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What is new in the landscape of insulin-sensitizing agents for polycystic ovary syndrome treatment

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Abstract: Polycystic ovary syndrome, the most common gynecological endocrinopathy, is burdened with a state of hyperinsulinemia and insulin resistance in 50–80% of affected women. Wherever the origin of these metabolic abnormalities lies, their pathogenetic role in determining, perpetuating, and worsening the clinical traits of the syndrome is ascertained. Many studies have already highlighted possible mechanisms: hyperinsulinemia and insulin resistance may contribute to hyperandrogenemia, chronic anovulation, and other comorbidities of the syndrome by differentially affecting the endocrine glands (ovaries, adrenals, and pituitary) and peripheral tissues (fat mass and skeletal muscle). Based on these evidences, in the past years, thorough research has been focused on the possible role of insulin-sensitizing agents in the treatment of polycystic ovary syndrome. Many compounds were tested to verify their efficacy against polycystic ovary syndrome–related metabolic dysfunction, both relying on previous acquired experiences in the field of diabetes mellitus and experimenting new agents, in particular, those belonging to the class of nutraceuticals. We sought to summarize the most relevant aspects of insulin-sensitizing treatments in polycystic ovary syndrome, by reporting the relevant literature on this topic and by keeping an attentive eye on the newly published international guidelines on polycystic ovary syndrome 2018. This overview encompasses metformin, thiazolidinediones, inositols, alpha-lipoic acid, and GLP1-R analogues. Starting from the analysis of the mechanisms of action, we anchored to the state of the art of the use of these drugs in polycystic ovary syndrome, to the most recent evidences for clinical practice and to the remaining open questions around indications, dose, treatment schedules, and side effects.

Keywords: Polycystic ovary syndrome, insulin, insulin sensitizer

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Why we are always looking for new solutions to insulin abnormalities in polycystic ovary syndrome

Hyperinsulinemia and insulin resistance affect from 50 to 80% of women with polycystic ovary syndrome (PCOS), depending on different populations, ethnicities and diagnostic methods.[1] These metabolic abnormalities are more prevalent in overweight-obese women, even if exaggerated circulating insulin levels and reduced insulin-mediated glucose metabolism are also found in up to 40% of nonobese subjects.[2]

The link between insulin resistance and PCOS seems to be genetic in origin,[3] even if also other factors are believed to play a role, since the intrauterine life, in the complex mechanisms underlying this association. It was hypothesized that a specific environment surrounding the fetus during its developmental phase may lead to reduced intrauterine growth and to a predisposition to insulin resistance later in life.[4] During puberty and adulthood, circumstances such as unbalanced diet, sedentary lifestyle and, ultimately, excessive body weight gain may trigger the clinical appearance of the metabolic disturbance in these women.[5]

Insulin is able to exert systemic effects that go well beyond the glucose metabolism. Excessive circulating levels of this hormone are considered key to the pathophysiology and clinical expression of PCOS. Actually, despite a systemic state of insulin resistance, the central paradox of the syndrome is that other districts, such as the ovary, the adrenal, and the pituitary, remain sensitive to insulin action, thus putting in place the framework of the 'selective insulin resistance' theory. In PCOS, the reduced glucose disposal into peripheral tissues is due, rather than to an altered affinity of the binding domain of the insulin receptor, to defects in the signal transduction inside the cell cytoplasm, which are typically tissue specific. The association of the hyper-phosphorylation of the Ser_{312} residue with the decrease in the insulin-mediated phosphatidylinositol-3-kinase activity on the insulin receptor substrate-1 (IRS-1) is the most important determinant of insulin resistance in the skeletal muscle.[6] Instead, defects of the PPAR-γ nuclear receptor and the glucose transporter GLUT4 account for insulin resistance in the adipose tissue.[7]

The distinctive anthropometrical features of PCOS women often exacerbate this picture. Beyond the high prevalence of overweight and obesity in this population, the body composition of PCOS subjects is characterized by increased fat mass and preferential accumulation of adiposity in the intra-abdominal compartment, even in lean subjects. It is well known that visceral fat hyperrespond to catecholamines by mobilizing free fatty acids (FFA) and discharging cytokines,[8] which further impair peripheral insulin sensitivity. Such a derangement is supposed to be magnified by the increased activity in the sympathetic nervous system which was reported in PCOS women by several investigators.[9,10] Finally, irrespective of body mass index (BMI), abnormal hepatic insulin clearance and increased pancreatic β-cell responsiveness may contribute to the exaggerated insulin circulating levels.[11]

