment for low HDL; serum triglycerides ≥ 1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides; abdominal obesity defined as a waist circumference ≥88 cm and a blood pressure ≥ 130/85 mm/Hg or drug treatment for elevated blood pressure.[20] These guidelines are an updated version of the criteria established in 2001 to include a lower threshold for fasting plasma glucose (previously defined as ≥6.1 mmol/L (110 mg/dL)), as well as present drug treatment to meet the definitions of hyperglycemia, dyslipidemia and hypertension. The rationale behind these changes, as reported by the National Heart Lung and Blood Institute (NHLBI) in collaboration with the American Heart Association (AHA), is that multiple marginal abnormalities significantly increase cardiovascular disease risk.[20] Additionally, the lower cutpoint for fasting plasma glucose was implemented to match the American Diabetes Association-modified definition for prediabetes (impaired fasting glucose) or diabetes.[20,21] While not entirely defined in the 2005 ATP 3 guidelines, diagnostic criteria established by the International Diabetes Federation (IDF) consider ethnic variations in waist circumference. For example, the threshold for abdominal obesity in Asian, Ethnic

South and Central American, Sub-Saharan Africans, Eastern Mediterranean, Arab and European women has been defined as a waist circumference ≥80 cm.[22] The higher cutpoint of 88 cm is currently used for all ethnic groups under the 2005 ATP 3 criteria; however, the NHLBI and AHA deem the lower cutpoint for Asian-Americans to be appropriate as this population has a relatively higher predisposition to insulin resistance, MBS and type 2 diabetes mellitus, with moderate increases in waist circumference.[20] In contrast, the IDF strongly recommends that ethnic group-specific cutpoints should be used for all subjects of epidemiological studies and clinical diagnoses regardless of their country of residence.[22] These diagnostic modifications complicate data comparisons between studies and overall prevalence estimates as the study population characteristics and the specific criteria used must be accounted for within each study. Based on data using the 2001 ATP 3 criteria and the revised glucose criterion, the prevalence of MBS in the United States from 1999 to 2000 in normal women aged 20–39 years old was approximately 19%.[23]

There are five applicable studies evaluating the prevalence of MBS in PCOS. Table 1 presents a summary of the original articles reporting prevalence estimates of PCOS with MBS with differing diagnostic criteria.[24] Of these studies, a retrospective study involving 106 women with PCOS presenting to an academic endocrinology clinic evaluated the prevalence of MBS in women with PCOS and found a twofold increased prevalence compared to healthy comparison groups (43% in women aged 20–39 vs 24% in the National Health and Nutrition Examination Survey III cohort, 1988–1994).[25] Furthermore, women with PCOS demonstrated markers of MBS earlier in life by 20 years compared to normal age-matched controls, with a 45% prevalence of MBS in PCOS in women aged 20–29 years, and of 53% in women aged 30 to 39 years. [25] Using the 2001 ATP 3 guidelines with elements of both the 2005 ATP 3 and World Health Organization criteria, an earlier case-control study with 129 cases of women with PCOS and 177 normally menstruating non-hirsute controls found comparable age-adjusted prevalence estimates of PCOS with MBS of 47.3% (95% confidence interval (CI) 35.3–56.9%) and in controls of 4.3% (95% CI 1.9–7.6%).[26] Another study using 2001 ATP 3 guidelines to evaluate the prevalence of MBS within a cohort of 394 women with PCOS that were enrolled in a therapeutic trial of troglitazone found that MBS was common (33.4%) and postulated that hyperinsulinemia was a common factor in PCOS and MBS, that increased BMI and insulinemia were correlated with MBS and that women with a BMI of 27 kg/m^2 or less did not have MBS in their cohort.[27] As mentioned previously, the 2005 updates in the ATP 3 guidelines added and expanded inclusion factors for meeting criteria. As such, usage of the 2001 criteria likely excluded participants meeting the current diagnosis for MBS. Therefore, these reported prevalence estimates are likely to underestimate the true MBS prevalence within each study population. These estimates may also be limited in that they do not consider ethnic-specific values for waist circumference.[24]

