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Antidiabetic Management Strategies for Treatment of Polycystic Ovarian Syndrome

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is a prevalent endocrine disorder characterized by metabolic and reproductive dysfunctions, with insulin resistance playing a central role. Antidiabetic drugs, particularly insulin sensitizers such as metformin, are essential in managing both metabolic and reproductive aspects of PCOS. This article explores the effectiveness of antidiabetic medications in PCOS management, focusing on metformin, GLP-1 receptor agonists, and DPP-4 inhibitors. The integration of these pharmacological agents with hormonal therapies, such as oral contraceptives, offers a comprehensive approach that targets both insulin resistance and hyperandrogenism. Additionally, the role of lifestyle interventions, including diet and exercise, is examined as a critical complement to pharmacotherapy. The article highlights the need for personalized treatment approaches and further research to optimize combination therapies for long-term outcomes. Ultimately, antidiabetic management strategies, when combined with hormonal and lifestyle modifications, represent a multifaceted approach to improving both metabolic and reproductive health in women with PCOS.

Keywords: *Polycystic ovarian syndrome (PCOS), Insulin resistance, Antidiabetic drugs, Metformin, GLP-1 receptor agonists, DPP-4 inhibitors, Hormonal therapy, Oral contraceptives, Lifestyle interventions, Metabolic syndrome, Reproductive health*

1. INTRODUCTION

PCOS is a prevalent endocrine illness that impacts around 5% to 10% of women who are fertile. It presents with a multifaceted range of issues related to metabolism, reproduction, and mental health. The symptoms of this disorder, which include polycystic ovaries, irregular menstrual periods, and hyperandrogenism, can significantly impair a woman's quality of life. Insulin resistance, which affects about 70% of women with PCOS, is a particularly problematic component of the disorder. This metabolic inefficiency greatly raises the risk of type 2 diabetes, cardiovascular disease, and various chronic medical conditions in addition to making PCOS symptoms worse. As a result, managing insulin resistance has become a

major feature in the care of PCOS, with specific attention on antidiabetic methods that can enhance metabolic health and general consequences [1]. The pathogenesis of PCOS is complicated, encompassing genetic susceptibility, hormone abnormalities, and environmental variables. This condition is frequently characterized by insulin resistance, which raises insulin levels and further stimulates the production of androgens by the ovaries, upsetting the delicate hormonal balance. A range of clinical symptoms, including as irregular menstruation, infertility, and the onset of metabolic syndrome, can be caused by this series of events. Treatment approaches that focus on this metabolic disturbance are crucial because of the substantial consequences of insulin resistance in PCOS. Numerous studies indicate that traditional therapeutic strategies, including as reducing weight and improved physical exercise, may enhance insulin sensitivity and help many women resume regular menstruation.

Pharmacological therapies have achieved importance in controlling insulin resistance and increasing reproductive consequences in PCOS patients, in addition to lifestyle approaches. In this situation, the well-known antidiabetic drug metformin is often used because of its capacity to increase insulin sensitivity and decrease blood levels of insulin. Metformin can help control menstrual periods, encourage ovulation, and enhance metabolic profiles in women with PCOS, according to clinical research. In addition to metformin, more recent antidiabetic medications such as sodium-glucose cotransporter 2 inhibitors and agonists of the glucagon-like peptide-1 receptor are showing promise as alternatives for treating insulin resistance in this patient population [2]. These drugs are appealing choices for women who struggle with PCOS and metabolic problems because they not only help with glycemic management but may also provide other advantages including losing weight and cardiovascular protection. In order to better understand the current antidiabetic therapy options for PCOS, this article will examine their mechanisms of action, clinical efficiency, and overall effects on metabolic and reproductive health. We can gain a better understanding of the significance of customized therapy plans that cater to the particular requirements of women afflicted with PCOS by exploring the connection between insulin resistance and the illness. In the end, improving our knowledge of antidiabetic management techniques in PCOS may lead to better treatment outcomes and a higher standard of living for people with this complicated illness.

2. PATHOPHYSIOLOGY OF POLYCYSTIC OVARIAN SYNDROME

The pathophysiology of PCOS is multifactorial, involving complex interactions between genetic, hormonal, and environmental factors (Figure 1).

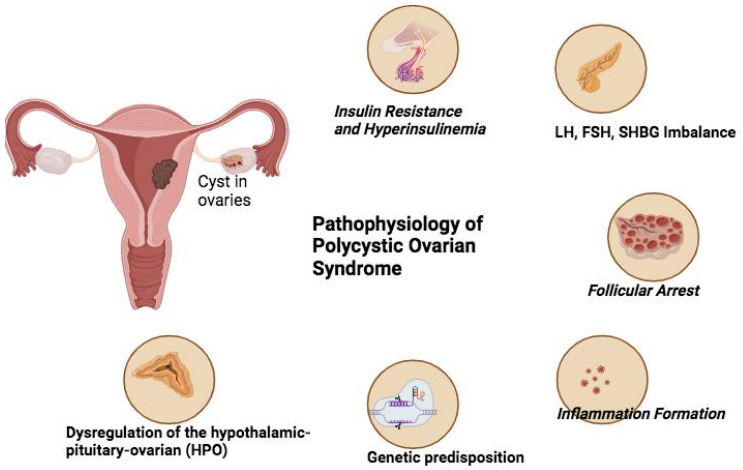

Figure 1: Mechanisms Underlying the Pathophysiology of PCOS

2.1 Insulin Resistance and Hyperinsulinemia

Insulin resistance and hyperinsulinemia are important components of PCOS pathogenesis, as they contribute to the disorder's metabolic and reproductive dysfunctions. Insulin resistance is the reduced capacity of target tissues (adipose, liver, and muscle) to react to the effects of insulin. Insulin is essential for the uptake and metabolism of glucose. When a person is insulin-resistant, their pancreas secretes more insulin to make up for it, which causes hyperinsulinemia. Insulin resistance is commonly linked to obesity; however, it has also been reported in women with PCOS who have a normal body mass index (BMI), suggesting that insulin resistance may be a component of the condition itself rather than just a result of being overweight [3]. The mechanisms underlying insulin resistance in PCOS are complicated and multifaceted, including abnormalities related to insulin receptor signaling and post-receptor pathways. According to some study, women with PCOS may have cellular abnormalities in insulin signaling, specifically in the phosphatidylinositol 3-kinase (PI3K) pathway, which is essential for the transfer of glucose. Consequently, there is a decrease in the absorption of glucose by fat and muscle cells, which raises blood sugar concentrations and causes compensatory hyperinsulinemia.

A substantial fraction of women who are of reproductive age suffer from polycystic ovarian syndrome (PCOS), a complicated endocrine and metabolic condition, for which hyperinsulinemia is a key pathophysiological factor. Hyperinsulinemia, or increased insulin levels in the bloodstream, is frequently caused by insulin resistance (IR), in which tissues such as muscle, fat, and liver have a reduced capability to respond to insulin. The effect that hyperinsulinemia has on ovarian function is one of the most important aspects of PCOS. The ovarian tissue has insulin receptors, especially in the theca cells, which produce androgens. Theca cells are directly stimulated by hyperinsulinemia in PCOS-affected women to create excess androgens, such as testosterone and androstenedione [4]. The hyperandrogenism associated with PCOS, which shows up medically as hirsutism (excessive hair growth), acne, and androgenic alopecia (hair loss), is mostly caused by this overproduction of androgens. Furthermore, insulin stimulates the generation of androgens by amplifying the effects of luteinizing hormone (LH) and acting independently on the ovaries. Elevated LH and hyperinsulinemia work together to increase androgen production, which is one of the factors that contributes to PCOS's hormonal imbalance. This hormonal disruption impairs normal follicular development in the ovaries, leading to prolonged anovulation and polycystic ovarian morphology. Infertility and irregular menstrual periods result from immature follicles building up in the ovaries in this condition, which prevents them from developing or ovulating. Furthermore, insulin is essential in lowering the liver's synthesis of sex hormone-binding globulin (SHBG). The bioavailability of circulating androgens is decreased by SHBG's binding to them [5]. Decreased SHBG levels in hyperinsulinemia situations lead to elevated blood levels of free androgens, which exacerbate hyperandrogenism symptoms. This rise in bioavailable testosterone feeds the cycle of hormonal dysregulation and exacerbates the clinical signs of PCOS, including acne and hirsutism.

