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Medical management of metabolic dysfunction in PCOS

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Abstract

Polycystic ovary syndrome (PCOS) is associated with metabolic derangements including insulin resistance, dyslipidemia, systemic inflammation and endothelial dysfunction. There is a growing need to develop pharmacologic interventions to improve metabolic function in women with PCOS. Medications that have been tested in patients with PCOS include metformin, thiazolidinediones, acarbose, naltrexone, orlistat, vitamin D and statins.

Metformin decreases hepatic gluconeogenesis and free fatty acid oxidation while increasing peripheral glucose uptake. Early studies in PCOS suggested that metformin indirectly reduces insulin level, dyslipidemia and systemic inflammation; however, recent placebo-controlled trials failed to demonstrate significant metabolic benefit. Thiazolidinediones act primarily by increasing peripheral glucose uptake. Most studies in PCOS have demonstrated that thiazolidinediones reduce insulin resistance; however, effects on dyslipidemia were disappointing. Use of thiazolidinediones is associated with weight gain and major complications. Acarbose reduces digestion of polysaccharides. Studies in PCOS yielded inconsistent effects of acarbose on insulin sensitivity and no significant improvement of dyslipidemia. Naltrexone reduces appetite and modulates insulin release; its use in PCOS may reduce hyperinsulinemia. Orlistat decreases absorption of dietary fats; studies in PCOS suggest beneficial effects on insulin sensitivity. Vitamin D may improve insulin sensitivity but mixed results on lipid profile in PCOS have been reported. Statins are competitive inhibitors of the key enzyme regulating the mevalonate pathway; their effects are related to reduced cholesterol production as well as anti-inflammatory and anti-oxidant properties. In women with PCOS, statins reduce hyperandrogenism, improve lipid profile and reduce systemic inflammation while the effects on insulin sensitivity are variable. Use of statins is contraindicated in pregnancy.

Keywords

Polycystic ovary syndrome; Metabolic dysfunction; Insulin sensitivity; Dyslipidemia; Inflammation

1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting between 6% and 8% of women in reproductive age [1]. It is associated not only with reproductive and cosmetic sequelae, but also with significantly increased risk of metabolic dysfunction including insulin resistance with consequent compensatory hyperinsulinemia, dyslipidemia, systemic inflammation, increased oxidative stress, and endothelial dysfunction (Fig. 1) [2,3]. In the long-term, women with PCOS may develop type 2 diabetes mellitus,

hypertension and atherosclerosis; ultimately, they are more likely to suffer from cardiovascular and cerebrovascular diseases [4–6].

First-line therapy for metabolic dysfunction typically consists of lifestyle modifications including a diet and exercise regimen. Unfortunately, long-term success of lifestyle modifications is often not achieved. Consequently, there is an urgent need to develop and validate appropriate pharmacologic interventions to improve metabolic function in women with PCOS. This brief review will present several currently available medical treatments of selected features of metabolic dysfunction and will discuss pros and cons of their use in PCOS.

2. Metformin

Metformin is a biguanide widely used in treatment of type 2 diabetes mellitus and, more recently, in treatment of other conditions including PCOS. The primary mechanism of action of metformin is believed to be related to reduction of hepatic gluconeogenesis [7,8]. In addition, metformin improves glucose uptake by peripheral tissues, decreases fatty acid synthesis and increases fatty acid oxidation. Metformin may also improve insulin sensitivity of skeletal muscles and reduce appetite. Furthermore, studies *in vitro* indicate that metformin may act on an ovarian level by reducing androgen production by theca cells [9].

Potential beneficial effects of metformin on metabolic function include improvement of glycemic control, insulin sensitivity, and lipid profile as well as fat loss and decreased systemic inflammation. Effects of metformin on reduction of the incidence of type 2 diabetes have been studied in a large randomized trial evaluating pre-diabetic subjects [10]. The participants were followed by an average of 2.8 years and cumulative incidence of diabetes was significantly decreased by 31% in the metformin-treated group when compared to the placebo group. However, an intensive lifestyle modification program was more effective than metformin and reduced the incidence of diabetes by 58%.