The earlier onset of MBS in women with PCOS may subsequently increase atherogenic cardiovascular disease. In one study using a risk factor model applied to 33 women with PCOS and 132 age-matched referents incorporated independent risks for myocardial infarction (age, hypertension, diabetes, central obesity and serum triglycerides) and found an increased relative risk (RR) of 7.4 for myocardial infarction among women with PCOS compared to their age-matched referents.[28] PCOS with MBS may manifest throughout the

life cycle, thereby conveying cardiometabolic risk into pregnancy and menopause.[25,29–33]

Given that 10% of reproductive aged women may suffer from PCOS, and of those up to 53% in their fourth decade of life may develop MBS, based on the study previously described, PCOS with MBS should be prioritized as a major public health issue with implications on long-term cardiovascular, metabolic and reproductive health. Therapeutic targets are key in preventing and curbing the sequelae of MBS.

1.3. Pathophysiologic concept of polycystic ovary syndrome and metabolic syndrome

Though the exact etiology of PCOS syndrome is unknown, it has a complex evolving pathophysiology in which genetic and environmental parts are interweaving, while hormonal and metabolic abnormalities are contributing to a broad spectrum of phenotypes. Hypothalamic function is altered, with notable increased pulse frequency of luteinizing hormone (LH) secretion, and a diminished sensitivity to estrogen feedback inhibition. [34] At the level of the ovary, dysregulated folliculogenesis arrests follicular growth at the mid-antral stage. Additionally, there is granulosa cell dysfunction with suggestion of a decrease in cell death markers despite a thinning of the granulosa cell layer.[35] There is hypertrophy of the theca cells, which are stimulated by LH and responsible for production of ovarian androgens.[36] Both of these findings predispose to polycystic ovarian morphology with multiple peripheral follicles in a string of pearls appearance.[37] Granulosa cell function under the stimulation of follicle stimulating hormone (FSH) is altered due to relatively lower FSH concentrations in women with PCOS [38] with findings of decreased expression of aromatase for conversion of androgens to estrogens.[39] This in combination with increased theca cell function, stimulated by increased LH, promotes increased production of the ovarian androgens, testosterone and androstenedione. Adrenal androgen production is also increased in PCOS with elevated dehydroepiandrosterone compared to ovulatory non-hirsute controls and may be due to adrenal hyper-responsiveness to corticotropin (ACTH).[40,41] Aspects of MBS may increase the severity of biochemical or clinical androgen excess through reduction of sex hormone-binding globulin (SHBG) by obesity and hyperinsulinemia. Hyperinsulinemia also directly stimulates ovarian androgen production. [37] PCOS is a heterogenous disease with individual-specific pathophysiology dependent on the individual’s phenotype.[42,43]

1.4. Pathophysiologic concept of metabolic syndrome in PCOS

MBS is defined as a constellation of cardiovascular risks and insulin resistance, with altered values of serum lipids, abdominal adiposity, blood pressure and blood glucose. [20,21,44–49] It is estimated that obesity is common occurring in approximately 49% of women with PCOS. [50] Central to MBS in PCOS is abdominal obesity and insulin resistance, with an estimated prevalence of between 20 and 40%.[51,52] However, insulin resistance is also present in one-third of lean women with PCOS compared to age-matched controls.[53] PCOS is also associated with an increased lifetime risk of dyslipidemia,[54,55] cardiovascular disease,[56,57] and type 2 diabetes.[58] Cardiovascular risk seems to be elevated in women with the constellation of PCOS with obesity, insulin resistance and

dyslipidemia.[59] Figure 1 summarizes the organs involved in PCOS with MBS as well as the corresponding treatment options.

1.5. Classic therapeutic options for PCOS and implications for MBS

Combined oral contraceptives (OCPs) and antiandrogens have been used as classical first-line treatments to target androgen excess in women with PCOS with effects at multiple sites.

