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Article

The Role of Melatonin in The Pathogenesis of Polycystic Ovary Syndrome and Its Association With Anovulation

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Abstract: Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder characterized by hyperandrogenism, obesity, irregular menstrual cycles, and anovulatory infertility. Melatonin, the primary hormone of the pineal gland, is synthesized from tryptophan and represents an indole derivative of serotonin. Melatonin regulates not only the sleep–wake cycle but also reproductive function. It acts as a potent antioxidant that neutralizes free radicals, thereby protecting ovarian follicles during their maturation. However, when melatonin synthesis is restricted — as may occur in the context of sleep disorders — the balance of the antioxidant defense system may deteriorate, consequently impairing the normal growth and maturation of follicles in patients with PCOS, who are known to exhibit elevated levels of lipid peroxidation products that cause oocyte damage.

Keywords: Melatonin. Polycystic ovary syndrome. PCOS. Hyperandrogenism. Antioxidant system

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1. Introduction

PCOS is one of the most frequent causes of menstrual and reproductive dysfunction. The prevalence of this condition is approximately 8–11% among women of reproductive age, and it accounts for up to 70% of all cases of endocrine infertility[1]. Since the seminal publication by Stein and Leventhal, numerous pathogenetic hypotheses have been proposed; however, the key underlying mechanisms remain a subject of ongoing debate[2]. In recent years, increasing attention has been directed toward the pineal hormone melatonin. Melatonin levels are regulated by the photoperiod, as its production and secretion are enhanced at night in response to darkness, while light exposure can suppress its secretion. Melatonin is also produced in other organs, including the gastrointestinal tract, skin, retina, bone marrow, and lymphocytes[3]. Furthermore, female reproductive organs — including follicular cells, oocytes, and cytotrophoblasts — also constitute sites of melatonin production [4]. The first evidence that this hormone is synthesized directly within the ovary was provided in 1997 by Masanori T. Ito [5]. It has been established that melatonin concentration in follicular fluid (FF) exceeds its plasma level, underscoring its local significance for oogenesis.

2. Materials and Methods

This study was based on the analysis and synthesis of scientific literature related to the role of melatonin in the pathogenesis of polycystic ovary syndrome (PCOS). Comparative, systematic, and analytical research methods were applied. International scientific publications, clinical studies, and evidence-based sources on melatonin, oxidative stress, insulin resistance, hyperandrogenism, and reproductive dysfunction in PCOS were reviewed. The collected data were evaluated to determine the relationship

between melatonin deficiency and anovulation, as well as the potential therapeutic effects of melatonin in improving reproductive and metabolic outcomes in women with PCOS.

3. Results and Discussion

Pathogenetic Association: Melatonin Deficiency and PCOS

In PCOS, a reduction in melatonin levels within FF and a disruption of its circadian secretion pattern are frequently observed. This leads to a series of adverse consequences:

Melatonin is a key regulator of circadian rhythms and exerts influence on the hypothalamic–pituitary–ovarian axis. Disruption of the circadian pattern of melatonin secretion distorts the pulsatile secretion of gonadotropin-releasing hormone (GnRH). In PCOS, an increase in the frequency and amplitude of GnRH secretion is observed, resulting in elevated production of luteinizing hormone (LH); this is likely a consequence of anovulation and low progesterone levels [6]. The frequency of pulsatile LH surges in women with PCOS is approximately 40% higher than in healthy individuals [7]. LH hyperstimulation disrupts folliculogenesis in the ovaries, leading to cystic follicular atresia with hyperplasia of theca cells and stroma, as well as increased androgen synthesis. Due to the relative deficiency of FSH, the conversion of androgens to estrogens is impaired.

Ovulation is a chemical, not a mechanical, process: follicular wall rupture represents a local inflammatory reaction requiring elevated levels of prostaglandins and cytokines, active proteolytic enzyme activity, and consequently enhanced cellular respiration with increased free radical concentrations generated by macrophages and neutrophils. This complex of reactions enables the oocyte to escape from the follicle [8]. However, in order to preserve the genetic material of the oocyte and protect it from free radical damage during this inflammatory response, a well-coordinated antioxidant defense system and adequate melatonin availability are essential. Melatonin deficiency in follicular fluid leads to the accumulation of reactive oxygen species (ROS), which promotes premature apoptosis of granulosa cells and reduces the expression of the aromatase enzyme (CYP19A1). This disrupts the conversion of androgens to estrogens and blocks the formation of the dominant follicle. An imbalance between cell proliferation and apoptosis is considered one of the key mechanisms in the development of PCOS . Melatonin, in turn, prevents granulosa cell apoptosis and oocyte DNA damage by neutralizing free radicals.