2.2 Hormonal Imbalance

A key feature of polycystic ovarian syndrome (PCOS) is hormonal imbalance, which plays a major role in the disorder's intricate clinical presentations. Hyperandrogenism, ovulatory failure, and polycystic ovarian morphology are the hallmarks of polycystic ovarian syndrome (PCOS), which is caused by underlying hormonal dysregulation. Androgens, insulin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone-binding globulin (SHBG) are the main hormones that cause abnormalities in PCOS. These hormonal abnormalities create a biochemical environment that disturbs normal ovarian function and is linked to a number of metabolic illnesses. A hallmark of PCOS, hyperandrogenism is described as increased levels of androgens like testosterone. It is the primary cause of many symptoms associated with PCOS, such as hirsutism, acne, and alopecia. Insulin resistance and hyperinsulinemia worsen the overproduction of androgens by the ovaries in women with PCOS [6]. Elevated insulin levels boost ovarian theca cell activity, enhancing the formation of androgens while simultaneously suppressing the hepatic synthesis of SHBG. As a result, there is a greater concentration of free androgens in the blood, which interferes with proper follicular development and exacerbates hyperandrogenic symptoms. Follicle growth and maturation are facilitated by the regulation of ovarian function in healthy women by FSH and LH.

An important aspect of PCOS is the dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis, which is critical to the regulation of reproductive hormones. Gonadotropin-releasing hormone (GnRH) is secreted by the hypothalamus, which causes the pituitary gland to release FSH and LH. The aberrant pulsatile release of GnRH in PCOS frequently causes an increase in the frequency of LH pulses in comparison to FSH. This change impairs the normal maturation of ovarian follicles and increases the amount of androgen produced by the ovaries. Hormonal imbalance is further exacerbated by the lack of progesterone production that follows an absence of ovulation. A lack of progesterone can cause irregular menstrual periods and an increased risk of endometrial hyperplasia. Progesterone is necessary for controlling the menstrual cycle and promoting prospective conception. Additionally, hormonal imbalance in PCOS is connected with alterations in other regulatory factors like as leptin and adiponectin, which are released by adipose tissue. Women with PCOS frequently have increased levels of leptin, which is correlated with body fat mass, and decreased levels of adiponectin. The inflammatory state and metabolic abnormalities that are frequently seen in PCOS are caused in part by this imbalance. Elevated leptin may further exacerbate insulin resistance and androgen production, reinforcing the cycle of hormonal dysregulation. The implications of hormonal imbalance in PCOS extend beyond reproductive health; they have significant consequences for cardiovascular health and overall metabolic function [7]. The risk of developing conditions such as metabolic syndrome, hypertension, and cardiovascular disease is notably higher in women with PCOS, driven in part by the systemic effects of hormonal dysregulation. The relationship between hormones, metabolic health, and reproductive function underscores the importance of addressing hormonal imbalances in the management of PCOS.

2.3 Chronic Anovulation and Follicular Arrest

Chronic anovulation and follicular arrest are critical elements in the pathophysiology of PCOS, significantly contributing to the reproductive dysfunction that characterizes this condition. PCOS is primarily a disorder of the ovaries, and its hallmark is the failure of follicles to develop fully, leading to the absence of regular ovulation. This chronic state of anovulation underlies many of the symptoms associated with PCOS, including menstrual irregularities, infertility, and polycystic ovarian morphology, and it is closely linked with hormonal imbalances that perpetuate the disorder. In a typical ovarian cycle, a cohort of follicles is recruited during the early follicular phase, with one follicle eventually maturing and ovulating under the influence of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). However, in women with PCOS, this process is disrupted. Instead of progressing to full maturation and ovulation, follicles become arrested in their development, often

accumulating as small cysts within the ovaries. This **follicular arrest** occurs at the antral stage of development, where follicles are unable to reach the pre-ovulatory phase [8]. This disruption in follicular development is a central feature of PCOS and leads to **chronic anovulation**, which manifests as infrequent or absent menstrual cycles (oligomenorrhea or amenorrhea).

The **imbalance between FSH and LH** is one of the primary mechanisms driving follicular arrest in PCOS. Women with PCOS often exhibit elevated levels of LH and relatively lower levels of FSH. Normally, FSH stimulates the growth and maturation of ovarian follicles, while LH triggers ovulation. However, the abnormally high LH levels in PCOS disrupt this delicate balance, leading to the premature luteinization of follicles and preventing their proper maturation. As a result, follicles remain at an immature stage, contributing to the characteristic "polycystic" appearance of the ovaries. The elevated LH levels are often driven by increased pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which favors the production of LH over FSH by the pituitary gland. This hormonal imbalance not only disrupts normal follicular development but also promotes androgen production by ovarian theca cells, further exacerbating the hormonal milieu in PCOS. **Hyperandrogenism** plays a crucial role in the perpetuation of follicular arrest. Androgens, such as testosterone, are produced in excess by the ovaries and adrenal glands in women with PCOS, and this excess contributes to the disruption of folliculogenesis. Normally, androgens are converted to estrogens by granulosa cells within the developing follicles, a process facilitated by FSH. However, in PCOS, the elevated androgen levels overwhelm this system, impairing the ability of granulosa cells to respond to FSH and inhibiting estrogen production [9]. This lack of estrogen feedback further inhibits follicular growth and maturation, creating a vicious cycle that perpetuates anovulation. Additionally, androgens can induce atresia of developing follicles, leading to their premature degeneration and further reducing the likelihood of ovulation. The chronic state of anovulation in PCOS has significant consequences for reproductive health. Without regular ovulation, women with PCOS are at an increased risk of infertility, as there is no release of an egg that can be fertilized during the menstrual cycle. Moreover, the absence of ovulation results in a lack of corpus luteum formation and, consequently, a deficiency in progesterone production. Progesterone is essential for regulating the endometrial lining of the uterus and maintaining normal menstrual cycles. In the absence of progesterone, women with PCOS often experience irregular or absent periods and are at an increased risk of endometrial hyperplasia, a condition in which the lining of the uterus becomes abnormally thickened due to prolonged unopposed estrogen exposure.

The accumulation of immature follicles within the ovaries also contributes to the characteristic appearance of polycystic ovaries, which are often larger in size and contain multiple small cysts when viewed via ultrasound. However, the presence of polycystic ovaries alone is not diagnostic of PCOS, as many women with polycystic ovaries do not exhibit the full spectrum of PCOS symptoms. Instead, it is the combination of polycystic ovarian morphology with other clinical features, such as hyperandrogenism and menstrual irregularities, that defines the syndrome. The chronic anovulation associated with PCOS has significant metabolic and hormonal consequences as well. The lack of regular ovulatory cycles and the corresponding deficiency in progesterone contribute to a state of unopposed estrogen exposure, which can disrupt the normal feedback mechanisms that regulate the hypothalamic-pituitary-ovarian axis [10]. This hormonal imbalance perpetuates the cycle of anovulation and contributes to the long-term risk of endometrial abnormalities, including hyperplasia and an increased risk of endometrial cancer. Additionally, the chronic state of anovulation is associated with other metabolic disturbances commonly observed in PCOS, such as insulin resistance, obesity, and dyslipidemia.

2.4 Hyperandrogenism

Hyperandrogenism is a defining feature of PCOS and plays a crucial role in its pathophysiology. It is characterized by elevated levels of androgens, which are male hormones such as testosterone, and can have profound effects on various physiological processes in women. Hyperandrogenism is often implicated in the manifestation of several symptoms associated with PCOS, including hirsutism, acne, scalp hair thinning, and irregular menstrual cycles. The underlying mechanisms of hyperandrogenism in PCOS are multifaceted, involving a complex interplay of genetic, hormonal, and environmental factors that disrupt normal ovarian function and contribute to the syndrome's clinical manifestations. The ovaries and adrenal glands are the primary sources of androgens in women. In PCOS, there is often an increase in androgen production due to dysregulation in the ovarian and adrenal pathways. This hyperandrogenism is primarily driven by the excess stimulation of theca cells in the ovaries, which are responsible for synthesizing androgens. The dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis plays a significant role in this process [11]. Women with PCOS frequently exhibit elevated luteinizing hormone (LH) levels, which promote the production of androgens from the theca cells, while the levels of follicle-stimulating hormone (FSH) are typically low. This imbalance leads to increased androgen synthesis and contributes to the characteristic symptoms of hyperandrogenism.

