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How do new therapeutic strategies for PCOS management influence the health of the affected individuals? The narrative review

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Abstract
Introduction and purpose: Management of polycystic ovary syndrome (PCOS) is difficult since the exact pathogenic mechanism has not been established yet. Due to that fact, the substances registered to treat PCOS are still lacking efficacy and are associated with a number of adverse effects. The aim of this study is to review new possible treatment approaches.
State of knowledge: Inositol administered alone or combined with oral contraceptive drugs improves patients' hormonal status and alleviates the weight increase in comparison to oral contraceptive drugs on their own. Berberine reduces insulin resistance, improves lipid metabolism, and reduces inflammatory reactions. Glucagon-like peptide-1 receptor agonists have a better weight loss effect and less severe adverse reactions than metformin. Thiazolidinediones combined with metformin improve ovulation rate, acne and increase SHGB levels. Thiazolidinediones have also less severe adverse reactions than metformin and can be useful in patients who are not able to tolerate metformin.
Summary: The review has shown that inositol, berberine, glucagon-like peptide-1 receptor agonists and thiazolidinediones have promising therapeutic effects in terms of PCOS treatment, however, more research is needed to establish safety and efficacy of those agents. Nonetheless, results of this study may be utilized in the education of health specialists in endocrinology departments.

Keywords: "polycystic ovary syndrome"; "gonadal disorders"; inositol; berberine; "glucagon-like peptide-1"; thiazolidinediones

Introduction and purpose
Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine and metabolic disorder. Affecting 5% to 10% of premenopausal women, it is considered to be one of the most common endocrinopathies among women of reproductive age [1]. PCOS is characterized by signs and symptoms of androgen excess and ovarian disfunction in the absence of other ovarian, adrenal and pituitary gland diseases [2]. Typical clinical features include hirsutism, acne, androgen-dependent alopecia, anovulation, and irregular menses [3]. It is often associated with insulin resistance, abdominal adiposity and obesity [4] and is thought to be responsible for 40% of female infertility cases [5]. Moreover,

Increased adiposity, chronic subclinical inflammation, and dyslipidaemia put women with PCOS at a very high cardiovascular risk [6]. PCOS also increases the incidence of endometrial cancer and ovarian cancer, as well as the risk of type 2 diabetes in 5–10% of patients [7].

The Rotterdam criteria are used for the diagnosis of PCOS in adult women. Patients must fulfil two of the three characteristics to be diagnosed with PCOS: clinical and/or biochemical hyperandrogenism, oligo- or anovulation, or polycystic ovary morphology on ultrasound with exclusion of other disorders. However, when it comes to adolescent girls, the diagnosis is based on the diagnostic features such as menstrual irregularity, clinical hyperandrogenism, and/or hyperandrogenaemia. Pelvic ultrasound scans are not necessary for the diagnosis of PCOS in adolescent girls [1].

Although numerous studies have been carried out, the exact pathogenic mechanism of PCOS remains unknown. However, the pathophysiology appears to be polygenic and multifactorial and includes non-inheritable intra- and extrauterine environmental factors. The female hypothalamic–pituitary–ovarian (HPO) axis is a precisely synchronized and tightly regulated network responsible for reproductive competence. It recognizes hormonal (i.e. hyperandrogenaemia) and neuronal internal signals as well as external environmental factors [1]. The disturbances in HPO axis stimulate the increase in pulsative secretion of gonadotrophin releasing hormone (GnRH), which results in the hypersecretion of luteinising hormone (LH), consequently triggering both ovarian androgen production and oocyte development. Disturbed ovarian-pituitary and hypothalamic feedback emphasizes the gonadotrophin abnormalities. As FSH concentrations and the conversion of androgens to estradiol are insufficient, the selection of dominant follicle is not possible, causing chronic anovulation. What is more, the anti-Müllerian hormone (AMH), which is secreted by granulosa cells in ovaries and is responsible for inhibiting the transition from primordial to primary follicles, is significantly higher in women with PCOS. The balance between the level of androgens, AMH and FSH is disrupted, leading to follicular arrest and typical polycystic morphology of the ovary. Moreover, abundant androgen levels are associated with decreased adiponectin secretion by adipocytes in women with PCOS, which decreases insulin sensitivity and may trigger insulin resistance (IR) and consequently increases compensatory insulin levels. Other potential mechanisms of IR and hyperinsulinemia are increased puberal androgen levels, defective post-receptor insulin activity, increased free fatty acids and cytokine secretion. In addition, genetic factors may also cause higher IR. Furthermore, IR in PCOS women is tissue-selective, as the resistance to metabolic actions of insulin have been recorded in skeletal muscle, adipose tissue and liver, while the adrenal gland and ovarian tissues remain sensitive to insulin actions. Finally, insulin can also reduce the hepatic synthesis of sex hormone-binding globulin (SHGB), increasing back the circulation of free androgens [8–11].

