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Exploring the role of circadian rhythms in Polycystic Ovary Syndrome

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Abstract. Polycystic Ovary Syndrome (PCOS) impacts 7% of women of reproductive age and is linked to metabolic syndrome, diabetes, cardiovascular conditions, and more. There hasn't been an exact explanation for the cause of this disease. Despite extensive research, the complete pathophysiology of PCOS remains elusive. One intriguing avenue of investigation is the association between PCOS and circadian rhythms. Sleep disorders, a symptom of PCOS, is controlled by circadian rhythms. Women with PCOS have been proven to suffer from sleep disorders, indicating a relation between the two. Furthermore, studies have shown that PCOS affects the endocrine system, which is vital in regulating circadian rhythms. Numerous studies have been done on the relationship between PCOS and circadian rhythms on a genetic level, where Cytochrome P450(CYP) genes and CLOCK genes are affected by PCOS pathogenesis. The regulation of circadian rhythms plays a positive role in the mitigation and treatment of PCOS. The physiological connections between PCOS and circadian clocks are presented in this review. It draws attention to the most recent studies on the relationships between circadian disorders and PCOS, which suggest a possible explanation and alleviation for the syndrome.

Keywords: PCOS, circadian rhythms, sleep disorders, Circadian genes.

1. Introduction

Polycystic Ovary Syndrome (PCOS) is a condition linked to female infertility. The condition is defined by elevated levels of androgens and tiny cysts in the ovarian sacs, resulting in infertility in females. Studies indicate that PCOS affects 5% to 10% of women aged 18 to 44, making it the most prevalent endocrine disorder in women of reproductive age [1].

Although the genetic etiology of PCOS is unclear, current literature suggests that a family history of PCOS is one of the causes [2]. Apart from toxins and infectious agents, unhealthy food choices and lack of exercise can worsen environmental factors associated with PCOS, like obesity.

The pathophysiology of PCOS involves hyperandrogenemia, a form of insulin resistance unique to affected women, primary defects in the hypothalamic-pituitary axis, insulin secretion and action, and ovarian function. Currently, there are three tools for diagnosing PCOS [3].

The symptoms of PCOS vary according to different patients. For example, women with PCOS may suffer from irregular menstrual cycles, hirsutism, acne, prolonged anovulation, and infertility, which are all caused by hormonal imbalances.

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PCOS can heighten the likelihood of severe complications in women. The common complications include diabetes, obesity, hypertension, and obstructive sleep apnea. These complications can lead to cardiovascular disorders, which may progress to cancer.

Circadian rhythms are the regular, approximately 24-hour cycles that govern behavioral, physiological, and molecular patterns in living organisms. These rhythms respond to light and dark cues, but other factors like food intake, stress, physical activity, social environment, jet lag, and temperature also influence them. The anterior hypothalamus in the brain contains the suprachiasmatic nuclei (SCN), which regulate the body's natural circadian rhythm and act as the central clock. While the body's other tissues and non-SCN brain structures work together to form the peripheral clock. The molecular mechanism of circadian rhythms involves a transcriptional–translational feedback loop cycling with a ~24-hour periodicity. Circadian genes such as Circadian Locomotor Output Cycles kaput (CLOCK) and Basic helix-loop-helix ARNT-like protein 1 (BMAL1) act as positive roles to activate the transcription, while genes including Period (PER) and Cryptochrome (CRY) play negative roles to inhibit the loop. There has been plenty of research conducted on the correlation between the genetic pathway and various factors in PCOS.

Androgens can act as a controller that impacts receptors in the SCN, changing circadian rhythms. Cytochrome P450 17A1 (CYP17A1), an essential enzyme involved in PCOS development, has been recognized as a possible target of CLOCK-BMAL1 in human peripheral blood mononuclear cells.

2. The potential correlations between PCOS and Circadian disorders

2.1. Women with PCOS tend to suffer from sleep disorders

Sleep disturbances can involve changes in how long someone sleeps, trouble falling asleep, trouble staying asleep, or waking up too early, and directly affecting the normal functioning of the circadian rhythms. Frequent stopping of breathing while sleeping is a feature of obstructive sleep apnea (OSA), which can coexist with other sleep disorders.

Currently, there is a lack of multi-center sample clinical studies to explore the probability of sleep disturbances in PCOS patients. However, many researchers have adopted different research methods and analytical approaches to explore the issue of sleep disorders in PCOS patients.

Hung et al. [4] used database analysis, and a comparison cohort was constructed of patients without PCOS who were matched according to age and sex. They found out that women with PCOS are more likely to be suffering from sleep disorders, with a hazard ratio of 1.495 [4], and most developed in the first period of diagnosis.