After reaching the target organs, hyperinsulinemia directly stimulates androgen secretion in the ovaries and the adrenals while suppressing the synthesis of sex hormone–binding globulin (SHBG) in the liver. Insulin seems also to interact with luteinizing hormone (LH) by enhancing its production at the central level and by exerting a synergic co-gonadotrophic effect on the thecal cells of the developing follicle,[12] which were reported to be intrinsically hyperresponsive to such a cross-talk. The final consequence is the increase of the free, biologically active, androgen levels.

Previously conceived as a one-way relationship, hyperinsulinemia and hyperandrogenemia may potentiate each other, thus perpetuating a vicious circle in some women with PCOS. Testosterone and dehydroepiandrosterone sulfate (DHEAS) promote lipolysis and the release into the circulation of FFA, known as one of the most potent triggers to insulin resistance. Further mechanisms, which need to be better clarified, include the androgen-driven pro-inflammatory cytokine secretion [i.e. tumor necrosis factor α, interleukin 6 (IL-6), resistin] and the interference with insulin signaling.

Since the 1990s, the derangement of gonadotrophin secretion together with the endocrine and paracrine effects of hyperandrogenemia and hyperinsulinemia has been considered responsible for the ovulatory disorder typical of PCOS.[13] More recently, the role of insulin was advocated in the pathway mediated through the anti-Müllerian hormone (AMH), which is able to inhibit early follicular recruitment, decrease aromatase activity, and raise the follicle-stimulating hormone (FSH) threshold for dominant follicle selection.[14,15]

The contribution to the appearance and the maintenance of chronic anovulation and clinical hyperandrogenism is not the only detrimental effect of hyperinsulinemia and insulin resistance in PCOS women: the alterations of glucose–insulin metabolism are responsible for an increased rate of complications during pregnancy (e.g. miscarriage, hypertensive disorders, gestational diabetes) and for a raised risk of cardiovascular disease, diabetes, and endometrial cancer later in life.[16]

This vast stock of knowledge has led to two main consequences in the scientific community: an increased attention toward the importance of diagnosing the metabolic alterations in PCOS and an increased interest in targeting insulin resistance as a treatment strategy for these women.

The novel international evidence-based guideline for the assessment and management of PCOS recommends to assess the glycemic status at baseline in all women with PCOS, and, thereafter, every

1–3 years by an oral glucose tolerance test (OGTT), fasting plasma glucose, or HbA1c.[17] However, measurement of insulin resistance was not incorporated into PCOS diagnostic criteria as well as into the general evaluation, because of the lack of accuracy of the currently available methods and inconsistencies in the proposed thresholds.

What solutions we found

In adjunction to lifestyle intervention, a plethora of possible medical treatments have been proposed in the past decades to correct the PCOS-related metabolic dysfunction. In the following paragraphs, novel and controversial aspects of this therapeutic approach will be summarized. Given the large number of treatments proposed, the list clearly cannot be exhaustive. Because of the lack of significant up-to-date scientific results and major uncertainties regarding outcomes, some options such as *N*-acetylcysteine, somatostatin, vitamins, and various nutraceuticals were not selected for this overview.

Metformin

Over the past 40 years, metformin has revolutionized the treatment of several metabolic conditions, ranging from diabetes mellitus type 2 (DM2) to metabolic syndrome. Out of the different classes of insulin-lowering drugs, metformin has been the most extensively investigated in both short- and long-term treatment schedules. Nevertheless, high-quality evidence in PCOS women is scarce,[18] and still there are several aspects of this old drug that remains novel and unexplored at this time.

Metformin belongs to the class of biguanides. It was reported to improve the glucose–insulin metabolism by decreasing intestinal absorption of glucose, gluconeogenesis, glycogenolysis, and lipogenesis and by enhancing glucose uptake in the liver, skeletal muscle, adipose tissue, and ovaries.