Traditional use of OCPs has been considered first-line therapy in women with PCOS who are not attempting pregnancy and who do not have contraindications to the use of OCPs. The estrogen component in OCPs stimulates increased hepatic production of binding globulins, of which increased production of SHBG correlates with decreased free serum androgens.[60–64] A limitation of OCPs is that this may not be an acceptable therapeutic in PCOS with MBS comprised of hypertension and obesity due to the risk of deep-vein thrombosis and worsening hypertension.[65,66]

Antiandrogen therapy includes use of cyproterone acetate, spironolactone and flutamide. The antiandrogen cyproterone acetate has an untoward side effect of increasing insulin resistance.[67] Spironolactone, another antiandrogen, acting as a competitive inhibitor of the androgen receptor with some block of peripheral conversion of testosterone to dihydrotestosterone by 5-alpha reductase, has the additional benefit of increasing HDL and decreasing triglycerides in lean patients on long-term therapy.[68] However, one study suggested decreased HDL in short-term spironolactone therapy in conjunction with OCPs in lean women with PCOS.[69] Flutamide, a non-FDA-approved non-steroidal selective androgen receptor blocker, does have an additional beneficial effect on lipid profiles including decreased total cholesterol, low density lipoprotein and triglycerides.[70]

2. Metabolic abnormalities in PCOS

2.1. Obesity

Obesity is increasing in incidence and itself is a risk factor for MBS and may compound the risk of MBS in women with PCOS.[71] The prevalence of central obesity among women with PCOS is estimated to range between 20 and 85.5%.[50] Furthermore, in two large population-based cohort studies, body mass index (BMI) in reproductive aged women was correlated with increasing serum total testosterone and inversely correlated with SHBG concentrations in both ovulatory and oligo-ovulatory women.[72–74] Obesity also appears to modify the characteristics and severity of metabolic dysfunction in women with PCOS and thus may explain the metabolic heterogeneity seen in PCOS women with MBS. For example, lean women with PCOS more often present symptoms consistent with a hyperinsulinemia-driven pathophysiology in the absence of insulin resistance compared to obese women who primarily demonstrate a metabolic profile compatible with insulin resistance, most likely associated with visceral adiposity.[75]

Several recent review articles comment on the currently available therapeutic agents for MBS in PCOS [76,77], with note that no single drug/agent will target all aspects. Metformin, a biguanide insulin sensitizer, has been discussed as one such drug thought to

impact nearly all aspects of MBS.[76] For some patients with PCOS and MBS, metfor-min has provided direct treatment of insulin resistance and weight loss.[4,78,79]

2.2. Insulin resistance

Insulin activity and glucose metabolism are aberrant in women with PCOS. Insulin resistance has been demonstrated in many target tissues such as skeletal muscle, fibro-blasts and adipose tissue with abnormalities suggested in insulin receptors and post-receptor signaling.[80,81] Counter to the insulin resistance noted in peripheral tissues, ovarian insulin responsiveness has remained intact in *in vitro* cell studies.[81,82] The prevalence of insulin resistance has been noted in 60–80% of women with PCOS and is compounded by obesity. Earlier studies reported a prevalence of impaired glucose tolerance of 35% and type 2 diabetes of 10% in women presenting with PCOS.[52] A more recent systematic review reported an increased odds of impaired glucose tolerance (OR: 2.54; 95% CI: 1.44, 4.47) and type 2 diabetes (OR: 4.00, 95% CI: 1.97, 8.10) among women with PCOS compared to BMI-matched controls.[83] Metabolic profile, more specifically insulin resistance, also appears to depend upon BMI status with age as the severity of insulin resistance has been shown to increase with age in PCOS women who are obese, but not in lean or overweight PCOS women.[84]

Classic treatment for insulin resistance includes peripheral insulin sensitizers, such as metformin [85], which decreases hepatic gluconeogenesis, increases peripheral glucose uptake and decreases gastrointestinal absorption of glucose.[86] Metformin has beneficial effects on inflammation and cardiovascular risk profile, such as improvement in endothelium-dependent vasodilation, endothelin-1, C-reactive protein (CRP), advanced glycosylation end points (AGEs) and adhesion molecules.[87,88] Further studies are needed to determine whether metformin provides long-term cardiovascular risk reduction in women with PCOS and markers of MBS with and without insulin resistance.