Furthermore, the study done by Lin et al. [5] drew similar conclusions. It was discovered in their research that women with PCOS have an increased possibility of OSA in later life in comparison to the control group, strengthening the links between sleep disorders and PCOS. However, researches are needed for the pathophysiology of OSA and PCOS.

Moran et al. [6] used cross-sectional analysis of data to explore the issue and concluded that compared to women of similar age without PCOS, women with PCOS almost twice as often experience sleep disturbances. To be more specific, PCOS was associated with an increasing occurrence of difficulty falling asleep, with an odds ratio of 1.94 [6]. The study also demonstrated that obesity and depression, two common side effects of PCOS, act as a moderator for the difficulty in maintaining sleep.

All of these studies suggest that patients with PCOS are at a higher risk of experiencing sleep disorders.

2.2. Changes of circadian rhythms in PCOS

Because PCOS involves metabolic disturbances and the endocrine system influences the sleep-wake cycle, it is possible that PCOS affects circadian rhythms or that their connection is more intricate.

2.2.1. PCOS and Melatonin secretion Human melatonin synthesis has already been shown to be correlated with the circadian clock.

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Jain et al. [7] used a control case study, carrying out a detailed history, clinical examination, and hormonal evaluation to study the role of melatonin in PCOS, and discovered that females with PCOS exhibit markedly elevated levels of melatonin in their bloodstream. The findings suggest that melatonin, known for its antioxidant properties, may influence androgen levels and contribute to the pathophysiology of PCOS. Using regression analysis, they found a positive correlation between melatonin levels and testosterone levels. More studies are required to investigate how adjusting melatonin levels can be used to treat PCOS symptoms and enhance reproductive health results.

Moreover, disruptions in SCN which acts as the central clock, would affect melatonin secretion as well [8]. During the 24-hour light-dark cycle, the SCN receives input from the retina and communicates with GnRH neurons. Next, it will trigger the pituitary gland to release gonadotropin, which regulates the daily cycle of the LH surge that triggers ovulation. SCN will also control the ovary's clock directly through the autonomic nervous system. The circadian rhythm of melatonin synthesis is also regulated by the SCN. Studies have shown that the melatonin receptors found in ovarian follicles indirectly control peripheral oscillators [9].

2.2.2. PCOS and Cortisol secretion Current findings concerning cortisol and women with PCOS have been contradictory.

In one study that measured the 24-hour blood profiles of cortisol in obese and not obese women with PCOS in a control group, their results turned out to be that While mean cortisol concentrations were similar, the cortisol profile pattern differed notably, with PCOS patients exhibiting significantly lower cortisol levels during the night. This was particularly evident in non-obese women with PCOS. Therefore, women with PCOS who were not obese showed the greatest reduction in nighttime cortisol levels [10].

Nevertheless, in another study assessing the cortisol plasma levels during nighttime and morning in women with PCOS, they discovered that women with PCOS exhibit significantly higher evening plasma cortisol levels compared to controls, while morning cortisol levels remain similar between the groups. This altered diurnal cortisol secretion pattern suggests a potential disruption in the hypothalamic-pituitary-adrenal (HPA) axis in PCOS patients, refuting the former study [11].

2.2.3. PCOS and Insulin Resistance Numerous studies have shown that insulin resistance can be deteriorated by sleep restriction adding to the substantial evidence linking sleep disturbances and insulin resistance.

A study by Vgontzas et al. [12] has built a robust connection between PCOS and OSA, emphasizing that women with PCOS have a much higher likelihood of experiencing sleep-disordered breathing and excessive daytime sleepiness when compared to controls. The study highlights insulin resistance as a key factor in this connection, regardless of obesity.

This hypothesis is additionally supported by the research of Tasali et al. [13], which finds a significant connection between sleep-disordered breathing (SDB) and disrupted glucose metabolism in women with PCOS. The research shows that women with PCOS have a higher chance of developing OSA, which worsens insulin resistance and glucose intolerance.

3. Molecular links between circadian clocks and PCOS

Research has identified specific genes involved in both circadian regulation and PCOS pathogenesis.

3.1. Cytochrome P450(CYP)

Research by Zhu et al. [8] discussed the role of Cytochrome (CYP) genes in PCOS and their regulation by circadian rhythms. Cytochrome P450 17A1 (CYP17A1), Cytochrome P450 19A1 (CYP19A1), and Cytochrome P450 11A1 (CYP11A1) are key enzymes in human steroidogenesis, with CYP17A1 and CYP19A1 playing crucial roles in androgen and estrogen synthesis, respectively. CYP17A1 is under direct regulation of the circadian clock genes CLOCK and BMAL1, while CYP19A1 is influenced by nuclear receptor subfamily 1 group D member 1 (NR1D1), which affects its expression and circadian

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rhythm. The activation of NR1D1 inhibits the expression of BMAL1, leading to the disorder of gene transcription. Such interactions highlight the role of circadian regulation in the pathophysiology of PCOS, impacting hormone synthesis and metabolic processes [8].