Several studies evaluating women with PCOS have demonstrated that metformin use led to marked improvement of various aspects of metabolic function including reduction of insulin and postprandial glucose level and improvement of various measures of insulin sensitivity [11–15]. In many studies metformin also had a beneficial effect on lipid profile improving, albeit inconsistently, several aspects of dyslipidemia. Thus, metformin use led to increased high-density lipoprotein (HDL) cholesterol, decreased low-density lipoprotein (LDL) cholesterol and/or decreased triglycerides [12–14,16,17]. Other beneficial effects of metformin included reduction of BMI and waist-to-hip ratio (WHR) as well as improvement of endothelial function, and decreased measures of systemic inflammation such as c-reactive protein (CRP) [13,14,16,17].

Unfortunately, many of the above-discussed effects of metformin were not observed consistently. Hence, for example, several studies, including placebo-controlled randomized trials failed to demonstrate beneficial effect of metformin on improvement of insulin sensitivity [18–20]. In a similar fashion, in many trials metformin failed to improve lipid profile [15,17,18]. Recent meta-analysis failed to detect a significant effect of metformin on fasting insulin level, waist circumference, HDL cholesterol, total cholesterol and triglycerides [21]. The same meta-analysis revealed that metformin induced a borderline reduction of WHR, a slight decrease of fasting glucose level and a modest reduction of systolic, but not diastolic pressure.

Discordant findings of the studies evaluating effects of metformin on metabolic function in PCOS may be related to many confounding factors, and especially to the selection of study subjects. One likely source of divergent observations is related to the recent change in the

definition of PCOS. Thus, most early studies used the NIH-consensus-based definition established in 1990, which included only subjects with clinical or chemical evidence of androgen excess and oligo-ovulation. In contrast, many recent studies used a more inclusive definition (Rotterdam criteria from 2003) accepting also patients without androgen excess (oligo-ovulatory with polycystic ovarian morphology) and normo-ovulatory patients (with androgen excess and with polycystic ovarian morphology). Such a change in the definition resulted in the inclusion of many women with little or no evidence of metabolic dysfunction. A closely related issue is that of great heterogeneity inherent to PCOS even among subjects defined by the more strict criteria from the NIH consensus of 1990. In particular, not all women with PCOS have evidence of insulin resistance and compensatory hyperinsulinemia. Since the primary mode of action of metformin is related to reduction of hepatic glucose output and consequent reduction of insulin level, it is not surprising that metformin may be more effective in populations with greater insulin resistance and higher insulin levels.

Indeed, there is evidence in support of this concept. For example, in women with PCOS defined according to NIH criteria and with hyperinsulinemia (based on fasting insulin level >17 mU/ mL) metformin was effective in increasing HDL cholesterol while reducing LDL-cholesterol and triglycerides [14]. In contrast, in another study, the same team of investigators failed to detect any significant effect of metformin on insulin level and lipid profile among women with PCOS defined according to Rotterdam criteria and with normal fasting insulin [17]. Similar findings were observed with regard to the effects of metformin on insulin resistance in a recent study evaluating effects of escalation of doses of metformin up to very high doses (3000 mg/day) in women with wide range of BMI [22]. Significant reduction of insulin was achieved only among women with high BMI (in the range of 35–40) and the reduction of insulin resistance was the greatest among subjects with the greatest baseline insulin resistance.

Metformin is typically prescribed in doses ranging from 500 mg/day to 850 mg three times a day. It is contraindicated in the presence of metabolic acidosis, renal and cardiac failure, dehydration and alcoholism. When using metformin, it is recommended to monitor renal function and discontinue treatment following trauma, in the presence of high fever, significant infection and within 48 h of use of intravenous contrast. Metformin has significant gastrointestinal side effects including reduced appetite, metallic taste, nausea, vomiting, flatulence and diarrhea. These side effects may be reduced and sometimes eliminated by taking it with food, by slowly increasing the dose of medication and/or use of extended release preparations. A potentially fatal adverse effect of metformin is lactic acidosis, but this is highly unlikely in women with PCOS. Metformin may interact with some other medications including ACE inhibitors and cimetidine. It is a pregnancy category B medication.

3. Thiazolidinediones

Thiazolidinediones encompass a family of related compounds acting as peroxisome-proliferator-activated receptor- γ (PPRA γ) agonists. Thiazolidinediones improve insulin sensitivity at the level of peripheral tissues including skeletal muscle and adipocytes. Beneficial effects of thiazolidinediones including rosiglitazone and pioglitazone on insulin sensitivity in women with PCOS have been documented in multiple studies including placebo-controlled trials [21,23–26]. Thiazolidinediones also improved systolic blood pressure, reduced markers of systemic inflammation and improved endothelial function [23,27]. However, effects on lipid profile were inconsistent and most trials failed to demonstrate significant improvement of dyslipidemia [21,24,27–29]. Rosiglitazone use was also reported to increase levels of homocysteine thereby potentially worsening cardiovascular risks [30]. Furthermore, use of thiazolidinediones is often associated with

weight gain rendering their use unattractive for many women with PCOS [26,29]. Combined therapy with metformin failed to demonstrate significant benefit above that of single-therapy [31].