The International PCOS Network guidelines list several substances as treatment options. Combined oral contraceptive pills (COCP) should be recommended for management of hyperandrogenism and/or irregular menses. Metformin combined with lifestyle changes could be recommended in women with PCOS with BMI $\geq 25 kg/m^2$ for management of weight, hormonal and metabolic outcomes. A combination of the COCP and metformin should be considered when the COCP and lifestyle changes do not achieve desired goals. Where COCPs are contradicted or poorly tolerated, anti-androgen agents should be considered to treat hirsutism and androgen-related alopecia [12].

The search for new treatment options for PCOS is still in progress. New substances and various combinations of those substances are being taken into consideration. This article will focus on new therapeutical approaches such as inositol, berberine, glucagon-like peptide-1 receptor agonists and thiazolidinediones.

State of knowledge

Inositol

There are 9 stereoisomers of inositol, with the myo-inositol (MI) and the D-chiro-inositol (DCI) being the most common. Their function in organisms differs, but generally, they are both responsible for lowering sugar levels, although with the utilisation of different pathways [13]. In several studies MI has proven to have an impact on several disorders such as depression, Alzheimer and others [14,15]. In turn, the DCI has been proven to be a useful agent in mood disorders, endometriosis, and management of other disfunctions [16].

The studies conducted by Pkhaladze et al. showed, that MI therapy, whether it is combined with oral contraceptive drugs or administrated alone, results in an improvement of patients' hormonal status. Moreover, both approaches in comparison with standard contraceptive therapy alleviated the weight increase [17]. The benefits of MI therapy (4000mg/day) also have been proven to provide a rather safe PCOS treatment option. Furthermore, this same study showed, that MI treatment enhanced the in-vitro fertilization process in such patients [18].

Myo-inositol can also mitigate other symptoms that appear in PCOS, such as hirsutism and acne. Jamilian et al. showed that MI in comparison to metformin lowers the level of total testosterone and modifies Ferriman-Gallwey scores in such patients [19]. The same authors conducted a study, in which it was proved that MI supplementation in PCOS patients has a positive outcome and can increase mental health status [20]. Another challenge in PCOS treatment that can be possibly managed by inositols is increased cardiovascular risk. The combined therapy with DCI and MI may result in lowering the LDL and triglyceride levels and increasing the HDL levels in obese patients with PCOS [21].

In recent findings, clinicians reported that patients diagnosed with PCOS should be treated with both MI and DCI in the 40:1 ratio respectively. Hormones such as free testosterone, FSH, LH, insulin and others can be restored to proper levels with these substances [22].

The most common adverse effects of inositol regard gastrointestinal conditions such as nausea or diarrhoea, which are not very frequent, which makes inositol is a fairly safe substance [23].

Berberine

Another example of natural substance that may be used in the treatment of PCOS is berberine. This alkaloid can be found in several herbs and medical plants, for example, Coptidis Chinensis [24]. In past years, berberine has been used in type 2 diabetes mellitus (T2DM) treatment. Berberine showed potential for lowering glucose, HbA1c, total cholesterol and LDL levels in the blood [25]. Moreover, patients with non-alcoholic fatty liver disease may be able to benefit from berberine as a therapeutic option as well. Yan et al. showed, that changing a patient's lifestyle, combined with berberine treatment may help patients with the reduction of hepatic fat content. This therapeutic strategy, in comparison to pioglitazone (15mg), has better outcomes in the reduction of body weight in these patients [26]. The mechanism of action of berberine and its metabolites covers many biochemical pathways, some of which overlap with those associated with PCOS pathogenesis [24]. In the terms of berberine being used as therapeutic agent in PCOS management, patients benefit from improved lipid metabolism, reduction of inflammatory reactions and insulin resistance [27]. Other metabolic advantage is reduction of waist-hip ratio (WHR) in the patients diagnosed with PCOS. It was shown that this therapeutic strategy provided better results in WHR than metformin treatment, with other metabolic benefits being similar for both drugs [28].

Kuang et al. concluded that berberine can be used as the therapeutic agent in the process of lowering inflammation process, which may lead to developing insulin resistance [29,30]. It was found that berberine can regulate the mTOR and IRS-1 kinase which are potential therapeutic targets in the PCOS management [30].

