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Adipose Tissue Dysfunction in PCOS

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Abstract

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine diseases among women of reproductive age; however, its aetiology is unclear. PCOS is linked to many metabolic manifestations and alterations such as obesity, insulin resistance, and cardiovascular diseases (CVD). Women with PCOS have intra-ovarian and systemic changes in their metabolite levels. Adipose tissue dysfunction plays a significant role in the pathophysiology of PCOS. Adipose tissue growth is disrupted by metabolic stress, leading to hypertrophy of adipocytes, which begin to express stress signals. Adipose tissue secretes autocrine and paracrine factors, called adipokines or adipocytokines. Adiponectin is an adipocyte-derived protein abundant in the bloodstream. Plasma adiponectin concentration is low in women with PCOS, obesity, CVD, and hypertension. Other adipocytokines with altered secretion in PCOS include leptin, resistin, apelin, visfatin, IL-6, IL-8, and TNF-α. Hormonal imbalance, untimely action of high LH, and consequent hyperandrogenism in women with PCOS may cause metabolic defects associated with adipose tissue dysfunction; however, there are no reports on the role of higher LH levels in adipose dysfunction and altered adipokine secretion. New medications with therapeutic potential have been developed that target adipokines for the treatment of PCOS. This review discusses the association between PCOS and altered adipokine production as a consequence of adipose dysfunction.

Keywords: Adipocyte, Adiponectin, Adipose Tissue, Follicle Stimulating Hormone, Luteinizing Hormone, PCOS

1. Introduction

Polycystic Ovary Syndrome (PCOS), or Stein-Leventhal syndrome, is a complex endocrine abnormality that affects 5 to 10% of women of reproductive age and accounts for 50-70 % of cases with anovulatory infertility. It is the most common endocrine disorder in women with menstrual irregularities and anovulation. PCOS is characterized by hyperandrogenism, anovulation, polycystic morphology of the ovary, and menstrual irregularities[1-3] [Figure 1]. One of the main endocrinological disturbances in women with PCOS is the increased levels of Luteinizing Hormone (LH), and consequently a high LH:FSH ratio[1-5]. Neuroendocrine defects in estrogen and progesterone feedback mechanisms lead to gonadotropin imbalance and hyperandrogenism in women[6]. High androgen levels also alter the hypothalamic inhibitory feedback of progesterone. Along with the reproductive anomalies observed in PCOS, metabolic defects including obesity, insulin resistance, T2DM, and CVD are also strongly associated with PCOS [Figure 1]. Women with PCOS also have an elevated risk of endometrial cancer[7] and early atherosclerosis[8].

In addition to overall obesity, women with PCOS are more likely to exhibit an abdominal or visceral fat distribution[9]. These depots are associated with an unfavorable metabolic profile and insulin resistance[10]. There is strong evidence linking androgen excess to insulin resistance[10]. Furthermore, hyperinsulinemia stimulates ovarian androgen production and decreases the hepatic production of Sex Hormone-Binding Globulin (SHBG)[4,10,11]. Some studies have strongly suggested that genetic factors play an important role in PCOS. Many potential genes implicated in insulin resistance, secretion, and ovarian and adrenal steroidogenesis have been positively associated with PCOS[10,12]. β-cell dysfunction in addition to peripheral insulin resistance is reported in women with PCOS[4,13].

Metabolic abnormalities and obesity are reported in 50-60 % of women with PCOS, strongly associated

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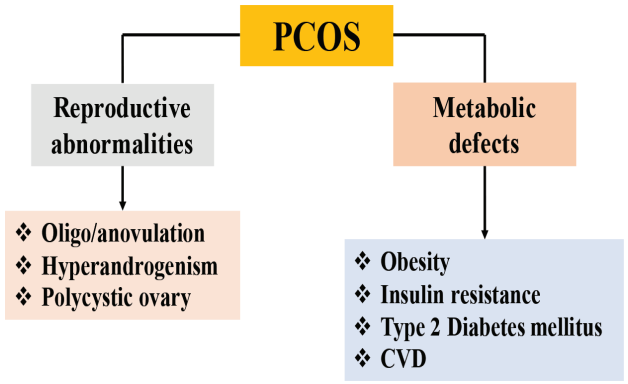

