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Berberine in the treatment of polycystic ovary syndrome

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Abstract

Introduction: Polycystic ovary syndrome (PCOS) is a hormonal disorder most common in women in reproductive age. The global incidence varies from 6% to 20% depending on the

diagnostic criteria used, and is also the most common cause of infertility. This disease is related to insulin resistance and hyperinsulinemia. Berberine is a compound that affects the cardiovascular system and carbohydrate metabolism, which is why there are attempts to introduce it into the therapy of patients with PCOS.

Material and methods: The literature was reviewed in the PubMed scientific base in the years 2012-2022 using the following keywords: berberine, polycystic ovary syndrome.

Results: Research show that the use of berberine may have a positive effect on the waist circumference and waist-to-hip ratio, improve lipid parameters, lower the concentration of androgens, and reduce insulin resistance. In addition, a promising effect is the stabilization of the menstrual cycle and improvement of ovulation. There are reports that this drug may also restore the normal composition of the intestinal microflora disrupted in PCOS. Side effects are rare and mild, which confirms the safety of this substance.

Conclusions: Polycystic ovary syndrome affects many women, leading to numerous and serious side effects, so it is important to develop an effective treatment with as few side effects as possible. Berberine is a promising prospect, but more studies are needed on larger groups of patients to confirm these reports and develop an effective treatment regimen.

Keywords: berberine, polycystic ovary syndrome.

Introduction

Polycystic ovary syndrome (PCOS) is a hormonal disorder most common in women in reproductive age. The global incidence ranges from 6% to 20% depending on the diagnostic criteria used, but it is more common in overweight or obese patients [1]. Moreover, it is the most common cause of infertility. This syndrome is associated with insulin resistance and hyperinsulinemia [2], and additional changes taking place in the hormonal balance are the increased level of androgens and a higher LH to FSH ratio. In combination with other civilization diseases, PCOS can cause significant cardiovascular and metabolic morbidity [3]. Berberine is an organic chemical compound, isoquinoline alkaloid of plant origin, showing a strong biological effect. It has a beneficial effect on the cardiovascular system by lowering cholesterol and blood pressure, and is also a compound that can effectively reduce insulin resistance [4]. Due to these actions, there are attempts to introduce it into the therapy of patients with polycystic ovary syndrome.

Material and methods

The literature was reviewed in the PubMed scientific database in 2012-2022 using the following keywords: berberine, polycystic ovary syndrome.

Results

Metformin is used in treatment to restore the normal metabolic balance and reduce insulin resistance. There are reports that berberine may show better effects compared to this drug. The study by Wei et al. on 89 patients with PCOS and insulin resistance compared the effects of berberine with cyproterone acetate (31 patients), metformin with cyproterone acetate (30 patients), and placebo with cyproterone acetate (28 patients). Berberine treatment in comparison with metformin showed a reduction in waist circumference and waist-to-hip

ratio, a reduction in total cholesterol, triglycerides and LDL cholesterol. There was an increase in HDL-C cholesterol and sex hormone binding globulin (SHBG). Moreover, a reduction in fasting glucose and insulin levels was observed in patients treated with berberine [5]. Another study in which berberine and metformin were administered to 150 infertile patients showed that, compared to placebo, both substances reduced testosterone levels, free androgen index, fasting glucose and insulin, HOMA-IR index, and increased sex hormone binding globulin (SHBG). It has been documented that 3 months of treatment with one or the other drug before IVF resulted in an increase in the pregnancy rate. What's more, berberine treatment was associated with a higher decrease in BMI, decreased lipid levels and total FSH requirement, and an increase in the live birth rate compared to metformin [6]. In another study 129 patients with PCOS participated. The influence of berberine, metformin and myoinositol on the course of this disease was analyzed. After 12 weeks of therapy, a statistically significant ($p = 0.0001$) decrease in mean body weight, waist circumference, waist-to-hip ratio, and BMI was found, regardless of the substance used. A significant reduction in waist circumference was noted after the use of berberine (80.86 ± 2.85) compared to metformin (85.95 ± 4.78) and myoinositol (88.24 ± 3.77). The waist-to-hip ratio decreased correspondingly to 0.82 ± 0.003 ; 0.87 ± 0.06 ; 0.89 ± 0.04 which also shows the superiority of berberine over other drugs. In all groups, there was a significant improvement in the parameters of carbohydrate metabolism (fasting glucose and insulin levels), a decrease in testosterone and free androgen index, as well as an increase in sex hormone binding globulin (SHBG). Moreover, berberine supplementation improved the lipid profile the most (lowering total cholesterol, LDL cholesterol, triglycerides and increasing HDL) [7]. In the study by Rondanelli et al., apart from the HOMA-IR index, the concentration of C-reactive protein (CRP), TNF- α and the level of acne were also assessed on the basis of the GAGS system and CADI index. After 60 days of berberine therapy, a decrease in the HOMA-IR index, reduced CRP and TNF- α levels and a decrease in the severity of acne were found [8].