It is clear, that berberine can improve patients' outcomes in several diseases [31]. For the PCOS it seems to be a safe agent, with very mild and rare adverse effects reported [27,28,32].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) is a peptide hormone, which is secreted by intestinal L cells and promotes the secretion of insulin. This hormone has many physiological effects, including inhibiting appetite and food intake and delaying gastric emptying [33]. Recent studies have shown that GLP-1 receptor agonists (GLP-1 RAs) improve insulin resistance and reduce weight in women with PCOS [34]. Glucagon-like peptide-1 receptor agonists which act as incretin mimetics are utilized as new anti-diabetes drugs [35].

Exenatide and liraglutide are examples of GLP-1 receptor agonists, that have recently been tested for treatment of PCOS, results of which were significant weight loss and improvement of glucose metabolism in patients with PCOS in comparison to placebo. The systematic review and meta analysis by Ma at al., summarized the results of 7 randomized controlled trials (RCT) to compare between glucagon-like peptide-1 receptor agonists and metformin in

terms of their efficacy and safety in the treatment of patients with PCOS. The results of the meta analysis showed that GLP-1 receptor agonists cause a better weight loss effect than metformin [34].

Liraglutide therapy has proven to be more efficient than treatment with metformin due to less gastrointestinal side effects and better weight loss [36]. A moderate weight loss was observed when liraglutide was administered alone or in combination with metformin, however, with higher dose of liraglutide alone there was an increased weight reduction reported [37]. Some studies have shown that liraglutide reduces the rate of major cardiovascular events in patients with type 2 diabetes mellitus as well [38].

In a RCT carried out by Elkind-Hirsch et al., overweight women with PCOS were randomly divided into groups in which they were treated with either metformin (1g 2/day), exenatide (10ug 2/day), or metformin + exenatide (1g+10ug 2/day) for a period of 2 months. The study showed that the combined therapy has better results in improving menstrual cycle and ovulation rate than treatments alone [39]. In another study, four months of treatment with exenatide on obese/overweight women with PCOS were associated with a weight loss of at least 3% and reduction in serum markers of endothelial, inflammation and clot function. It showed that this therapy may prevent from cardiovascular risk incidents in these patients, which is an additional benefit of this therapy [40].

Thiazolidinediones

There are two thiazolidinediones (TZDs), rosiglitazone, and pioglitazone currently registered to treat type 2 diabetes mellitus. Acting as insulin sensitizers, those drugs can help with glycemic control and insulin resistance [41]. TZDs could prove useful to treat PCOS, since they can decrease androgen synthesis in ovaries by ameliorating peripheral insulin resistance indirectly, thus improving endothelial function, ovulation, and reducing IR [7].

When compared with metformin, pioglitazone appears to be equally effective in the treatment of PCOS [6], however studies have shown that pioglitazone could improve the menstrual cycle and ovulation better than metformin [7]. What is more, studies in diabetics revealed that although pioglitazone may increase peripheral fat, it reduces visceral fat stores. Reducing ectopic fat in the liver and muscles, may enhance tissue sensitivity to insulin [7], which is associated with improved inflammatory and cardiovascular risk markers [42]. Moreover, combined therapy including TZDs and metformin was associated with an increase of SHBG and improvement of the menstrual cycle and appeared to be the best intervention for promoting menstrual recovery in comparison to metformin alone [43]. What is more, not only TZDs combined with metformin can improve ovulation rate and acne [43], but it also may alleviate psychological distress, which is prevalent among women with PCOS [44]. Another study showed that pioglitazone combined with Diane-35 (an oral contraceptive with anti-androgen properties) [45] can significantly improve the symptoms of sex hormone secretion in PCOS patients [46].

Several studies have shown that insulin sensitizers might act as anticancer agents in ovarian and endometrial cancers, which are of elevated prevalence in PCOS patients [47]. Pioglitazone alone may be a useful, alternate treatment for PCOS patients who are not able to tolerate or do not respond to metformin [48].

Furthermore, as IR and hyperinsulinemia are key metabolic features in women with PCOS, their improvement through TZDs could increase conception rates. However, both rosiglitazone and pioglitazone are classified as pregnancy category C drugs according to the Food and Drug Administration (FDA), since they carry the potential risk of causing fetal growth restriction in animal models [49].

Summary

Although abundant amount of research has been carried out, PCOS still remains a great challenge for clinicians and researchers. As the exact pathogenic mechanism has not been established yet, it is not an easy task to find an optimal treatment approach. Studies performed on inositol, berberine, GLP-1 receptor agonists and thiazolidinediones show promising results in terms of treatment of PCOS, especially considering how currently registered substances are not without flaws significant for patients' wellbeing. More research however is needed, to determine whether those new agents can indeed be a part of efficient and safe therapeutic strategy.

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