One of the most noticeable clinical consequences of hyperandrogenism is hirsutism, which is the excessive growth of facial and body hair in a male pattern. This symptom results from increased levels of testosterone and its more potent derivative, dihydrotestosterone (DHT), which can stimulate hair follicle growth in androgen-sensitive areas. The extent of hirsutism often correlates with the degree of hyperandrogenism, and it can have significant psychological and social impacts on affected women. Additionally, hyperandrogenism can lead to other skin manifestations, such as acne and seborrhea, due to the influence of androgens on sebaceous gland activity and keratinization. The hormonal imbalances caused by

hyperandrogenism also contribute to menstrual irregularities commonly seen in PCOS. Elevated androgen levels can disrupt the normal feedback mechanisms between the ovaries and the pituitary gland, leading to chronic anovulation and irregular menstrual cycles. Without regular ovulation, the hormonal environment becomes skewed, resulting in prolonged unopposed estrogen exposure. This condition can further complicate the clinical picture, leading to endometrial hyperplasia and increasing the risk of endometrial cancer over time. Furthermore, the lack of progesterone due to anovulation can exacerbate menstrual irregularities and contribute to the risk of infertility in women with PCOS. Hyperandrogenism is also linked to metabolic dysfunction in PCOS. Many women with PCOS exhibit insulin resistance, which can be exacerbated by elevated androgen levels [12]. Insulin resistance leads to compensatory hyperinsulinemia, which can further stimulate androgen production by the ovaries. This creates a vicious cycle where hyperinsulinemia drives hyperandrogenism, and elevated androgens, in turn, worsen insulin resistance. The association between hyperandrogenism and metabolic disturbances increases the risk of developing obesity, type 2 diabetes, and cardiovascular disease in women with PCOS.

2.5 Chronic Low-Grade Inflammation

Chronic low-grade inflammation is increasingly recognized as a significant contributor to the pathophysiology of PCOS, a complex endocrine disorder affecting women of reproductive age. In PCOS, this inflammatory state manifests as an ongoing, subtle immune response characterized by the presence of elevated pro-inflammatory cytokines, which play a critical role in the development and exacerbation of various symptoms associated with the syndrome. This inflammation is not only localized within the ovaries but can also have systemic implications, contributing to insulin resistance, metabolic syndrome, and cardiovascular risks that are commonly associated with PCOS. The origins of chronic low-grade inflammation in PCOS are multifactorial. One primary contributor is obesity, which is prevalent among women with PCOS. Adipose tissue, especially when in excess, is not merely a passive storage depot for fat but is an active endocrine organ that secretes a variety of bioactive substances, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP). These cytokines create a microenvironment that promotes insulin resistance and disrupts normal hormonal regulation, ultimately leading to the characteristic symptoms of PCOS [13]. This inflammatory milieu not only hinders normal insulin signaling but also promotes the overproduction of androgens by the ovaries, further perpetuating the hormonal imbalances that define the syndrome. Moreover, insulin resistance itself contributes to the inflammatory state in PCOS. Elevated insulin levels can stimulate the production of inflammatory mediators, exacerbating the inflammatory response. The relationship between insulin resistance and chronic inflammation is bidirectional; while insulin resistance can provoke inflammation, inflammation can also worsen insulin sensitivity. This vicious cycle results in a worsening metabolic profile for women with PCOS, increasing their risk for type 2 diabetes and cardiovascular diseases. Studies have shown that markers of inflammation, such as high-sensitivity C-reactive protein (hs-CRP), are often elevated in women with PCOS, correlating with insulin resistance and metabolic disturbances.

In addition to obesity and insulin resistance, other factors contributing to chronic low-grade inflammation in PCOS include genetic predisposition and environmental stressors. Genetic studies have identified several polymorphisms associated with inflammatory pathways that may predispose women to develop PCOS. Additionally, environmental factors such as exposure to endocrine-disrupting chemicals, sedentary lifestyle, and poor dietary habits can trigger or exacerbate the inflammatory response, further complicating the clinical picture of PCOS. Chronic low-grade inflammation has significant implications for the ovarian function in women with PCOS. The inflammatory cytokines released into the systemic circulation can alter the ovarian microenvironment, leading to follicular dysregulation and anovulation. For instance, the increased levels of IL-6 and TNF-α can negatively impact oocyte quality and promote follicular arrest, contributing to the reproductive challenges faced by women with PCOS [14]. Furthermore, this inflammatory environment may also interfere with the ovarian response to hormonal signals, resulting in impaired gonadotropin release and further exacerbating menstrual irregularities. The consequences of chronic low-grade inflammation extend beyond reproductive health, affecting the overall well-being of women with PCOS. The inflammatory state is associated with mood disorders, including anxiety and depression, which are more prevalent in this population compared to the general population. The psychological burden of dealing with chronic symptoms and the stigma associated with the physical manifestations of PCOS can contribute to a cycle of stress and inflammation, further complicating management strategies. Addressing chronic low-grade inflammation may, therefore, provide an avenue for improving both physical and mental health outcomes in women with PCOS. Therapeutic strategies aimed at mitigating chronic inflammation in PCOS are essential for improving the overall management of the condition. Interventions such as lifestyle modifications—including weight loss, exercise, and dietary changes—have shown promise in reducing inflammatory markers and improving metabolic profiles. Pharmacological treatments, such as metformin, can also be effective in addressing insulin resistance and its associated inflammatory pathways. Additionally, anti-inflammatory agents and supplements with known anti-inflammatory properties, such as omega-3 fatty acids and vitamin D, are being explored for their potential benefits in managing the inflammatory aspect of PCOS [15].

2.6 Genetic and Environmental Factors

The pathophysiology of PCOS is a complex interplay of genetic and environmental factors that collectively contribute to the manifestation of this heterogeneous disorder. Understanding the roles of these factors is crucial, as they can influence not only the development of PCOS but also the severity of its clinical features. Genetic predisposition has been widely recognized

as a significant contributor to PCOS, with numerous studies indicating that women with a family history of the condition are at a higher risk of developing it. Twin studies have also suggested a heritability rate of approximately 70%, indicating a strong genetic component. Specific genes involved in insulin signaling, androgen biosynthesis, and inflammatory pathways have been identified, suggesting that genetic variations can predispose individuals to metabolic dysfunctions and hormonal imbalances characteristic of PCOS. For instance, polymorphisms in genes such as the insulin receptor substrate (IRS) and the luteinizing hormone receptor (LHR) have been associated with insulin resistance and hyperandrogenism, respectively, which are hallmark features of the syndrome. On the other hand, environmental factors also play a crucial role in modulating the expression of genetic predispositions in PCOS. These factors include lifestyle choices, dietary habits, and exposure to endocrine-disrupting chemicals. Lifestyle factors, such as sedentary behavior and high-calorie diets rich in refined carbohydrates and sugars, can exacerbate the risk of obesity and insulin resistance in genetically susceptible individuals. The westernization of lifestyle, with its accompanying increase in processed food consumption and decrease in physical activity, has been linked to a rising prevalence of PCOS globally [16]. This relationship underscores the importance of environmental influences in the pathogenesis of the disorder, suggesting that while genetic predisposition may set the stage, environmental factors can act as significant modulators of disease expression.