Other insulin sensitizers have been used in this population, such as the thiazolidinedione class of drugs like rosiglitazone and pioglitazone. The thiazolidinediones act through the peroxisome-proliferator-activated-gamma-receptor (PPAR-gamma) and improve insulin sensitivity; however, they are associated with weight gain.[60,89,90] Treatment of insulin resistance with thiazolidinediones are associated with a reduction in serum androgens and may also have beneficial effects at the level of ovarian steroidogenesis by altering the function of steroidogenic enzymes of 3β-hydroxysteroid dehydrogenase.[61–63] However, there have been no subsequent large randomized trials of thiazolidinediones in PCOS.[64] Additionally, a recent FDA advisory reported a linkage between pioglitazone to bladder cancer.[91] The risk–benefit ratio may also be less favorable for infertility because animal studies suggest that thiazolidinediones may be associated with fetal loss (FDA Pregnancy Category C).[92]

2.3. Dyslipidemia

Abnormalities in lipid metabolism and fasting lipid profiles in women with PCOS are variable and are due to a combination of insulin resistance,[93] obesity,[94] with additional modification by diet,[95–97] amount of exercise[98] and genetic predisposition.[99–103]

The general trend is a lowering of HDL, elevation of total cholesterol, low-density lipoproteins and triglycerides.[104–106] One study reported presence of oxidized LDL as an early marker of altered metabolism in young women.[107]

It is notable that lean women with PCOS androgen excess have lipid profile abnormalities compared to normal women of lowered HDL.[108] However, in another study of obese women with PCOS, there was a slight but statistically significant increase in HDL.[54] Further research is needed to better understand the pathophysiology and early clinical biomarkers of abnormal lipid metabolism in PCOS with MBS.

2.4. Liver

Serum SHBG, produced by the liver, corresponds with the bioavailable concentration of androgens and is decreased by elevated circulating androgens and obesity.[109–111] Nonalcoholic fatty liver disease has been described occurring in 2–30% of women with PCOS; however screening guidelines do not recommend routine screening of liver enzymes or imaging of the liver.[112–115] Further studies are needed to accurately quantify this risk and guide clinical screening recommendations.[116]

2.5. Cardiovascular risk

Cardiovascular risk seems to be elevated in women with the constellation of PCOS with MBS, or obesity, insulin resistance/impaired glucose tolerance and dyslipidemia.[59] The absolute risk of cardiovascular disease is not well established. Cardiovascular risk may depend on the severity of PCOS, [117] as well as individual risk predictors such as BMI, [118] genetic predisposition, diet[95–97] and lifestyle factors. In a systematic review of the RR of fatal or non-fatal coronary heart disease (CHD) and stroke, women with PCOS had 1.55 times the risk of CHD or stroke compared to women without PCOS after adjusting for BMI.[119] Additionally, in one large prospective cohort study, menstrual irregularity was associated with an increased risk of non-fatal (age-adjusted RR: 1.25) and fatal (RR: 1.67) CHD.[57] Emerging literature demonstrates that women with PCOS have increased serum markers of inflammation such as CRP [120] and white blood cell count,[27] abnormalities in the renin–angiotensin system [28] and endothelial dysfunction [121–124], which may predispose to CHD seen in PCOS. At least two studies, Talbott and colleagues as well as Shroff et al., have suggested that the cardiovascular risk in women with PCOS may be mediated through early atherosclerotic disease.[125,126]

3. Novel therapeutic targets for PCOS with MBS

The ideal therapeutic for PCOS with MBS is one that addresses the underlying etiology to restore normal hypothalamic pituitary function, with return of normal steroidogenic function at the level of the ovary, and resultant normalization of androgen excess and insulin resistance. Ultimately, the normalization of the hypothalamic pituitary ovarian adrenal axis would lead to a normalization of the attributable component of MBS, notably obesity, insulin resistance, lipid profile, liver dysfunction and amelioration of cardiovascular risk. No single therapeutic has achieved this goal to date. First-line therapeutics, such as OCPs, antiandrogens and insulin sensitizers, have resulted in changes in the level of the