Rosiglitazone is usually prescribed at an initial dose of 4 mg/ day; if needed, the dose is increased to 8 mg/day after 8–12 weeks. Pioglitazone is initially used at a dose of 15 mg/day with subsequent increase of the dose to 30–45 mg/day. Contraindications include hypersensitivity, symptomatic heart failure, pregnancy, lactation and hepatic dysfunction. Liver functions should be evaluated before initiation of thiazolidinediones and periodically thereafter. Adverse effects include weight gain, fatigue, edema, diarrhea, sinusitis, anemia, congestive heart failure, and in particular for pioglitazone, increased risk of bladder cancer. Rosiglitazone use is associated with significantly increased risk of myocardial infarction and its use is highly restricted; it is unlikely that rosiglitazone will ever be used again in women with PCOS. Thiazolidinediones interact with many medications: their effects are increased with concomitant use of NSAIDs, sulfonamides, fluconazole and gemfibrozil while effects are decreased by phenytoin, carbamazepine, phenobarbital and rifampicin. Thiazolidinediones are listed as pregnancy category C medications.

4. Acarbose

Acarbose is a complex oligosaccharide inhibiting α -glucosidase in the brush border of the small intestine. It decreases digestion of polysaccharides and hence reduces glucose absorption in the gut and decreases postprandial insulin levels. To date few studies addressed the effects of acarbose on women with PCOS [32–36]. In only two studies acarbose reduced insulin level and/or parameters of insulin resistance [32,35] while in other studies no improvement was noted [33,36]. A beneficial effect of acarbose on lipid profile was also reported by some [34,35] but not all investigators [36]. One placebo-controlled trial indicated that acarbose reduced blood pressure and improved endothelial function [34]. Two reports from one center documented reduction of BMI [33,34] but other studies failed to detect any significant change in BMI [32,35,36].

Acarbose treatment is typically initiated at a dose of 25 mg/day with a subsequent gradual increase up to 25 mg/t.i.d and if needed up to 50 mg/t.i.d. Contraindications include ketoacidosis, cirrhosis, significant gastrointestinal disorders and significantly reduced creatinine clearance. Adverse effects are very common and include flatulence, diarrhea, abdominal pain, nausea and vomiting. It may induce potentially fatal hepatotoxicity. Liver function tests are recommended every 3 months in the first year and periodically thereafter. It interacts with multiple drugs such as thiazides, steroids, warfarin and chlorpromazine. It may also reduce bioavailability of dioxin. It is listed as a pregnancy category B medication.

5. Naltrexone

Naltrexone is a competitive nonselective antagonist of opioid receptors. Use of naltrexone in treatment of PCOS is based on the evidence that PCOS is characterized by increased activity of sympathetic nervous system, altered central opioid tone and elevated beta-endorphin release [37–39] There is also a growing body of evidence demonstrating that beta-endorphins exert profound effects on insulin release [37].

In several studies oral administration of naltrexone in women with PCOS resulted in a significant reduction of fasting insulin level and insulin area under the curve following glucose load without adversely affecting glucose levels [40–44]. Villa and associates found that naltrexone use led to decreased insulin area under the curve only in hyperinsulinemic and not in normoinsulinemic women [41]. However, in contrast, recent trials evaluating hyperinsulinemic women with PCOS failed to detect an improvement of either fasting or

glucose-induced insulin levels [45]. Some, but not all studies demonstrated a naltrexone-related reduction of BMI [41,43,44]. To date, there is no evidence that naltrexone has a significant effect on lipid profile, systemic inflammation or endothelial function in women with PCOS.