Where lifestyle interventions are not sufficient, the 2018 international evidence-based guideline for the assessment and management of PCOS recommends the administration of metformin for women with PCOS for the prevention of weight gain, hormonal (testosterone), and metabolic outcomes (cholesterol and triglycerides), and for prevention of weight gain and metabolic outcomes [cholesterol, and low-density lipoprotein (LDL)], in particular, in women with PCOS with BMI $\geqslant$25.[17]

What metformin should actually add to diet and exercise is still a matter of debate. Seven randomized controlled trials (RCTs) that addressed the comparison between lifestyle *versus* metformin + lifestyle were identified in the most up-to-date meta-analysis published on this topic.[19] In overweight-obese PCOS adolescents and adults, no statistically significant differences were reported for BMI and weight management in this body of evidence which was at low to moderate risk of bias.

Nonetheless, in the same meta-analysis, metformin alone resulted superior to placebo concerning the most important clinical outcomes. In total, 20 RCTs comparing these two interventions were analyzed: independently of the anthropometrical features, metformin resulted better than placebo for BMI, testosterone, total cholesterol, and triglycerides. When only participants with a BMI $\geqslant$25 kg/m^2 were combined in subgroup analyses, it was found that metformin offered additive benefits for weight, BMI, total cholesterol, and LDL. On the contrary, interestingly, there were differences in terms of WHR (waist to hip ratio) reduction in favor of metformin in the BMI $<$25 kg/m^2 subgroup. The majority of studies included for this comparison were at moderate risk of bias; thus, caution should be exercised when considering the effect estimates across all outcomes. Based on the inconsistent data regarding the improvement of acne, alopecia, and hirsutism, metformin is not considered a first-line treatment in PCOS women with these complaints.[20]

As far as the reproductive outcomes regard, metformin can be administered alone, or in combination with estro-progestin drugs, ovulation induction agents or during *in vitro* fertilization (IVF) programs depending on the clinical need. In a Cochrane review that included a meta-analysis of 42 randomized clinical trials, metformin therapy resulted able to improve menstrual pattern, ovulation rate, and clinical pregnancy rate in PCOS women.[18] Metformin should be added, rather than persisting with clomiphene citrate alone or gonadotrophins alone, in PCOS women with anovulatory who result nonresponder to the ovulation induction agent, to improve ovulation, pregnancy, and live birth rates.[17] In women with

PCOS undergoing an IVF/ICSI (intracytoplasmic sperm injection) therapy for infertility, adjunct metformin therapy is beneficial before and during ovarian stimulation to improve the clinical pregnancy rate and reduce the risk of ovarian hyperstimulation syndrome (OHSS).[21] Metformin should also be administered in combination with oral contraceptives (OCPs) in women with PCOS for management of metabolic features. This association is considered most beneficial in women belonging to high metabolic risk groups, including those with diabetes risk factors, specific ethnic groups, and in adolescents with BMI $\geqslant$25.[17] In these categories of patients, the administration of metformin during pregnancy could be considered a safe option to lower the risk of early pregnancy loss, while its putative role in the prevention of hypertensive disorders and gestational diabetes occurrence was not confirmed.[22,23] This drug was also reported to improve endothelial function and measures of systemic inflammation, thus theoretically reducing the long-term risk for cardiovascular disease.[24]

Four hot topics regarding metformin therapy in PCOS women deserve attention and, hopefully, more good-quality research in the future:

1. Side effects and safety: Common metformin-related disturbances are gastrointestinal (GI) symptoms including abdominal pain, nausea, vomiting, diarrhea, taste disturbances, and appetite loss (reported in 10–60% of patients).[25] The side effects are generally self-limiting and of mild to moderate intensity. However, these symptoms may cause discontinuation of treatment in some subjects and reduce compliance in those who continue. In order to minimize the side effects, taking the drug with food and a low starting dose, with 500 mg increments 1–2 weekly, should be recommended.[26] Metformin is off label in many countries for PCOS management; however, it is not explicitly restricted from use, provided that health professionals inform women and discuss the evidence with them. On the contrary, data on the safety profile of metformin are mostly based on other populations, especially DM2 patients. Specific studies on the benefit/risk ratio in PCOS are strongly needed.
2. Dose: Few studies in literature have addressed this issue. Overall, there is inadequate evidence to suggest whether one dosing regimen of metformin is superior to another. The effects of metformin treatment on weight, metabolic, and reproductive outcomes in PCOS seem independent of the administered dose (in the range 1000–2250 mg/day orally), probably because of high individual variability in the pharmacodynamics and pharmacokinetics of this drug.[27] In a previous study, the lack of a dose–effect relationship was confirmed irrespective of the baseline BMI and degree of hyperinsulinemia.[28] Hence, low doses should be preferred in the clinical practice to reduce the side effects.
3. Duration of treatment: Metformin use appears safe in the long term, even if some concerns on vitamin B12 deficiency have emerged.[29] More research is needed on this last aspect and on the optimal duration of metformin treatment, as most of the studies do not exceed 24 months of observation.
4. Metformin formulation: Metformin is now available on the market in two formulations: the traditional immediate release (IR) formulation (to be administered up to three times daily), and the novel extended release (XR) formulation (a once daily dosing option).[30,31] In diabetic patients, metformin XR was proven to be equally, or even more, effective in improving glycemic control,[32–34] probably thanks to greater patient adherence to treatment[35,36] and better GI tolerability compared with metformin IR.[37,38] A clinical pilot trial on metformin XR was carried out in 2017 in a small group of PCOS women: the endpoint of the study was the comparison with other drugs' associations rather than the evaluation of the efficacy and safety of the formulation XR itself that still need to be accomplished.[39]

Thiazolidinediones

Thiazolidinediones (TZD) act through a selective binding to the nuclear transcription factor PPARγ, which is mainly expressed in adipocytes, pancreatic β cells, vascular endothelium, macrophages and, in lower percentage, in heart and skeletal muscle tissue.[40] Mechanisms of action include the stimulation of fatty acid uptake and storage in subcutaneous adipose tissue and the enhancement of adiponectin secretion from adipose, which increases insulin sensitivity, particularly in the liver. TZD also inhibit hepatic gluconeogenesis,

ameliorate dyslipidemia, and promote anti-inflammatory and anti-arteriosclerotic effects.

Among the molecules belonging to this pharmacological class, pioglitazone and rosiglitazone were most extensively tested in PCOS women.

Pioglitazone is deemed to positively modulate ovarian androgen synthesis: in cultured granulosa cells, it influences the metabolism of ovarian steroid hormone via the upregulation of progesterone biosynthesis, the inhibition of testosterone, and the production of E2 through insulin-dependent and insulin-independent pathways. A recent Cochrane review[18] concluded that pioglitazone may improve the menstrual pattern in PCOS, while no difference was found between pioglitazone and placebo as far as anthropometric outcomes (BMI, WHR), endocrine outcomes (testosterone, SHBG), or metabolic outcomes (fasting insulin) regard.

Data from a network meta-analysis comparing insulin-sensitizing drugs indicated that rosiglitazone had the most favorable effect on PCOS patients in terms of DHEAS, total testosterone, FSH, and LH, while metformin performed better in terms of estradiol, free testosterone, and androstenedione.[41] Another meta-analysis of 11 RCTs showed no significant differences among both treatments in terms of fasting glucose, insulin, or homeostasis model assessment of insulin resistance.[42]

However, it cannot be disregarded that glitazones may be associated with relevant adverse effects: weight gain, fatigue, edema, diarrhea, anemia, congestive heart failure, and, in particular, for pioglitazone, increased risk of osteoporosis and bladder cancer. TZD are also placed in the pregnancy category C medications.