Furthermore, the timing and nature of environmental exposures can have a lasting impact on an individual's health trajectory. For instance, fetal exposure to excess androgenic hormones during critical periods of development can program the reproductive system, leading to a higher likelihood of developing PCOS in adulthood. This developmental programming highlights the interplay between genetic susceptibility and environmental influences, emphasizing that both factors can converge to affect ovarian function and metabolic health later in life. Moreover, factors such as obesity, which is prevalent in many women with PCOS, can also have epigenetic effects, modifying gene expression and contributing to the disorder's pathophysiology. Studies have also indicated that inflammation plays a pivotal role in the interaction between genetic and environmental factors in PCOS. Women with PCOS often exhibit elevated levels of inflammatory markers, which can exacerbate insulin resistance and contribute to metabolic dysfunction. Environmental factors, including obesity and physical inactivity, can promote a chronic low-grade inflammatory state, further complicating the clinical picture of PCOS. The genetic predisposition to inflammation can interact with these environmental triggers, leading to a vicious cycle that perpetuates the symptoms and complications associated with the disorder [17].

3. CONVENTIONAL ANTIDIABETIC THERAPIES IN PCOS

3.1 Metformin

One of the most critical features of PCOS is insulin resistance, a condition that impairs the body's ability to utilize insulin efficiently, leading to elevated insulin levels (hyperinsulinemia). Due to this insulin resistance, antidiabetic therapies play a vital role in PCOS management, with Metformin being the most widely prescribed drug. Metformin is an oral antidiabetic medication primarily used to treat type 2 diabetes. It belongs to the biguanide class of drugs and has been in use for several decades due to its proven efficacy in managing insulin resistance and improving metabolic parameters. Metformin primarily works by improving insulin sensitivity, making it a valuable tool for addressing the insulin resistance that underlies much of the metabolic dysfunction seen in PCOS. Insulin resistance in PCOS patients leads to elevated levels of insulin in the bloodstream. These elevated insulin levels stimulate the ovaries to produce excess androgens (male hormones), which contribute to many of the symptoms of PCOS, such as irregular menstrual cycles, acne, hirsutism (excessive hair growth), and difficulty with ovulation. Metformin reduces insulin resistance by inhibiting gluconeogenesis, the process by which the liver produces glucose, thereby lowering blood sugar levels. Additionally, it enhances the uptake of glucose in muscle tissues and decreases the absorption of glucose from the intestines, all of which work together to reduce circulating glucose and insulin levels. By lowering insulin levels, Metformin indirectly decreases androgen production, which helps alleviate many of the hormonal imbalances associated with PCOS [18]. This mechanism not only helps regulate menstrual cycles and restore ovulation but also mitigates symptoms like hirsutism and acne, contributing to improved reproductive and dermatological outcomes for women with PCOS.

Studies have shown that Metformin can lead to more regular menstrual cycles in women with PCOS, even in those who have not responded to other forms of treatment such as oral contraceptives or ovulation induction agents. Furthermore, Metformin is often prescribed alongside fertility treatments like Clomiphene citrate or Letrozole for women who are trying to conceive. By improving insulin sensitivity and enhancing the body's response to fertility medications, Metformin significantly boosts the chances of successful ovulation and conception in women struggling with infertility due to PCOS. Over time, women may experience a reduction in hirsutism and acne as their androgen levels normalize [8]. Although Metformin may not eliminate these symptoms entirely, it provides a non-hormonal approach to managing the androgen excess that drives many of the physical manifestations of PCOS. When combined with other treatments, such as anti-androgens (e.g., spironolactone) or laser therapy for hair removal, Metformin can significantly improve the quality of life for women dealing with the effects of elevated androgens. Furthermore, Metformin may have an appetite-suppressing effect, which can aid in weight management. Losing weight is particularly important in PCOS because even a modest reduction in weight—5-10% of body weight—can significantly improve insulin sensitivity, reduce androgen levels, and promote more regular menstrual cycles.

For overweight women with PCOS, Metformin serves as both a tool for improving metabolic health and a support mechanism for weight loss efforts, making it a key component of comprehensive PCOS management strategies. Furthermore, Metformin has favorable effects on other metabolic parameters associated with PCOS, such as improving lipid profiles by reducing total cholesterol and low-density lipoprotein (LDL) levels. By addressing both insulin resistance and dyslipidemia, Metformin helps reduce the overall risk of cardiovascular disease, which is another major concern for women with PCOS. This dual benefit—reducing the risk of both type 2 diabetes and cardiovascular disease—makes Metformin a critical component of the long-term management of PCOS, especially in women with metabolic risk factors such as obesity, a family history of diabetes, or elevated cholesterol levels [19].

Bridger T et al researched-on metformin for treating PCOS. The results showed significant decline in mean serum testosterone concentration with metformin and high-density lipoprotein cholesterol levels increased by 6.98 mg/dL with metformin vs a decrease of −2.33 mg/dL with placebo (95% confidence interval, 0.78 to 18.23 for the mean difference between groups). Lovik TS et al researched metformin to treat pregnant women with polycystic ovary syndrome. The results showed that the rate of late miscarriage and preterm birth was lower in the metformin group (5%) compared to the placebo group (10%), although this difference was not statistically significant ($p = 0.08$). However, a post-hoc pooled analysis combining this study with two previous trials revealed a significant reduction in these adverse outcomes (5% in the metformin group vs. 10% in the placebo group, $p = 0.004$). The study did not find a significant impact of metformin on secondary outcomes such as gestational diabetes and preeclampsia. Overall, the trial suggested that while metformin might reduce the risk of miscarriage and preterm birth, it does not prevent gestational diabetes in pregnant women with PCOS. El Maghraby HA et al performed Randomized controlled trial of the effects of metformin versus combined oral contraceptives in adolescent PCOS women through a 24 month follow up period. The results showed that both treatments were effective but had different impacts. Metformin primarily improved insulin sensitivity and helped with weight management. On the other hand, COCs were more effective in regulating menstrual cycles and reducing androgen levels, leading to improvements in hyperandrogenic symptoms like acne and hirsutism. Over the long term, these results highlight the potential of both treatment options depending on the specific goals, such as metabolic improvements or hormonal regulation in adolescent PCOS patients.

3.2 Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs), including drugs like pioglitazone and rosiglitazone, are conventional antidiabetic therapies that have been explored for their potential in managing Polycystic Ovary Syndrome (PCOS). As insulin sensitizers, TZDs target one of the central metabolic disturbances in PCOS: insulin resistance. Women with PCOS often exhibit higher insulin levels, which exacerbate hyperandrogenism by stimulating the ovaries to produce more androgens. In addition to improving insulin resistance, studies have shown that TZDs can positively influence ovulatory function and restore menstrual regularity in women with PCOS. By lowering insulin and androgen levels, TZDs may promote follicular maturation and ovulation, thereby increasing fertility rates in PCOS patients who struggle with anovulation. Another significant aspect of TZD therapy in PCOS is its impact on adipocyte differentiation and inflammatory markers. PCOS is often associated with a pro-inflammatory state, and TZDs have been shown to exert anti-inflammatory effects by reducing the levels of inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) [20]. This anti-inflammatory action is linked to the drug's ability to promote fat cell differentiation and reduce the release of free fatty acids from adipose tissue, which contributes to the improvement of insulin sensitivity. TZDs also help redistribute fat from visceral to subcutaneous stores, which is metabolically more favorable. These effects can help mitigate some of the long-term metabolic risks, including cardiovascular disease and type 2 diabetes, that are associated with PCOS. However, the potential for weight gain and the long-term risks associated with TZDs, particularly concerns regarding bone density and cardiovascular health, have made clinicians cautious in prescribing these drugs for PCOS, especially for younger women or those planning to conceive. As a result, the use of TZDs in PCOS is generally reserved for cases where other insulin-sensitizing agents like metformin are not effective or well-tolerated (Figure 2).