Figure 1. PCOS is characterized by reproductive abnormalities that lead to infertility, and these women are more likely to develop metabolic disorders.

with a greater waist-to-hip ratio, larger adipocytes, decreased adiponectin levels, and lower lipoprotein lipase activity[8,14]. In women with PCOS, the prevalence of dyslipidemia was reported to be 70%. Low-density lipoprotein cholesterol, free fatty acid, and triglyceride levels are elevated in women with PCOS[15]. On the contrary, high-density lipoprotein cholesterol levels are reduced in women with PCOS[16,17]. Numerous studies have established that Non-Alcoholic Fatty Liver Disease (NAFLD) is highly prevalent in women with PCOS[18]. The close association between PCOS and metabolic syndrome has led to the assumption that dysregulation of adipose tissue function may contribute to many of the metabolic abnormalities observed in women with PCOS, as it is known to occur in metabolic syndrome. Here, we discuss the association of altered adipokine production as a consequence of adipose dysfunction in women with PCOS.

2. Methods

We searched PubMed for articles published in English. The search terms used were as follows: polycystic ovary syndrome, polycystic ovary disease, LH, hCG, insulin resistance, adipocytes, White Adipose Tissue (WAT), adipocytokines, adipose tissue dysfunction, obesity, visceral obesity, and metabolic syndrome. Studies that evaluated adipose tissue function in women with PCOS identified by the National Institute of Health (1990), Rotterdam Criteria (2003), and/or Androgen Excess and PCOS Society (AE-PCOS) criteria (2006) and compared findings with controls with normal Body Mass Index (BMI) were considered eligible for inclusion. We broadened the search to include references from the retrieved articles.

3. Adipose Tissue Dysfunction in PCOS

Adipose tissue is a loose connective tissue composed of mature adipocytes, pre-adipocytes, mesenchymal cells, and various immune cells. Mesenchymal cells differentiate into preadipocytes and mature adipocytes[19]. The main function of adipose tissue is to insulate the body, store Free Fatty Acids (FFAs) after food consumption, and release FFAs during a fasting state to maintain a suitable energy level. After triglyceride hydrolysis, FFAs are absorbed from the circulation in adipose tissue during the postprandial period. Following the hydrolysis of TG from triglyceride-rich lipoproteins (chylomicrons, Very Low-Density Lipoprotein Cholesterol (VLDL-C), and their remnants) by lipoprotein lipase, adipose tissue absorbs FFAs from the blood during the postprandial period. Hormone-Sensitive Lipase (HSL) breaks down intracellular TG to release fatty acids. Changes in adipose tissue growth occur owing to the differentiation and proliferation of adipocyte progenitors, which increase the number of adipocytes and replace larger, older, and defective adipocytes. In response to chronic changes in energy balance and nutrient content, the proliferation of preadipocytes, differentiation into mature adipocytes, and adipocyte growth are affected, leading to hypertrophy, and eventually adipocyte apoptosis and/or necrosis[20]. Furthermore, nutritional status alters the rates of angiogenesis, extracellular matrix remodeling, and relative distribution of the immune cell population in adipose tissue[21]. The cells collectively work as endocrine organs, secreting a variety of signaling chemicals that influence feeding behavior, energy expenditure, metabolism, reproduction, and endocrine and immunological functions[22]. As the size and number of fat cells are associated with insulin sensitivity, glucose uptake, and fatty acid uptake, alterations in the function and cellular makeup of fat tissue can alter the metabolic state and result in medical complications[23,24].