Inositols

Inositols, in particular, the active molecules myoinositol (MI) and D-chiro-inositol (DCI), support the intracellular formation of insulin second messengers: phospho-myo-inositol-3-phosphate (PIP3) and inositolphosphoglycan (IPG). MI is involved primarily in cellular glucose uptake: its concentrations are high in brain and heart as tissues with high glucose utilization and consumption.[43,44] MI also reduce the release of FFA from adipose tissues through inhibition of adenylyl cyclase.[43] Conversely, DCI levels are high in tissues that store glycogen, such as liver, muscle, and fat.[44]

The possible use of DCI as an insulin-sensitizing agent is supported by the evidence that IR is associated with reduced availability of DCI[45] and with increased urinary clearance of DCI in both PCOS and non-PCOS women with IR.[46–48] Accordingly, several studies have reported reduced DCI-IPG release in the blood of diabetic subjects during a glucose tolerance test[49] and blunted DCI-IPG release in women with PCOS during euglycemic hyperinsulinemic clamp.[46]

MI is not only a second messenger of insulin action. In the ovary, MI at least partially mediates the follicular response to gonadotropins. Inositol trisphosphate (IP3) promotes meiotic progression during the final stages, thus playing a pivotal role in oocyte maturation. Furthermore, MI derivatives participate in cytoskeletal regulation and modulate AMH serum levels.[50]

The tissue-specific MI/DCI ratio depends on the activity of epimerase, the enzyme deputed to transform MI in DCI. Epimerase activity is stimulated by insulin and is reduced in the presence of insulin resistance. In the ovaries, which are insulin-sensitive, the physiologic MI/DCI ratio should be 100:1. In hyperinsulinemic women with PCOS, the enzymatic epimerase activity is enhanced in the gonad, thus leading to lower MI/DCI ratio at this level.[51]

The imbalance in the inositol pathway inside the ovary is believed to play a role in the ovulatory dysfunction of PCOS.

Therefore, during the past decades, oral nutritional supplementation with MI has been proposed as a novel therapy in these women. The treatment was reported to enhance insulin sensitivity and improve the clinical and hormonal characteristics of patients with PCOS.[52–54]

The Cochrane review[18] found evidences that DCI may improve ovulation rate in the syndrome. There was no conclusive evidence that DCI had an effect on BMI, WHR, or blood pressure, on hormonal parameters except for serum SHBG levels, on fasting glucose, fasting insulin, and lipids (total cholesterol, triglycerides).

Given the lack of strong evidence, the new international guideline gives cautious recommendations on the use of inositols: inositol (in any form) should currently be considered an experimental therapy in PCOS, with emerging evidence on efficacy highlighting the need for further research.

Alpha-lipoic acid

Alpha-lipoic acid (ALA), a biological antioxidant and natural cofactor of mitochondrial dehydrogenase complexes, was originally investigated in patients with type 2 diabetes on the basis of the close relationship between oxidative stress and insulin resistance.[55] There is a growing body of evidence that ALA may act indirectly to maintain cellular antioxidant status by either inducing the uptake or enhancing the synthesis of endogenous low-molecular-weight antioxidant or antioxidant enzymes.[56] Several studies have suggested that the oral supplementation with ALA may improve insulin sensitivity in the peripheral tissue and may help in maintaining glycemic control in patients with diabetes mellitus.[57] The hypothesized mechanism of action relies on the property of stimulating glucose uptake through an intracellular redistribution of GLUT1 and GLUT4 transporters.[58,59]

Oxidative stress is increased in PCOS women because of an increased production of free radicals associated with impaired plasma total antioxidant capacity (TAC) in both obese and normal-weight PCOS women.[60] The increased oxidant status could participate in the onset and maintenance of insulin resistance in these patients.

Few studies analyzed the effect of the administration of ALA as unique treatment in PCOS subjects. The oral supplementation was evaluated in both lean and obese subjects by different investigators.[61,62] ALA, at a daily dose of 400 mg, resulted was able to improve triglyceride levels, insulin sensitivity, menstrual frequency, and parameters of liver function.

Other studies reported on the effects of a variety of preparations containing ALA, in particular, in association with MI.[63–65] Results are inconsistent, even if a general positive profile of action was reported by all the studies in terms of BMI, glucose metabolism, lipid metabolism, clinical signs of hyperandrogenism, and menstrual irregularities in heterogeneous groups of PCOS women. One study compared the association of ALA + MI *versus* MI alone in a small group of PCOS women undergoing IVF/ICSI: the adjunction of ALA did not seem to yield benefits over MI alone as far as the reproductive outcomes regard.[66] Another study compared metformin 3 g/day *versus* ALA + MI + metformin 1.7 g/day, providing evidence for a better response in terms of hyperandrogenism, BMI, and homeostatic model assessment (HOMA) index in the multiple treatment combination compared with isolated high-dose metformin.[67]