Froment P et al studied Thiazolidinediones in PCOS. The study hypothesizes that TZDs exert their positive effects not only by enhancing glucose uptake in tissues like muscle and fat but also through direct actions on the ovarian cells, potentially impacting steroidogenesis. This dual mechanism may explain the improvement in both metabolic and reproductive abnormalities in PCOS women. By lowering insulin resistance and improving fat distribution, TZDs help restore normal reproductive function, making them a useful therapeutic option for women with PCOS struggling with infertility. Du Q et al researched-on Effects of thiazolidinediones on polycystic ovary syndrome: a meta-analysis of randomized placebo-controlled trials [21]. The study found that TZDs significantly improved insulin sensitivity, reducing insulin levels and fasting blood glucose in women with PCOS, which is important due to the common insulin resistance associated with this condition. However, while TZDs were beneficial for metabolic improvements, they did not show significant changes in androgen levels or hirsutism, two key features of PCOS. Additionally, TZD use was associated with an increase in body mass index (BMI), raising concerns about weight gain, which can be particularly problematic for women with PCOS who often already struggle with weight management. The study by Seto-Young et al. explored the direct effects of thiazolidinediones (TZDs) on human ovarian cells, focusing on both insulin-independent and insulin-sensitizing actions. The researchers found that TZDs, which

are primarily known for their role in enhancing insulin sensitivity in peripheral tissues, also directly affect steroidogenesis in the human ovary. Specifically, the study showed that TZDs stimulated the production of steroid hormones and increased the secretion of insulin-like growth factor binding protein-1 (IGFBP-1), suggesting that TZDs could potentially play a significant role in modulating ovarian function and addressing hyperandrogenism in conditions like polycystic ovary syndrome (PCOS) [22].

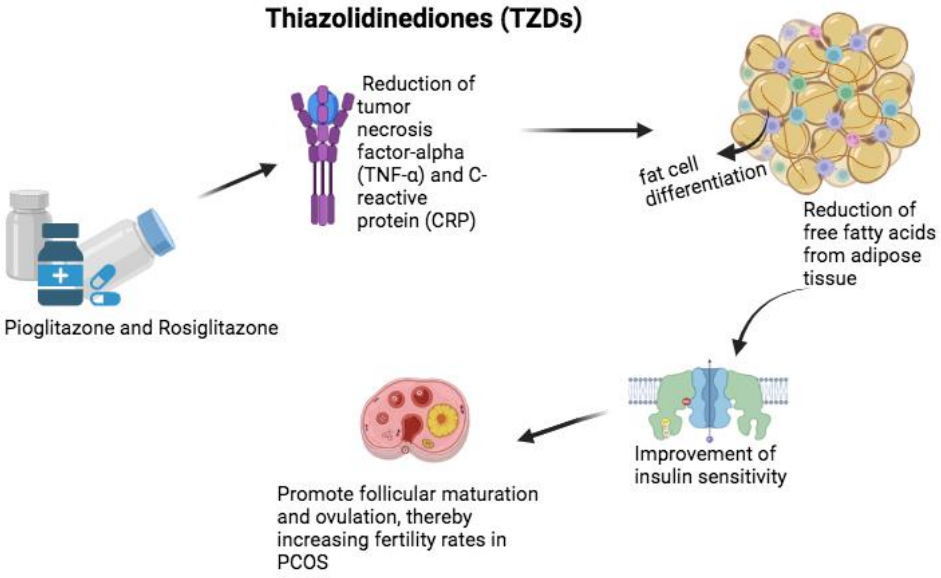

Figure 2: Mechanism of thiazolidinediones for treatment of PCOS

3.3 Inositols

Inositols, particularly myo-inositol (MI) and D-chiro-inositol (DCI), have garnered significant interest as potential therapeutic agents for managing Polycystic Ovary Syndrome (PCOS), especially in the context of insulin resistance and metabolic dysregulation. PCOS is characterized by a complex interplay of hormonal imbalances, including hyperandrogenism, menstrual irregularities, and insulin resistance, which collectively contribute to the diverse clinical manifestations of the disorder. Insulin resistance is a pivotal component in the pathophysiology of PCOS, as it can lead to compensatory hyperinsulinemia, exacerbating the hormonal imbalance and promoting metabolic issues such as obesity and dyslipidemia [13]. Clinical studies have demonstrated the efficacy of inositols in improving metabolic parameters and reproductive outcomes in women with PCOS (Table 1). Research indicates that supplementation with myo-inositol, often in combination with folic acid, can significantly enhance insulin sensitivity, reduce serum insulin levels, and improve ovarian function. For instance, one pivotal study found that women receiving myo-inositol showed a marked improvement in ovulatory function and a decrease in hyperandrogenic symptoms, such as hirsutism and acne. In contrast, D-chiro-inositol supplementation has been associated with improved lipid profiles and reduced weight, contributing to the overall management of metabolic disturbances. The physiological balance between MI and DCI is crucial, as excessive DCI may disrupt ovarian function and negatively impact insulin sensitivity. The optimal therapeutic approach often involves a combination of both inositols, reflecting their natural ratio in the body (approximately 40:1 for MI to DCI), which has been shown to maximize their beneficial effects on ovulatory function and metabolic health [14]. In addition to their metabolic benefits, inositols offer a favorable safety profile, making them an attractive adjunctive therapy for managing PCOS. Unlike conventional pharmacological agents such as metformin, which can have gastrointestinal side effects and other potential complications, inositols are generally well-tolerated and associated with minimal adverse effects. This characteristic is particularly important for women of reproductive age who may seek to avoid the side effects of more aggressive treatments while managing their PCOS symptoms. Furthermore, the growing body of evidence supporting the role of inositols in improving fertility outcomes in women with PCOS has encouraged their use in clinical practice. Women seeking to conceive may benefit from inositol supplementation, as it not only addresses insulin resistance but also promotes hormonal balance and enhances ovarian function, thereby increasing the likelihood of successful ovulation and conception [23].

Table 1: Clinical Research Studies on Antidiabetic Management in PCOS

Study	Objective	Population	Treatment /Intervention	Outcome Measures	Findings	Reference
Metformin in PCOS	Effect of metformin on insulin sensitivity & ovulation	50 women with PCOS, ages 18-35	Metformin 500 mg, 3x/day for 6 months	Ovulation rate, fasting insulin, weight	Improved ovulation and insulin sensitivity	[38]
Myo-Inositol vs. D-chiro-Inositol	Compare insulin resistance & androgen levels	60 women with PCOS	Myo-inositol 2000 mg vs. D-chiro-inositol 1000 mg/day	Insulin sensitivity, androgen levels, ovulation	Myo-inositol improved insulin sensitivity more	[39]
Pioglitazone in PCOS	Pioglitazone effects on insulin sensitivity & menstrual cycles	45 overweight women with PCOS	Pioglitazone 30 mg daily for 3 months	Fasting insulin, menstrual regularity, testosterone	Improved insulin sensitivity & menstrual regularity	[40]
Lifestyle Intervention	Diet & exercise on insulin resistance	100 women with PCOS, BMI > 30	Diet & exercise (150 min/week) for 12 weeks	Insulin sensitivity, weight, menstrual regularity	Improved insulin sensitivity, weight loss, cycle normalization	[41]
Exenatide + Metformin	Exenatide + metformin vs. metformin alone	70 women with PCOS, ages 18-40	Exenatide 5 mcg twice daily + metformin	Weight, insulin sensitivity, menstrual cycle regulation	Better weight loss & insulin sensitivity with combo	[42]
Berberine vs. Metformin	Berberine vs. metformin on insulin resistance	90 women with PCOS	Berberine 500 mg 3x/day vs. metformin 500 mg 3x/day	Insulin sensitivity, menstrual regularity	Berberine improved menstrual regularity more	[43]
Liraglutide in Obese PCOS	GLP-1 agonists for weight & insulin sensitivity	120 obese women with PCOS	Liraglutide 1.8 mg daily for 16 weeks	Weight, glucose, insulin sensitivity, androgens	Significant weight loss, improved insulin sensitivity	[44]
Metformin + Clomiphene Citrate	Combination to improve ovulation	80 women with PCOS, trying to conceive	Metformin + clomiphene citrate 50-150 mg	Ovulation rate, pregnancy rate	Higher ovulation & pregnancy rates with combo	[45]
Rosiglitazone in	Rosiglitazone effects on	60 women with PCOS	Rosiglitazone 4	Insulin resistance,	Improved insulin	[46]