Adipose tissue dysfunction is referred to as a state of hypersecretion of adipocytokines, which are pro-inflammatory, pro-atherogenic, and pro-diabetic, along with reduced anti-inflammatory and adiponectin secretion. An imbalance between pro- and anti-inflammatory adipokines can lead to insulin resistance, low-grade inflammation, and hypertension. Both lean and obese

women with PCOS have abnormal adipose tissue shape, which is considered a major characteristic of adipose tissue dysfunction[14,25-27]. Adipocytes have the ability to store lipids, perceive regional and systemic cues, and respond by controlling the amount of energy mobilized by secreting paracrine and endocrine hormones. In addition to their function in glucose and lipid metabolism, adipocytes release endocrine factors that control glucose homeostasis, insulin sensitivity, inflammation, and tissue repair[28]. Adipocytes release exosomal microRNAs, peptides (adipokines), and lipids (lipokines)[28], and dysregulated adipocytokine production leads to the development of common metabolic disorders[29,30]. Accumulation of adipose tissue increases the production and secretion of Tumor Necrosis Factor α (TNF-α) and resistin, which can play an important role in the development of insulin resistance in obese patients[29,30]. In obesity, adipocytes become enlarged to store excess energy. Adipocyte hypertrophy (an increase in adipocyte cell size) is caused by changes in adipocyte storage or lipolytic capacity. Under these conditions, adipocytes in adipose tissue are hypertrophic, insulin-resistant, unable to store triglycerides, and exhibit reduced energy expenditure. As a result, fatty acids are released into the bloodstream and build up in other organs, disrupting the metabolism which is a symptom of chronic metabolic illnesses like T2DM and CVD[28] [Figure 2].

Adipose tissue is characterized by hypertrophic adipocytes, a pro-inflammatory gene expression profile, dysregulated secretion of adipose-specific proteins, cytokines, and other proteins, and an increase in the macrophage and immune cell population in obese people[31,32]. Similar alterations were observed in adipose tissues of women with PCOS. Additionally, hypertrophic adipocytes lead to decreased adiponectin[32]. In PCOS, the pro-inflammatory condition of obesity promotes insulin resistance and atherosclerosis, and adipose tissue expansion leads to hypoxia-related adipocyte death, which induces an influx of Mononuclear Cells (MNC) into the stromal-vascular compartment[21]. MNCs undergo morphological changes and develop into macrophages. The primary source of TNFα and interleukin 6 (IL-6) synthesis in adipose tissue is macrophages, which also promote cytokine production in adipocytes[33]. Studies have demonstrated that IL-6 and TNF-α levels are elevated in PCOS[34,35]. Adipocytes larger than 75 µm are associated with insulin resistance, increased insulin levels, and metabolic syndrome[36]. Adipocyte diameter is usually increased by approximately 25% in women with PCOS compared to obese control women without PCOS[26,37]. Hypertrophic adipocytes are insulin-resistant[31]. Insulin receptor phosphorylation in adipocytes is reduced in women with PCOS, resulting in decreased GLUT4