hypothalamus–pituitary–ovarian axis (OCPs), decreased androgens (OCPs and antiandrogens) and improved glucose metabolism (metformin). Metformin has addressed several of these pathways but has fallen short as a panacea,[127,128] particularly in the reduction of androgen excess in obese individuals with PCOS.[86,129,130] Furthermore, women with PCOS-MBS who desire fertility pose an additional challenge to most of the mentioned therapeutics due to contraindications and safety in pregnancy. Despite these limitations, there are several emerging therapeutics for PCOS with MBS. Though most of these emerging therapeutics do not seem to address all pathways, addressing key factors of MBS may succeed in diminishing long-term cardiovascular risk. In this vein, acarbose and orlistat may improve dietary parameters influencing lipid profiles and obesity. Table 2 summarizes the associated pathophysiological effects and novel therapeutic targets for PCOS with MBS under each criterion defined by the 2005 ATP 3 guidelines for women.

3.1. Obesity

Acarbose is a complex oligosaccharide that inhibits alpha-glucosidase resulting in decreased digestion and absorption of polysaccharides. There are a few promising studies within the PCOS population, but further research is needed to address conflicting reports on lipid metabolism, insulin, BMI reduction and cardiovascular parameters.[131–135] Orlistat inhibits the hydrolysis of triglycerides and acts as a gastric and pancreatic lipase inhibitor, thereby reducing dietary fat absorption. Orlistat, which has been studied in PCOS-MBS, may hold promise as studies demonstrate reduction of AGEs, which are known to be elevated in PCOS and have associated cardiovascular risk.[96,136]

3.2. Insulin resistance

D-chiro-inositol, a newer insulin sensitizing agent, may ultimately prove to help women with PCOS and MBS. [137,138] More studies are required regarding the model of its action and its efficacy. Vitamin D, a key factor in calcium homeostasis and bone metabolism, has been evaluated in other populations, with note that normal levels of vitamin D are associated with normal insulin metabolism.[139] Two studies do suggest a potential benefit for vitamin D evaluation and treatment in PCOS-MBS,[140,141] but further research is needed regarding the utility of vitamin D supplementation or treatment in women with PCOS-MBS.

3.3. Dyslipidemia

After diet and exercise, statin therapy is a common therapeutic to address clinically relevant dyslipidemia in the adult population. Statin therapy, acting by inhibiting cholesterol synthesis at HMG co A reductase, improves lipid profiles and has demonstrated long-term treatment benefit in cardiovascular disease risk reduction. Some studies support pluripotent effects of hypolipidemic treatment on multiple organ systems including cardiovascular risk, hyperandrogenemia, insulin resistance and mood disturbance.[142] There are limitations to the use of statins in women who are attempting pregnancy, or who are pregnant, over concern of fetal teratogenicity [143] with the recommendation of stopping statin treatment prior to attempts at conception. In women with PCOS in whom pregnancy is not a current concern, and in whom therapy is warranted, statins may be considered. There are a few studies of statin therapy in women with PCOS with lipid abnormalities replicating this finding. [144,145] The additional benefits of statins include a reduction of ovarian androgen

synthesis as noted by a study of atorvastatin on metabolic profile of women with PCOS.[146]

3.4. Other emerging therapeutics

Emerging therapeutics that may act at the level of the hypothalamus and pituitary are important to consider. Naltrexone, an opioid antagonist acting through increase of beta-endorphins and sympathetic nervous system activity, has been shown to normalize response to GnRH stimulation in women with PCOS [147] and improve insulin sensitivity.[148] Liraglutide, a glucagon-like peptide 1 (GLP-1) receptor agonist, has been shown to induce greater increases in weight loss compared to met-formin in a subset of PCOS women with a high-risk profile for MBS.[149] Targeting Neuropeptide Y, which has abnormal secretory profiles in women with PCOS in relation to ghrelin, may provide a novel future therapeutic.[150] Finally, there may be promise in evaluating the obesity-related hormones of leptin and ghrelin in targeting novel pathways for treatment of PCOS-MBS.[151,152]