Insulin Resistance	insulin sensitivity		mg/day for 6 months	ovulation, androgen levels	sensitivity, decreased androgen levels	
Metformin in Adolescent PCOS	Metformin's impact on adolescent PCOS	70 adolescent girls with PCOS	Metformin 500 mg, 2x/day for 6 months	BMI, insulin resistance, cycle regularity	Decreased insulin levels, improved cycle regularity	[47]
Inositol & Lifestyle Combo	Inositol + lifestyle on metabolic symptoms	100 women with PCOS	Myo-inositol + diet & exercise for 6 months	Weight, insulin resistance, cycle regulation	Enhanced insulin sensitivity & cycle regulation	[48]
Metformin vs. Lifestyle	Lifestyle vs. metformin in PCOS	80 women with PCOS, BMI > 25	Metformin vs. diet & exercise	Weight, insulin sensitivity, ovulation rate	Lifestyle modification was as effective as metformin	[49]
Metformin & Ovarian Function	Effect of metformin on ovarian function	50 women with PCOS	Metformin 850 mg twice daily	Ovulation, menstrual cycle regularity	Improved ovulation rates, normalized cycles	[50]
Vitamin D & Metformin	Combo effect on insulin & androgen levels	60 women with PCOS, low Vitamin D	Vitamin D 4000 IU/day + metformin	Insulin sensitivity, androgen levels	Improved insulin sensitivity, decreased androgens	[51]
Omega-3 with Metformin	Omega-3 & metformin on insulin & lipid levels	85 women with PCOS	Omega-3 1000 mg/day + metformin	Insulin, lipid profile, cycle regularity	Improved insulin & lipid levels	[52]
Flaxseed Supplementation	Flaxseed on insulin levels & menstrual regularity	70 women with PCOS	Flaxseed 30g/day for 3 months	Insulin sensitivity, menstrual regularity	Improved insulin sensitivity, better cycle regularity	[53]
Acupuncture + Metformin	Acupuncture + metformin vs. metformin alone	60 women with PCOS	Acupuncture 3x/week + metformin	Insulin, weight, menstrual regulation	Improved insulin sensitivity, menstrual regularity	[54]
Chromium Picolinate	Chromium on insulin & androgen levels	60 women with PCOS	Chromium picolinate 200 mcg/day	Insulin sensitivity, androgen levels	Increased insulin sensitivity, reduced androgens	[55]
SGLT-2 Inhibitor	SGLT-2 inhibitors on weight & insulin resistance	100 women with PCOS, BMI > 30	Empagliflozin 10 mg daily for 6 months	Weight, glucose, insulin levels	Significant weight loss, improved insulin sensitivity	[56]

Cinnamon Supplementation	Cinnamon's effect on insulin resistance in PCOS	45 women with PCOS	Cinnamon 1.5g/day	Insulin sensitivity, menstrual regularity	Improved insulin sensitivity and cycle regularity	[57]

The systematic review and meta-analysis by Greff et al. (2023) evaluated the efficacy and safety of inositol in treating polycystic ovary syndrome (PCOS). The study analyzed data from 26 randomized controlled trials (RCTs), covering 1,691 women with PCOS. The researchers compared the effects of inositol (specifically myo-inositol, D-chiro-inositol, or a combination of the two) against placebo and metformin, a common treatment for insulin resistance in PCOS. Key findings showed that inositol significantly improved several aspects of PCOS management, including the normalization of menstrual cycles and a reduction in body weight. The risk ratio (RR) for menstrual cycle normalization was 1.79, meaning women treated with inositol were nearly twice as likely to experience normalized cycles compared to those receiving a placebo. Inositol also showed a favorable safety profile, with fewer reported side effects compared to metformin. The article by Unfer et al. (2017) conducted a meta-analysis on the effects of myo-inositol (MI) in women with polycystic ovary syndrome (PCOS). The study included nine randomized controlled trials (RCTs) involving 247 cases and 249 controls. The key findings indicated that MI supplementation significantly improved several metabolic markers in women with PCOS. Notably, MI reduced fasting insulin levels (standardized mean difference (SMD) = −1.021 μU/mL) and homeostasis model assessment (HOMA) index (SMD = −0.585), both key indicators of improved insulin sensitivity. A significant increase in sex hormone-binding globulin (SHBG) levels was observed in participants who received MI for at least 24 weeks, indicating reduced free androgen levels, which could mitigate hyperandrogenic symptoms like acne and hirsutism. The systematic review and meta-analysis conducted by Fitz et al. (2024) assessed the efficacy of inositol in treating polycystic ovary syndrome (PCOS) to inform the 2023 update of the International Evidence-Based PCOS Guidelines. The findings indicated that inositol supplementation significantly improved insulin sensitivity, which is crucial for many women with PCOS who experience insulin resistance. Additionally, inositol was shown to enhance ovulatory function and restore menstrual cycle regularity. The review highlighted that myo-inositol, in particular, had a positive impact on metabolic parameters, leading to reduced fasting insulin levels and improved glucose metabolism [24].

3.4 GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1 RAs) have gained attention as a potential therapeutic option for managing Polycystic Ovary Syndrome (PCOS), especially given their role in improving insulin sensitivity and addressing obesity, which are common concerns in this condition. These medications, such as liraglutide and semaglutide, mimic the action of glucagon-like peptide-1, a hormone that regulates glucose metabolism by enhancing insulin secretion in response to meals, inhibiting glucagon release, and promoting satiety. The multifaceted actions of GLP-1 RAs make them particularly well-suited for addressing the metabolic derangements associated with PCOS, where insulin resistance and weight gain are prevalent [18,19]. Insulin resistance is a hallmark of PCOS, contributing not only to the metabolic issues faced by these women but also to the reproductive challenges, including anovulation and menstrual irregularities. By improving insulin sensitivity, GLP-1 RAs can help mitigate these problems, potentially restoring normal menstrual cycles and enhancing fertility outcomes. Clinical trials have provided compelling evidence for the efficacy of GLP-1 RAs in women with PCOS. Furthermore, GLP-1 RAs have shown promise in enhancing ovulatory function, with some studies reporting improved ovulation rates in women treated with these agents compared to those receiving traditional therapies such as metformin [25]. The safety profile of GLP-1 RAs is generally favorable, with the most commonly reported side effects being gastrointestinal in nature, such as nausea and vomiting. While these effects can be bothersome for some patients, they often diminish with continued use of the medication. This aspect, coupled with the significant benefits in weight management and metabolic improvement, makes GLP-1 RAs an attractive option for women with PCOS who may not respond adequately to other treatments. Importantly, the integration of GLP-1 RAs into treatment protocols for PCOS could enhance the overall management strategy for this complex disorder, providing an innovative approach that addresses both metabolic and reproductive aspects. As research continues to evolve, the potential of GLP-1 receptor agonists in the management of PCOS is likely to be further elucidated, offering new avenues for improving the health and quality of life for women affected by this syndrome [21,26].

The study by Han et al. (2019) conducted a systematic review and meta-analysis comparing GLP-1 receptor agonists to metformin in the treatment of polycystic ovary syndrome (PCOS). The analysis revealed that GLP-1 receptor agonists were more effective than metformin in improving insulin sensitivity and reducing body mass index (BMI) among women with PCOS. Additionally, GLP-1 receptor agonists resulted in better weight loss outcomes. The authors suggest that these findings support the use of GLP-1 receptor agonists as a promising alternative in managing metabolic issues related to PCOS. The article by Lamos EM, Malek R, and Davis SN discusses the role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in treating polycystic ovary syndrome (PCOS). It highlights that PCOS is a common endocrine disorder associated with insulin resistance, obesity, and metabolic dysregulation. The authors emphasized that while initial findings were encouraging, further research was necessary to confirm the long-term efficacy and safety of GLP-1 RAs in this patient population. They advocated for more extensive clinical trials to fully understand how these agents could be optimally utilized in the

management of PCOS, which remains a prevalent and complex disorder with significant health implications for affected women. In their article, Cena, Chiovato, and Nappi (2020) highlight the significant link between obesity, polycystic ovary syndrome (PCOS), and infertility, emphasizing the potential of GLP-1 receptor agonists as a therapeutic avenue. They concluded that these agents could not only improve metabolic parameters but also enhance reproductive outcomes by promoting weight loss in women with PCOS. The authors stressed the need for further research to substantiate these findings and better understand the mechanisms through which GLP-1 receptor agonists can influence fertility in this patient population [27].