In polycystic ovary syndrome, menstrual disorders such as scanty periods, amenorrhea, prolonged and irregular bleeding are common. Moreover, endocrine and metabolic disorders inhibit the development of the dominant follicle and ovulation does not occur [9]. For this reason, a study was conducted to see if berberine could positively affect ovulation. Ovarian morphology, hormone levels and glycolipid metabolism were assessed in a PCOS rat model. The following groups were distinguished: model group, with a low dose of berberine and a high dose of berberine, with metformin and a control group. In the model group, an increase in the number of cystic follicles and a decrease in the number of corpus luteum were found, while in the group with a high dose of berberine, the trend was reversed. The use of berberine decreased the concentration of LH, total cholesterol, and improved glucose tolerance without affecting the fasting insulin concentration. Moreover, higher expression of LHCGR and CYP19A1 proteins was investigated in ovarian granular cells, which may have a positive effect on ovulation [10]. Another study looked at the effects of berberine on the menstrual cycle, ovulation rate, and hormone profile in non-ovulating Chinese women with PCOS. 98 patients completed the 4-month therapy, 69 of whose were of normal weight and 29 were overweight or obese. 14 women regained their regular periods and the ovulation rate was 25% in the whole group (22.5% in the normal weight group and 31.0% in the overweight or obese group). Moreover, in the group of women with normal body weight, parameters of lipid metabolism and carbohydrates improved [11].

Kuang et al. investigated insulin signaling pathways of mTOR (the mammalian target of rapamycin) and IRS-1 (insulin-1 receptor substrate) in patients with polycystic ovary syndrome, and the changes after berberine were analyzed. In women with PCOS, mTOR activity in granular cells it was increased ($p = 0.008$), and the activity of IRS-1 was

significantly reduced ($p = 0.017$). Whereas, berberine significantly decreased mTOR RNA expression ($p = 0.001$) and increased IRS-1 RNA expression ($p = 0.009$), which may suggest that this substance improves insulin sensitivity [12].

It has been reported that chronic inflammation, oxidative stress and cell apoptosis may also be involved in the pathogenesis of PCOS. In patients with PCOS, significantly increased levels of pro-inflammatory cytokines such as IL-1, IL-6 and IL-17 have been shown compared to healthy women, which negatively affects the metabolism of glycolipids, promotes insulin resistance and disturbs normal ovulation [12]. An animal model study was performed and the apoptosis rate was found to be significantly lower in the berberine-treated group. In addition, the administration of this substance caused a significant decrease in the mRNA expression of pro-inflammatory factors (TNF- α , IL-1, IL-6, TLR4, LYN, PI3K, NF- κ B), which was more visible in the group of PCOS rats fed a high-fat diet, which may additionally, suggest a positive effect of berberine on metabolic disorders [13].

In a study by Li et al., berberine was used at various concentrations on the human tumor cell line KGN to assess cell viability, apoptosis, levels of intracellular reactive oxygen species, mitochondrial depolarization, and activation of related signaling pathways. Administration of this compound was found to depolarize mitochondria and accumulate AMP through ubiquitination of SIRT3 which in turn promoted glucose uptake and inhibited mitochondrial function. This process is probably related to the regulation of autophagy in ovarian cells, which could be the basis for the development of new drugs, but further research is needed to confirm [14].

The study by Zhang et al. investigated the insulin resistance index (HOMA-IR), the insulin sensitivity index (ISI), and the expression of the GLUT4 glucose transporter in the ovaries of female PCOS rats. It was found that berberine therapy helped to restore normal ovarian morphology, as well as HOMA-IR and ISI values to reference values. Moreover, it was noticed that the expression of the GLUT4 transporter was increased, which may be caused by the activation of the PI3K / AKT signaling pathway and suppression of the MAPK pathway [15]. Increased expression of this transporter stimulates glucose uptake.

The intestinal microflora creates a relationship with the host and maintains internal balance and the external environment of the body. It has been suggested that α diversity correlates with ecosystem health and can be used to assess species abundance and diversity. In patients with polycystic ovary syndrome, there is a decreased α variety and changes in certain types of bacteria such as Bacteroidetes and Firmicutes, which may be related to the increased concentration of androgens, characteristic of this syndrome [16]. Moreover, intestinal dysbiosis may aggravate endocrine and metabolic disorders [17]. Therefore, it is important to restore the normal bacterial flora, which may have a positive effect on the course of the disease. In the study by Shen et al., clear changes in the composition of the intestinal microflora were found after the use of berberine. In terms of class assignment, Bacteroidetes and Firmicutes dominated, while at the genus level berberine significantly influenced the relative abundance of Romboutsia, Bacteroides [18]. This drug can effectively restore the normal composition of the bacterial flora, but further extensive research is needed to confirm this.

Berberine is a safe compound for premenopausal women and for those who want to become pregnant. Some studies reported side effects such as bitter taste, nausea, vomiting, diarrhea, flatulence, constipation, but all these symptoms were mild and transient [19]. In another study, side effects were assessed on the basis of the parameters of the liver, kidney and creatine phosphokinase levels. After 60 days of berberine therapy, no statistically significant differences were found compared to the results before treatment [8]. This is a confirmation of the high safety of using this drug in women.

Conclusions

Polycystic ovary syndrome affects many women, leads to numerous and serious side effects, so it is important to be treated effectively with as few side effects as possible. Berberine is a promising prospect because it shows a number of positive effects, such as improving carbohydrate and lipid metabolism, correcting hormonal disorders, and influencing ovulation and the menstrual cycle. However, more studies on larger groups of patients are needed to confirm these reports and develop an effective treatment regimen.

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