In addition to the above therapeutic targets, lifestyle modification programs utilizing increased physical activity, techniques to decrease perceived stress and a group care model for women with PCOS-MBS may provide multiplicative benefit to use of a single or combination pharmaceutical therapeutic. Regarding stress reduction, studies incorporating low-frequency electroacupuncture (EA) may be useful in the treatment of hyperandrogenism and menstrual frequency. In a randomized controlled trial of 84 women with PCOS, women randomized to a 16-week regimen of EA had a 25% decrease in serum testosterone as well as an increase in menstrual frequency from 0.28 per month at baseline to 0.69 per month. Interestingly, the magnitudes of these changes in testosterone and menstrual frequency were significantly greater that what was seen in women randomized to a 16-week regimen of physical exercise ($p = 0.038$ and $p = 0.018$, respectively).[153] Group medical care and group-centered therapy have not yet been applied to women with PCOS-MBS, but have been evaluated in the prenatal population with interesting outcomes. In one early study, group prenatal care was compared to standard prenatal care with notable improvements in psychosocial aspects (prenatal education, preparedness for labor and delivery) and a 33% reduction in preterm birth in the group care participants; all outcomes were strengthened in the African American population of participants of that study.[154] A group care model, with a structured and varying exercise program, may prove critical for long-term treatment compliance and achievement of the greatest risk reduction in women with PCOS-MBS.

3.4.1. Evidence targeting lifestyle therapeutics—Lifestyle modification including diet, exercise and group-centered therapy may benefit women suffering from MBS with PCOS. The majority of current literature on diet and lifestyle modifications are focused on evaluating short-term reproductive outcomes such as clinical pregnancy rates and have secondary aims of metabolic parameters of a short time interval.[155,156] In a prospective intervention study comparing the effect of exercise between overweight women with and without PCOS, exercise training improved insulin resistance in women with PCOS by 16% and resulted in a more significant reduction in serum triglycerides compared to women without PCOS.[157] Another systematic review reported that exercise of any form, frequency or duration was associated with benefits including improved ovulation, weight

loss and improved insulin resistance.[158] One main issue with lifestyle intervention is difficulty in long-term compliance.[159] Furthermore, there is a great need for future studies on diet/lifestyle modifications and their long-term impact on the reduction and prevention of MBS.

4. Conclusion

We feel that the beneficial effect of any therapeutic target will be enhanced by lifestyle modification. In addition to a selection of any particular individual pharmaceutical therapeutic, recommendation of lifestyle and diet modification is of critical importance in addressing MBS in PCOS women. Despite the trials of single or combination pharmacologic therapeutics, the literature has reiterated that lifestyle modification is superior to any single pharmacologic therapeutic alone.[160,161] In some instances, improved outcomes are noted when lifestyle interventions are combined with targeted pharmacologic therapeutics.[162–165]

5. Expert opinion

PCOS is the most common endocrinopathy affecting women of reproductive age, with a prevalence of 6–7%, and concern that the incidence, severity and risk of MBS may be increasing due to its relationship with obesity. However, no effective treatment options are currently available to target the constellation of symptoms found in PCOS-MBS. This may be due to the lack of a final common targetable cellular pathway, or that the pathways are complex and interrelated, requiring more than one intervention. Understanding the pathophysiology of PCOS with MBS is an area of importance for future research. Because the data on lifestyle intervention, including physical exercise, is so compelling for treatment benefit, we feel that the study of lifestyle interventions in combination with pharmacotherapy is critical in further addressing PCOS-MBS in a way that no single pharmacologic intervention can. Furthermore, if PCOS with MBS is not addressed or prevented at an early stage, significant morbidity at an earlier age is expected. In the worst-case scenario, treatment will consist of a pharmacopeia – including but not limited to insulin-sensitizing agents, anti-hypertensives and anti-hyperlipidemics. Therefore, early diagnosis, prevention and lifestyle modification along with judicious use of classic or novel therapeutics for PCOS-MBS tailored to each patient is recommended. Future studies combining the use of the mentioned novel therapeutics toward early treatment and PCOS-MBS risk reduction as well as studies elucidating the complex mechanisms of PCOS-MBS and physical activity-related life-style modification will be critical. Furthermore, continuing the search for modifiable early exposures that predispose to PCOS-MBS is also critical.