3.5 SGLT2 Inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors represent a novel class of antidiabetic medications that have garnered significant attention for their role in managing type 2 diabetes mellitus (T2DM) and, more recently, for their potential benefits in treating polycystic ovary syndrome (PCOS). PCOS is a common endocrine disorder characterized by insulin resistance, hyperandrogenism, and ovulatory dysfunction, affecting a substantial number of women of reproductive age. SGLT2 inhibitors, such as canagliflozin, empagliflozin, and dapagliflozin, function by inhibiting the SGLT2 protein in the renal proximal tubules, thereby reducing glucose reabsorption and promoting urinary glucose excretion. This mechanism not only lowers blood glucose levels but also results in weight loss, a significant consideration for many women with PCOS who often experience obesity or overweight [28]. The weight-reducing effects of SGLT2 inhibitors can help alleviate insulin resistance and improve the overall metabolic profile of affected individuals. Furthermore, studies have indicated that these agents may also have a positive impact on lipid profiles and blood pressure, contributing to a more comprehensive approach to managing the metabolic disturbances commonly associated with PCOS. The potential benefits of SGLT2 inhibitors in women with PCOS extend beyond glycemic control. Recent research suggests that these medications may have a favorable effect on ovarian function and reproductive health. By improving insulin sensitivity, SGLT2 inhibitors may help restore normal ovarian function, thereby enhancing menstrual regularity and ovulation rates in women with PCOS. This is particularly important for those seeking to conceive, as PCOS is a leading cause of infertility due to anovulation. Additionally, the anti-inflammatory properties of SGLT2 inhibitors may contribute to reducing the low-grade inflammation often observed in women with PCOS, further supporting reproductive health [25,29].

The study by Lempesis et al. (2023) explored the cardiometabolic effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors in women with polycystic ovary syndrome (PCOS) and revealed significant findings regarding their efficacy. The research highlighted that SGLT2 inhibitors effectively reduced body weight and improved insulin sensitivity among the study participants. Additionally, notable improvements were observed in cardiovascular risk factors, including reductions in blood pressure and favorable changes in lipid profiles. The study also reported a decrease in markers of systemic inflammation, which is particularly relevant given the inflammatory nature of PCOS. The article by Rakic et al., titled *"The Potential of SGLT-2 Inhibitors in the Treatment of Polycystic Ovary Syndrome.* The article concluded that while SGLT-2 inhibitors show promise for managing PCOS, especially for patients with metabolic complications, their use is still not widespread. Further clinical trials are needed to determine their long-term efficacy and safety compared to current treatments such as metformin and oral contraceptives. The article by Tzotzas et al. (2017) explores the use of glucagon-like peptide-1 (GLP-1) receptor agonists in treating obese women with polycystic ovary syndrome (PCOS). The study found that GLP-1 receptor agonists significantly contributed to weight loss and reductions in body mass index (BMI) in obese women with PCOS. There were also modest improvements in insulin sensitivity and reductions in androgen levels, which are commonly elevated in PCOS. However, the effects on menstrual regulation and reproductive function were not as pronounced in the observed data.

3.6 DPP-4 Inhibitors

Dipeptidyl Peptidase-4 (DPP-4) inhibitors, commonly known as "gliptins," represent a class of oral antidiabetic medications that have gained attention in managing insulin resistance in women with polycystic ovary syndrome (PCOS). These drugs work by inhibiting the enzyme DPP-4, which breaks down incretin hormones like glucagon-like peptide-1 (GLP-1). Incretins are responsible for enhancing insulin secretion and reducing glucagon release, especially post-meal. By inhibiting DPP-4, gliptins prolong the action of incretins, leading to improved insulin sensitivity and better glycemic control. This mechanism is particularly relevant in PCOS, where insulin resistance is a hallmark feature, often exacerbating the hyperandrogenism and menstrual irregularities characteristic of the condition. In women with PCOS, insulin resistance not only contributes to metabolic disturbances but also amplifies the overproduction of androgens, further disrupting ovarian function. Studies evaluating the use of DPP-4 inhibitors in PCOS have shown promising results in improving insulin sensitivity, which could have downstream benefits for weight management, ovulation, and hormonal balance. Although research on the direct effects of DPP-4 inhibitors in PCOS is limited, early studies suggest that they may be useful as an adjunct therapy, especially for women who are overweight or obese and suffer from insulin resistance. When combined with lifestyle interventions such as diet and exercise, DPP-4 inhibitors could help address the metabolic complications of PCOS without causing significant weight gain, a common side effect of some other antidiabetic drugs like insulin or sulfonylureas [30] Additionally, DPP-4 inhibitors are generally well-tolerated, with a low risk of hypoglycemia, making them an attractive option for long-term management in PCOS patients.

The study by Ferjan, Janez, and Jensterle (2018) evaluated the effectiveness of the DPP-4 inhibitor sitagliptin as a treatment option for metformin-intolerant obese women with polycystic ovary syndrome (PCOS). The pilot randomized study demonstrated that sitagliptin was well tolerated and showed promising results in improving insulin sensitivity and reducing fasting glucose levels. Additionally, there was a modest reduction in body weight and a favorable impact on androgen levels, which are often elevated in women with PCOS. The study by Jensterle, Goricar, and Janez (2017) investigated the effects of the DPP-4 inhibitor alogliptin, both alone and in combination with pioglitazone, on β-cell function and insulin sensitivity in women with polycystic ovary syndrome (PCOS) who were already receiving metformin treatment. The findings indicated that adding alogliptin, whether alone or in combination with pioglitazone, significantly improved β-cell function and insulin sensitivity compared to metformin alone. Participants demonstrated enhanced insulin secretion and reduced fasting glucose levels, indicating a positive effect on their overall metabolic profile. The study also noted that the combination therapy yielded additional benefits in managing body weight and lipid levels, suggesting a multifaceted approach to treating insulin resistance in this population. The study by Ferjan et al. (2017), involved a comparison between two groups: one receiving sitagliptin alongside a lifestyle intervention and the other receiving only the lifestyle intervention as a control. The findings indicated that women in the sitagliptin group experienced a significantly lower rate of weight regain compared to the control group. Specifically, the sitagliptin group showed a preserved weight loss over the treatment period, suggesting its potential role in maintaining weight management in this population. Additionally, metabolic parameters such as insulin sensitivity and glucose levels were also assessed, showing favorable changes in the sitagliptin group. The study concluded that sitagliptin could be an effective strategy for preventing weight regain in obese women with PCOS who are transitioning from liraglutide treatment [230,31].

4. COMBINATION THERAPIES

Combination therapies for managing polycystic ovary syndrome (PCOS) in the context of conventional antidiabetic treatments are gaining traction due to their potential to address both metabolic and reproductive aspects of the condition. PCOS is frequently associated with insulin resistance, leading to an increased risk of developing type 2 diabetes and cardiovascular diseases. Traditional treatments, such as metformin, primarily target insulin sensitivity and glucose metabolism, but their efficacy can be enhanced when combined with other pharmacological agents. One promising combination is metformin with DPP-4 inhibitors or GLP-1 receptor agonists. Metformin has been widely used as a first-line treatment for improving insulin sensitivity in women with PCOS. However, many patients do not achieve optimal weight loss or metabolic improvements with metformin alone [30]. Integrating DPP-4 inhibitors like sitagliptin can further enhance glycemic control and promote weight loss, addressing both insulin resistance and obesity in PCOS patients.This dual approach not only targets the metabolic aspects of PCOS but may also improve reproductive outcomes, such as ovulation and menstrual regularity, thereby reducing the risk of complications like infertility. Moreover, the combination of metformin with thiazolidinediones (TZDs), such as pioglitazone, has shown benefits in improving insulin sensitivity and lipid profiles in women with PCOS. TZDs work by activating peroxisome proliferator-activated receptors (PPARs), which play a crucial role in glucose and lipid metabolism. The synergistic effects of metformin and TZDs may lead to better management of metabolic dysfunctions associated with PCOS. Additionally, lifestyle modifications such as diet and exercise are often included in these combination therapies, further supporting weight loss and improving insulin sensitivity. Combination therapies can also include the use of hormonal contraceptives, which can regulate menstrual cycles and reduce hyperandrogenism in women with PCOS. When combined with antidiabetic medications, hormonal therapies can address both the endocrine and metabolic disturbances present in PCOS, making treatment more holistic and effective [31]. As the understanding of PCOS continues to evolve, future research will likely focus on optimizing these combination therapies to tailor treatments to individual patient needs, potentially improving overall outcomes for women suffering from this complex syndrome.