3.2. Circadian rhythm genes

Li et al. [14] used rat models to investigate the problem by subjecting rats to either constant light or darkness for 8 weeks. Exposure to continual darkness led to reduced levels of BMAL1 in the brain and muscles, causing insulin resistance through Glucose transporter-4 (GLUT4), while reduced levels of PER1 and PER2 resulted in increased androgen levels. This study clarified the important role of circadian clock genes, such as BMAL1, PER1, and PER2, in PCOS.

Another research project utilized blood samples from individuals without PCOS, those with the condition, and mice for experiments. Two genes identified to be involved in increased negative feedback in PCOS are PERs and CRYs. Additionally, the levels of core clock genes in peripheral blood were decreased in mice with induced PCOS, leading to a loss of rhythmicity. This finding implies that the circadian clock plays a role in excessive androgen production in PCOS by regulating the metabolism of androgens in peripheral tissues [15].

4. Controlling circadian rhythms alleviates PCOS symptoms

Comprehending the interaction between circadian rhythms and PCOS may result in innovative treatment approaches.

Researcher Tamura et al. [16] used mice experiments to examine whether long-term melatonin treatment would affect the aging of ovarian, and the current findings show that melatonin inhibits autophagy, increases SIRT expression, preserves telomeres, and acts as an antioxidant to postpone the aging of the ovaries. These findings indicate that melatonin may offer the potential as a beneficial treatment for reducing ovarian aging and enhancing reproductive health.

A different research study exposed rats to constant light or darkness for eight weeks while using human leukocytes and serum from patients with and without PCOS. The researchers discovered that rats exposed to darkness displayed changes in circadian clock gene expressions that were similar to those observed in PCOS patients. Additionally, melatonin therapy alleviated the rats' hyperandrogenism and hyperinsulinemia through BMAL1, PER1, and PER2 [14].

A clinical study has been done on humans exploring the effect of circadian rhythm disorder based on in vitro fertilization-embryo transfer (IVF-ET) in the PCOS population. The clinical data of patients with tubal factors and PCOS who underwent IVF were retrospectively analyzed. The findings indicated a notable discrepancy in the circadian rhythm disorder between patients with fallopian tube factors and PCOS patients, and circadian rhythm disorder has a significant impact on PCOS. The androgen levels and number of retrieved eggs in the PCOS circadian rhythm disorder group were significantly higher than those in the PCOS circadian rhythm group. This indicates that circadian rhythm disorders are not only a predisposing factor for PCOS, but are also associated with adverse outcomes of IVF-ET in PCOS patients. For people at high risk of PCOS and people with PCOS, if genetic factors cannot be changed, they should avoid intentionally disrupting their circadian rhythms.

5. Conclusion

This essay presents a conclusion of current literature on the possible relationship between PCOS and circadian rhythms. Polycystic Ovary Syndrome is a quite complicated disease, characterized by hyperandrogenism, and in the long term leads to other diseases such as diabetes and heart problems. Studies have discovered that sleep disturbances plague PCOS patients and disruptions in clock-gene expression further complicate the picture. Researchers have found that women with PCOS have elevated melatonin levels, affecting their circadian rhythm regulation through the endocrine system, and ultimately worsening sleep disorders due to insulin resistance. However, studies about whether cortisol levels change with PCOS remain controversial. On the genetic level, it is noted that circadian clock genes change with the disease. To be more specific, studies have shown that CYP genes, which are

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under direct regulation of the circadian clock, play a role in androgen excess. Studies have also suggested that clock genes are reduced under PCOS and show loss of periodicity, suggesting that CLOCK is crucial in regulating the levels of androgens in patients with PCOS. Despite what cutting-edge research has already covered, limitations of this research and further problems remain. For example, there is a shortage of large-scale clinical studies to prove the therapeutic effect of regulating the clock on PCOS. Therefore, large-scale clinical studies should be carried out on this in the future. Furthermore, the relationship between PCOS and sleep disturbances is not clearly understood, and robust data across well-characterized PCOS phenotypes are still scarce. Further investigating the connection between circadian rhythm and PCOS pathways is extremely important, as it might contribute to the study of the cause of PCOS and its treatment in the future.

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