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Reference annotations

* Of interest

** Of considerable interest

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Article highlights

- No single drug/agent targeting all aspects of metabolic syndrome (MBS) in women with polycystic ovary syndrome (PCOS) is currently available.
- Though most emerging therapeutics for PCOS with MBS do not appear to address all pathophysiological pathways, addressing key factors of MBS may succeed in diminishing long-term cardiovascular risk.
- In addition to the discussed therapeutic targets, lifestyle modification programs and a group care model for women with PCOS-MBS may provide multiplicative benefit to use of a single or combination pharmaceutical therapeutic.

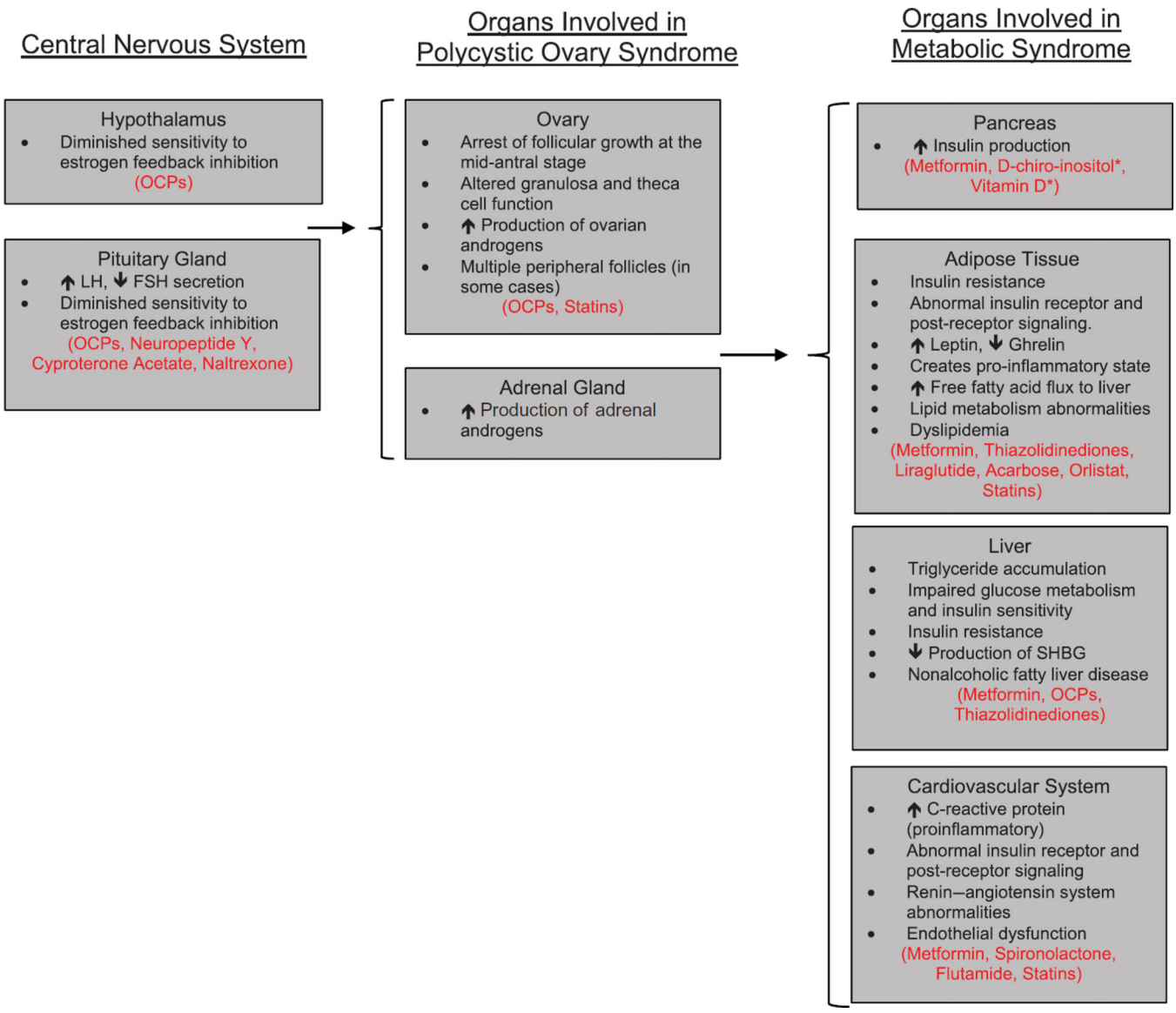

Figure 1.