5. RISKS AND CHALLENGES OF ANTIDIABETIC THERAPY IN PCOS

5.1 Side Effects of Medications:

Antidiabetic medications are commonly employed in managing PCOS. However, these medications can have significant side effects that impact patient adherence and overall treatment outcomes. Metformin, the most frequently prescribed medication, is well-regarded for its ability to enhance insulin sensitivity and promote weight loss in women with PCOS [32]. Despite its benefits, Metformin is often associated with gastrointestinal side effects, including nausea, vomiting, diarrhea, and abdominal cramping. These symptoms can be severe enough to lead some patients to discontinue treatment or to take lower doses than prescribed, which undermines the potential benefits of therapy. Thiazolidinediones (TZDs), while effective in enhancing insulin sensitivity, have been linked to weight gain and fluid retention, which can exacerbate the already challenging symptoms of PCOS. This is particularly concerning as many patients struggle with weight management. Fluid retention is another common side effect of TZDs, leading to peripheral edema, which can cause discomfort and distress. GLP-1 receptor agonists, such as liraglutide, are gaining popularity for their efficacy in promoting weight loss and improving glycemic control. However, they are not without their challenges. Many patients experience gastrointestinal symptoms similar to those seen with Metformin, including nausea, vomiting, and diarrhea, particularly during the initial weeks of treatment as the body

adjusts to the medication. Although these symptoms often diminish over time, their presence can discourage patients from continuing therapy. There is also a potential risk of pancreatitis associated with GLP-1 receptor agonists, which necessitates close monitoring for symptoms of abdominal pain, especially in patients with a history of pancreatitis. DPP-4 inhibitors (e.g., sitagliptin, saxagliptin) are generally well tolerated, with minimal side effects reported. However, some patients may experience mild gastrointestinal symptoms, including nausea and diarrhea. There is also an increased risk of pancreatitis associated with this class of medications, similar to GLP-1 receptor agonists, which requires monitoring and patient education about the signs and symptoms of this serious condition. Additionally, skin reactions or hypersensitivity can occur, although these are relatively rare.

5.2 Insulin Sensitivity Variability

Insulin sensitivity variability is a significant consideration in the management of PCOS, particularly when utilizing antidiabetic therapies. The variability in insulin sensitivity presents several challenges in the pharmacological management of PCOS. Antidiabetic medications, such as Metformin, are commonly prescribed to improve insulin sensitivity and regulate metabolic processes. While Metformin is effective for many patients, those with less severe insulin resistance may not experience significant improvements, leading to frustration and potential discontinuation of therapy. This can create a cycle where patients who do not respond well to Metformin feel disheartened and may not seek alternative treatments or lifestyle interventions that could be beneficial. Furthermore, the dosage and choice of medication can greatly differ based on an individual's insulin sensitivity. For patients with higher insulin sensitivity, lower doses of Metformin may suffice, while those with greater resistance may require higher doses or additional medications. This necessitates ongoing monitoring and adjustments to treatment plans, which can complicate the management process and place additional burdens on healthcare providers and patients alike [33]. The fluctuations in insulin sensitivity not only affect the effectiveness of antidiabetic medications but also have broader implications for overall health. Women with varying degrees of insulin sensitivity may experience different metabolic challenges, such as weight gain, dyslipidemia, and increased risks of cardiovascular disease. Weight management can be particularly challenging; women with higher insulin resistance may struggle more to lose weight, leading to frustration and a decrease in quality of life.

5.3 Hormonal Imbalance

Hormonal imbalance poses a significant challenge in managing Polycystic Ovary Syndrome (PCOS) with antidiabetic therapy. While medications like metformin are effective in improving insulin sensitivity and addressing metabolic issues, they do not directly target the hormonal dysregulation that is characteristic of PCOS. Women with this condition often experience elevated androgen levels, leading to symptoms such as hirsutism, acne, and irregular menstrual cycles. These hormonal imbalances can severely impact a patient's quality of life and require additional therapeutic interventions to manage effectively. The complexity of treating hormonal imbalance complicates the overall management plan for PCOS patients. Many women may need to combine antidiabetic therapy with other treatments, such as hormonal contraceptives or anti-androgens, to achieve better control over their symptoms. This multifaceted approach can lead to difficulties in medication adherence, as patients may feel overwhelmed by the number of prescriptions they need to manage and the potential side effects associated with each [34,35]. Additionally, the lack of direct action on hormonal regulation by antidiabetic medications may result in patient frustration, particularly if they do not observe improvements in their symptoms despite diligent adherence to their prescribed treatment. Therefore, addressing hormonal imbalance is crucial for providing comprehensive care and ensuring that patients achieve optimal treatment outcomes in their management of PCOS.

5.4 Long-term Efficacy

Long-term efficacy is a critical concern in the management of Polycystic Ovary Syndrome (PCOS) with antidiabetic therapy, particularly regarding medications like metformin. While these drugs are effective in improving insulin sensitivity and may assist with weight management, their impact on the broader spectrum of PCOS symptoms over the long term remains uncertain. Studies suggest that while metformin can lead to improvements in menstrual regularity and ovulatory function, its effects on fertility and long-term metabolic health outcomes are not fully established. As such, patients may question the value of continued antidiabetic therapy, especially if they do not experience significant symptomatic relief or if their primary concerns, such as infertility, remain unaddressed. The uncertainty surrounding long-term efficacy can also pose challenges in treatment adherence [36]. Patients may become discouraged if they do not see tangible results from their medication, which can lead to inconsistent use or complete discontinuation. Moreover, the variable response to antidiabetic therapies among women with PCOS complicates the treatment landscape, as individual results can differ widely based on factors such as age, weight, and the severity of insulin resistance. This variability necessitates ongoing monitoring and adjustments to the treatment plan, requiring a collaborative approach between healthcare providers and patients. Thus, ensuring that patients understand the potential benefits and limitations of antidiabetic therapy is vital for promoting adherence and optimizing long-term health outcomes in women with PCOS.

5.5 Cultural Norms Around Family Planning and Fertility:

Family planning and reproductive wellness are extremely delicate subjects in numerous cultures, frequently encircled by customs and ideologies. PCOS-afflicted women may face fertility-related difficulties, which can cause worry and anguish,

particularly in cultures where motherhood is highly valued [37]. Women may have emotions of inadequacy as a result of cultural pressure to conceive, which may have an adverse effect on their mental health and willingness to seek antidiabetic treatments. Furthermore, talking about fertility treatments can be forbidden or stigmatized, which would further isolate women who are juggling the demands of society and managing their illness.

6. CONCLUSION

Since insulin resistance is a common feature of the illness, the research highlights the importance of antidiabetic drugs like metformin in enhancing the metabolic and reproductive health of afflicted women. Metformin is still the mainstay of treatment, but research into newer antidiabetic drugs like DPP-4 inhibitors and GLP-1 receptor agonists offers encouraging adjunct therapies that improve glycemic control and aid in weight loss, both of which lessen PCOS symptoms. Furthermore, a more complete approach that successfully controls menstrual periods and manages hyperandrogenism can be achieved by combining these pharmacological techniques with hormonal therapies. In order to improve patient outcomes, the article promotes a customised approach to treatment that takes into account each patient's unique metabolic profile and reaction to medicine. It is recommended that future studies look into the safety and long-term effects of these combination medicines as well as how they affect PCOS-afflicted women's general quality of life. Incorporating lifestyle changes, like dietary adjustments and physical exercise, into these treatment techniques is ultimately seen to be crucial for long-lasting health gains, providing a comprehensive strategy to treating the various PCOS indications.

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