Naltrexone is typically used orally at a dose of 25–50 mg daily. Administration with food or shortly after meals may reduce gastrointestinal side effects. It is contraindicated in patients using opioids chronically, as well as in the presence of hepatitis or hepatic failure. Since naltrexone is excreted primarily in the urine, its use should be avoided in the presence of renal impairment. Adverse effects may include abdominal pain, nausea, vomiting, anorexia, diarrhea, headaches, chest and muscle pains and thrombocytopenia. Interactions of naltrexone with medications other than opioids is not well known; however, it should be administered with caution in the presence of concomitant use of drugs associated with potential liver toxicity such as acetaminophen and disulfiram. It is listed as a pregnancy category C medication.

6. Orlistat

Orlistat is a gastric and pancreatic lipase inhibitor reducing absorption of dietary fats by inhibition of hydrolysis of triglycerides. It has been approved for management of obesity and has been recently tested in several trials evaluating women with PCOS [46–49]. In three of these studies, orlistat improved parameters of insulin sensitivity and reduced insulin level with concomitant decrease of BMI [46,47,49]. However, in one of the studies, orlistat while reducing BMI, had no significant effect on insulin sensitivity and no effect on lipid profile [48]. Orlistat use was also associated with decreased levels of advanced glycation end-products (AGEs) [47]. AGEs are substances elevated in PCOS and are associated with increased oxidative stress and cardiovascular risks [50,51]. The major limitation of all the above trials is the use of orlistat in combination with diet; hence the dissociation of the effects of orlistat from diet is not possible.

Orlistat is typically administered orally at a dose of 120 mg three times a day during or within 1 h of a fat-containing meal. It is contraindicated in the presence of chronic malabsorption syndrome and cholestasis. Rarely, cases of severe hepatotoxicity have been reported. Adverse effects are common and very unpleasant including fecal urgency and incontinence, fatty stools or discharge, flatulence and increased defecation. It can also cause headaches, abdominal pain and back pain. Drug interactions include risk of decreased absorption of amiodarone, it may also reduce the serum level of various medications including cyclosporine, levothyroxine, paracalcitol and fat-soluble vitamins. It also may enhance the anticoagulant effect of warfarin. Orlistat is a pregnancy category B medication.

7. Vitamin D

The primary role of vitamin D pertains to regulation of calcium homeostasis and bone metabolism. Vitamin D promotes intestinal absorption of dietary calcium. Vitamin D receptors are present in most tissues in the body and effects of vitamin D include inhibition of cell proliferation, induction of cell differentiation and immunomodulation. Low levels of vitamin D are associated with insulin resistance while administration of Vitamin D may improve insulin sensitivity; however, the mechanisms of this effect are still not clear [52–54].

To date, few studies have evaluated effects of vitamin D on metabolic aspects of PCOS and there are no placebo-controlled or randomized trials [55,56]. In all these trials, vitamin D administration was associated with an improvement of insulin sensitivity and/or decreased insulin level. However, effects on lipid profile were not impressive: in one study a modest

reduction of triglycerides and an increase of HDL-cholesterol were observed [52], while in another study a reduction of triglycerides was accompanied by an increase of total and LDL-cholesterol [56]. Vitamin D does not appear to affect BMI. Effects of vitamin D on blood pressure, systemic inflammation and endothelial function are yet to be assessed.

Vitamin D is usually given orally in the form of vitamin D₂ or D₃ at a dose of 1000–2000 units/day or at a dose of 50,000 units/ weekly depending on the severity of deficiency. The goal is to achieve serum level of 25(OH)D above 30 ng/mL; monitoring of serum level is recommended within 3 months of initiation of treatment. Contraindications to administration of vitamin D include excessive levels of vitamin D, primary hyperparathyroidism, hypercalcemia, malabsorption syndrome and renal failure. Adverse effects are related to hypercalcemia and include headaches, nausea, vomiting, dizziness, loss of appetite and dry mouth. Vitamin D is pregnancy category C.

8. Statins

Statins are competitive inhibitors of the rate-limiting enzyme in the cholesterol biosynthetic pathway: 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Statins improve the lipid profile, primarily by decreasing total cholesterol and LDL-cholesterol levels [57,58]. Statins also exert many other potentially beneficial effects including improvement of nitric oxide-mediated endothelial function as well as anti-inflammatory and anti-proliferative actions [59,60]. In the long-term, statins decrease both cardiovascular morbidity and mortality [58].