Organs involved in polycystic ovary syndrome with metabolic syndrome and corresponding treatment options.

*Sites of action at specific tissues are currently unknown.

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Table 1

A summary of the original articles describing prevalence estimates of polycystic ovary syndrome (PCOS) with metabolic syndrome (MBS).

First author/year	Study design	Prevalence MBS/PCOS	Metabolic Syndrome Factors			
			Abnormal glucose metabolism	Abnormal lipids	Abdominal obesity	Elevated blood pressure
Glueck 2003[1]	RC	46% (64/138)	11% (HI)	56% HTRIG	98% high WC	70% HTN
Dokras 2005[2]	RC	47% (61/129)	12% (IFG)	46% HTRIG 63% Low HDL-C	72% high BMI	29% HTN
Apridonidze 2005[3]	RC	43% (46/106)	20% (IFG, IGT, NIDDM)	70% HTRIG 91% low HDL-C	91% high BMI	74% HTN
Vrbikova 2005[1]	CC	1% (1/64)	0 (IFG)	5% HTRIG 34% low HDL-C	11% high WC	13% HTN
Ehrmann 2006[1]	MCT	33% (123/368)	5% (IFG)	32% HTRIG 66% low HDL-C	80% high WC	21% HTN

Notes: BMI = body mass index; CC = case control; HI = hyperinsulinemia; HTRIG = hypertriglyceridemia; HTN = hypertension; IFG = impaired fasting glucose;IGT = impaired glucose tolerance; MCT = multicenter clinical trial; NIDDM = non-insulin dependent diabetes mellitus; RC = retrospective cohort; WC = waist circumference.

[1]2001 Adult Treatment Panel 3 (ATP 3) criteria.

[2]Modified 2001 ATP 3 criteria that include the diagnosis of type 2 diabetes mellitus as meeting the criterion for abnormal glucose metabolism. World Health Organization criterion for abdominal obesity (BMI ≥ 30 kg/m^2) used to substitute waist circumference measurement.

[3]Modified 2001 ATP 3 criteria that substitute BMI ≥ 32 kg/m^2 for waist circumference measurement to meet abdominal obesity criterion.

Table 2

Novel Therapeutic targets for polycystic ovary syndrome with metabolic syndrome.

Metabolic syndrome criteria[1]	Definition/diagnosis	Associated pathophysiological effects	Treatment options/therapeutic targets
Abnormal glucose metabolism	Glucose ≥ 5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose	Insulin resistance Hyperinsulinemia Increased androgen production Decreased SHBG	Metformin, thiazolidinediones, D-chiro-inositol, naltrexone: improve insulin sensitivity Vitamin D: Associated with normal insulin metabolism
Abnormal lipid profile	HDL cholesterol: <1.3 mmol/L (50 mg/dL) or drug treatment for low HDL triglycerides ≥ 1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides	Increased androgen production Insulin resistance Decreased SHBG	Spironolactone: increases HDL and decreases triglycerides Flutamide: decreases total cholesterol, LDL and triglycerides Statins: inhibits cholesterol synthesis and improves lipid profiles
Abdominal obesity	Obesity with a waist circumference ≥ 88 cm	Increased androgen production Insulin resistance Decreased SHBG production	Metformin: incudes modest weight loss Liraglutide: induces weight loss Acarbose: decreases digestion and absorption of polysaccharides Orlistat: reduces dietary fat absorption Diet modification: reduces AGEs
Elevated blood pressure	Blood pressure ≥ 130/85 mm/Hg or drug treatment for hypertension	Increased C-reactive protein Endothelial dysfunction Pro-inflammatory state	Metformin: Improves endothelium-dependent vasodilation

Notes: ATP 3: Adult Treatment Panel III; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SHBG: sex hormone-binding globulin, AGEs advanced glycosylation end products.

[1] Based on the 2005 ATP 3 Guidelines for women.