Glucagon-like peptide 1 receptor agonists

Glucagon-like peptide 1 (GLP-1) receptor agonists belong to the class of incretin mimetics. Incretins, such as the glucose-dependent insulinotropic peptide (GIP) and GLP-1, are gut hormones secreted from enteroendocrine cells in response to the ingestion of food.[68] The mechanisms of action of GLP-1 include the stimulation of insulin secretion, the inhibition of glucagon secretion, and the suppression of food intake and appetite which, in concert, are able to improve glucose homoeostasis.[69] Two injective forms of GLP-1R agonists are now available in the market (exenatide and liraglutide), while oral forms are currently under development. These antidiabetic drugs are mainly employed in the management of obesity and abnormalities of glucose homeostasis. However, the promising results observed in patients with type 2 diabetes have fostered in the past decade the research on the effects of these compounds in PCOS women. The first study investigating the role of exenatide in this population was published in 2008.[70] Several other investigations on liraglutide followed the first report and were recently reviewed by two different groups.[71,72] The outcomes of interest of these studies were weight loss, improvement of menstrual frequency, and reduction of hyperandrogenism.[71,72]

GLP-1 R agonists are able to significantly reduce BMI to an extent which seems similar to that achieved in the diabetic population. This effect seems to be mediated, or at least potentiated, by the improvement in eating behavior as assessed by eating pattern questionnaires.[73] By converse, data are inconsistent in terms of modulation of the body fat distribution (WHR) and amelioration of menstrual cycle frequency. Some studies reported improvement of indexes of insulin resistance (HOMA) and testosterone levels following treatment.[74] However, it cannot be ruled out that these

Table 1. Treatment outcomes of insulin sensitizers in polycystic ovary syndrome.

	Menstrual pattern	Ovulation	Hyperandrogenism	Weight loss	Insulin resistance
Metformin	X	X	X	X	X
Thiazolidinediones	X		X		X
Inositols		X			X
Alpha-lipoic acid	X				X
GLP1-R analogues			X	X	

outcomes are at least partially related to the weight loss: no multivariate analyses were provided in order to detect a possible direct effect of the drugs on either peripheral insulin sensitivity or androgen production. Of notice, the majority of the aforementioned studies are weakened by the small sample size and are poorly generalizable since only overweight and obese PCOS women were enrolled. Some authors compared the GLP-1 R agonists with metformin and the combination of the two drugs, thus suggesting a possible synergistic action on clinical and metabolic parameters.[75] The most common side effect either probably or possibly related to liraglutide is nausea, with no significant differences compared with metformin. Compliance with treatment was also hindered by the parenteral route of administration, which represents a major obstacle to treatment adherence in women with PCOS, in particular, in the lower age range.

Comparative studies

Few meta-analyses addressed the question of the superiority of one insulin sensitizer over another. In terms of endocrine outcomes, no significant difference was detected when metformin was compared with TZD[76,77] or inositol.[78] In terms of metabolic outcomes, metformin seems to display a more beneficial profile of action for triglycerides compared with TZD,[77] while the opposite was found after comparing the effects of these two drugs on fasting insulin and HOMA index.[76] No significant different metabolic effects were found when comparing metformin with inositol (Table 1).[78]

Conclusion

The management and treatment of metabolic dysfunction in patients with PCOS is a crucial challenge in our clinical practice and it is still a matter of debate. In fact, many treatments are proposed as insulin-sensitizing, but we are a long way from a univocal indication and modality of prescription of these drugs. Research made great progress in this field and now we have some evidence to lead our practice.

Metformin is nowadays the only insulin-sensitizing agent whose prescription is mentioned in the 2018 international evidence-based guideline for the assessment and management of PCOS and for the treatment of weight, hormonal, and metabolic outcomes, even if the schedule of treatment is not standardized.

The other proposed therapies so far debated (TZD, inositols, ALA, and GLP1-R analogues) have been widely experimented, but overall, studies show great variability with regard to combination of therapies, dose, and target population. Even if findings of reported studies show generally promising clinical results, all these treatments should currently be considered experimental in PCOS.

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