Several clinical trials evaluated effects of statins on women with PCOS and demonstrated significant improvement of many clinical, metabolic and endocrine aspects of this disorder. In the first trial women with PCOS defined according to Rotterdam criteria were randomized to oral contraceptive pill (OCP) alone or to OCP plus simvastatin (20 mg/day) for 12 weeks followed by crossover across groups [61]. Simvastatin induced a significant reduction of LDL-cholesterol and prevented OCP-induced increase of triglycerides. Simvastatin also decreased levels of markers of systemic inflammation and endothelial inflammation: CRP and soluble vascular cell adhesion molecule 1 (sVCAM). A subsequent trial was performed without OCP and compared effects of simvastatin with effects of metformin and the combination of simvastatin plus metformin [17]. After 6 months, simvastatin alone induced marked improvement of lipid profile, as well as a reduction of CRP and sVCAM; the combination of simvastatin and metformin did not improve upon effects of simvastatin alone. Other investigators evaluated effects of simvastatin (20 mg/day) and atorvastatin (20 mg/ day) on women with PCOS defined according to Rotterdam criteria [62,63]. Both treatments resulted in significant improvement of lipid profile as well as a reduction of CRP, oxidative stress and homo-cysteine level. Atorvastatin treatment was associated with improvement of insulin sensitivity. These findings were consistent with observations of a placebo-controlled trial evaluating effects of atorvastatin (20 mg/day) over a 12-week period [64]. In that study, atorvastatin improved lipid profile, reduced CRP and improved insulin sensitivity. However, effects of statins on insulin sensitivity are not consistent; in a recent placebo-controlled trial, administration of atorvastatin (40 mg/day) for 6 weeks resulted in a significant increase in insulin levels indicating reduced insulin sensitivity [65]. Further studies are needed to determine whether differences in the duration of therapy and the dose of atorvastatin may explain these divergent observations.

Simvastatin is usually prescribed at a dose of 10–40 mg/day, while atorvastatin may be used over a wider range of 10–80 mg/ day; preferably, it should be taken in the evening with or without food. Use of statins is contraindicated in the presence of ketoacidosis, decompensated liver cirrhosis and significant renal impairment. Statins interact with may

medications and most importantly potentially fatal interactions may occur in users of cyclosporins, gemfibrozil, niacin or protease inhibitors due to increased risk of rhabdomyolysis, hepatotoxicity and renal failure. Levels of statin may also be increased in users of various medications including verapamil, diltiazem, imatinib and erythromycin (this is not an all-inclusive list). Careful review of drug interactions is essential. Consumption of more than one liter of grapefruit juice per day is contraindicated since it may significantly increase statin level. Liver function should be monitored regularly (e.g. every 2–3 months), especially during the first year of treatment; subsequent testing may be less frequent. The most important adverse effect is related to myotoxicity, especially at high doses of statins. Monitoring of symptoms such as muscle weakness and myalgia is essential. Usually statins are well tolerated, but headaches and gastrointestinal disturbances are occasionally reported. Statins currently are listed as pregnancy category X medications and should be used in women using reliable contraception.

9. Conclusions

At first glance, review of the literature may suggest the availability of a plethora of medical treatments to correct metabolic dysfunction associated with PCOS. However, upon closer inspection of the studies, the evidence for real long-term benefit of currently available treatments is, at best, very limited. Metformin appears to alleviate some aspects of metabolic dysfunction, but the improvement is modest while the side effects are very common and significant. Furthermore, response to metformin varies, likely depending, at least in part, on the presence of insulin resistance. Thiazolidinediones are unlikely to be used in the future in view of long-term concerns including potentially fatal cardiac complications and risk of bladder cancer. To date, very few studies addressed metabolic effects of acarbose, naltrexone, orlistat and vitamin D. Furthermore, acarbose and orlistat are associated with extremely unpleasant gastrointestinal side effects and long-term patient compliance in using these medications is likely to be poor. Statins consistently improve lipid profile and markers of systemic inflammation; however, their effects on insulin sensitivity in women with PCOS are still not well understood.

The decision to initiate potentially long-term medical therapy with any of the above reviewed medications is further complicated by several other concerns. First, there is no long-term data regarding risk-to-benefit ratio of any of these drugs. Most women with PCOS are young and are expected to live for more than 50 or 60 years. Hence, the decision to initiate medical treatment that may be continued for many decades cannot be made lightly. A second and closely related issue is that of the effect of any treatment on quality of life, especially since all available treatments carry potentially significant and unpleasant side effects. Finally, in view of the heterogeneous nature of PCOS, there is an urgent need to identify likely responders and non-responders to each individual therapy.

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Fig. 1.
Reproductive and metabolic effects of PCOS.