Melatonin crosses the hemato-follicular barrier and binds to MT1 and MT2 receptors localized in the granulosa and theca cells of the ovary. Activation of these receptors participates in the regulation of folliculogenesis, steroidogenesis, and enhances follicular sensitivity to follicle-stimulating hormone (FSH). In patients with PCOS, an increased frequency of gonadotropin secretion amplifies LH secretory pulse frequency. Despite elevated LH secretion, FSH levels remain in the lower follicular range due to negative feedback. As a result of the altered LH/FSH ratio, androgen production by ovarian theca cells is increased; however, due to low FSH levels, the maturation of follicular cells is markedly impaired. Reduced melatonin levels are regarded as one of the factors capable of aggravating the dysregulation of ovarian steroidogenesis. It is hypothesized that melatonin deficiency may be accompanied by altered sensitivity of theca cell receptors to LH, thereby promoting androgen overproduction. Chronic hyperandrogenism and impaired folliculogenesis are among the principal factors contributing to the formation of the “polycystic” ovarian morphology.

Insulin Resistance and Metabolic Syndrome

Melatonin ensures the synchronization of metabolic processes with the nocturnal period — the time evolutionarily programmed in humans for fasting — and may exert an inhibitory effect on insulin secretion [9]. Disruption of this balance (e.g., through extended wakefulness, artificial light exposure, nocturnal eating, or shift work) leads to hyperinsulinemia. Excess insulin directly stimulates cytochrome P450c17 in the ovaries, driving increased production of androgens (testosterone), which constitutes a hallmark feature of PCOS. MT1 and MT2 melatonin receptors are located directly on the insulin-producing beta cells of the pancreas, and any dysfunction in this system adversely affects

carbohydrate metabolism. An additional aggravating factor in the impairment of melatonin synthesis is the disruption of circadian sleep–wake rhythms, which may in turn lead to metabolic disturbances. A substantial body of evidence now supports an elevated risk of metabolic syndrome in individuals with sleep restriction due to night-shift work, academic demands, or lifestyle factors. Sleep curtailment is associated with weight gain and obesity, reduced tissue sensitivity to insulin, and the potential development of type 2 diabetes mellitus [10]. An indirect assessment of circulating melatonin levels may be obtained by measuring its concentration in saliva and its metabolite 6-sulfatoxymelatonin in urine; notably, BMI may exert a significant influence on these parameters [11].

Clinical Evidence and Therapeutic Potential

Clinical studies in patients with PCOS — a syndrome frequently accompanied by metabolic and reproductive disorders — have demonstrated a beneficial effect of exogenous melatonin administration on menstrual function and the androgen profile [12]. Several studies have compared the advantages of melatonin supplementation with other treatment modalities commonly used to improve IVF outcomes in patients with PCOS, such as myo-inositol, vitamin E, statins, and others. It was established that melatonin in combination with myo-inositol and folic acid, vitamin E, or metformin exerts a superior effect on oocyte quality and embryo fertilization [13].

It has also been demonstrated that melatonin administration in patients with PCOS significantly influences anthropometric parameters, including reductions in body weight, body mass index, and visceral adipose tissue volume [14]. Furthermore, an experimental study in rats showed that melatonin therapy — particularly in combination with metformin — can reduce elevated collagen fiber content in uterine horns and increase embryo implantation rates [15].

In recent years, a growing body of research has confirmed the beneficial effects of exogenous melatonin in patients with PCOS and obesity. However, the underlying mechanisms of these effects have not yet been fully elucidated. Larger randomized clinical trials are clearly needed to comprehensively characterize the mechanism of action of melatonin in patients with polycystic ovary syndrome and to assess its potential as an adjunctive therapeutic agent.

4. Conclusion

PCOS is a heterogeneous disorder in whose pathogenesis a decline in melatonin secretion plays a significant role. The identified relationships between melatonin, hyperandrogenism, and insulin resistance open new therapeutic avenues. The inclusion of melatonin preparations in treatment regimens for patients with PCOS may improve oocyte and embryo quality, restore menstrual cyclicity, and increase the number of mature oocytes, thereby enhancing fertilization rates and pregnancy outcomes. Administration of melatonin in combination with other agents increases intrafollicular melatonin concentrations, reducing oxidative stress. Melatonin demonstrates high efficacy in correcting the metabolic profile: it reduces body weight and visceral fat volume, improves tissue insulin sensitivity, and attenuates the systemic low-grade inflammation underlying insulin resistance. The potential influence of melatonin on hormonal balance, oxidative stress, sleep quality, and mood is under active investigation. It has been shown to enhance insulin sensitivity, regulate sex hormones, and modulate gonadotropins, which opens promising prospects for addressing the complex hormonal dysregulation characteristic of PCOS.

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