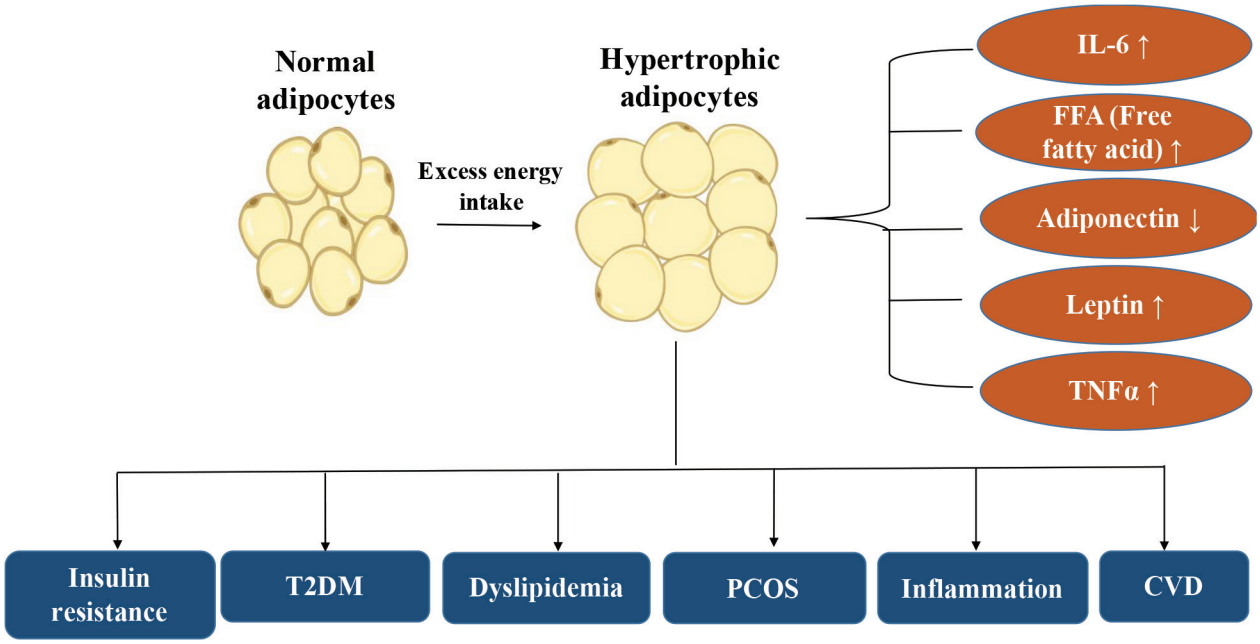

Figure 2. Due to excess energy intake, adipocytes become hypertrophic, insulin resistant, and unable to store triglycerides and fatty acids that are released into the bloodstream and build up in other organs, leading to ectopic lipid accumulation and disruption of metabolism, symptoms of chronic metabolic illnesses such as type 2 diabetes mellitus, PCOS, and CVDs.

translocation and altered insulin-dependent glucose uptake[38]. A study conducted by Chang *et al.* revealed that women with PCOS have lower insulin-stimulated serine phosphorylation of Glycogen Synthase Kinase-3 β (GSK3β)[19]. Adipocytes from women have increased activity and tyrosine phosphorylation of GSK3β. These findings imply that GSK3β is hyperactivated in PCOS[39]. Subcutaneous abdominal preadipocytes cultivated *in vitro* from women with PCOS and controls were studied by Corbould and Dunaif[40]. They found no differences in basal glycogen synthesis or glucose transport in preadipocytes in women with PCOS and controls, proving that, unlike skeletal muscle, the adipocyte lineage from PCOS women does not appear to have intrinsic abnormalities in insulin sensitivity[40]. The correlation between hypertrophic adipocytes and insulin resistance *in vivo* is therefore probably caused by external factors such as elevated circulating testosterone levels[41]. In patients with diabetes or glucose intolerance, adipocyte size is increased compared to those with normal glucose tolerance[41,42].

Studies have shown that subcutaneous adipocytes from women with PCOS have lower levels of Hormone-Sensitive Lipase (HSL) expression and activity, as well as decreased catecholamine-mediated lipolysis. On the other hand, women with PCOS and hyperinsulinemia have increased catecholamine-induced lipolysis in adipocytes, raising blood-free fatty acids and causing dyslipidemia. As a result, the liver produces more free fatty acids, which increases the blood levels of Very Low-Density Lipoprotein (VLDL) and Triglycerides (TG)[43]. Paradoxically, some studies have shown that subcutaneous adipocytes from PCOS women have lower levels of hormone-sensitive lipase expression and activity as well as decreased catecholamine-mediated lipolysis[37,27]. A study conducted by EK *et al.* revealed marked lipolytic catecholamine resistance in lean PCOS women compared with healthy non-obese control women, which includes a 7-fold decrease in lipolytic sensitivity, and maximal lipolytic reaction to endogenous catecholamine noradrenaline stimulus was reduced by approximately 35%[27]. The expression of CD36/Fatty acid translocase, a key membrane glycoprotein involved in the transportation of fatty acids, is upregulated in adipocytes of women with PCOS, and its expression correlates with insulin resistance[44,45]. Adipose tissue produces pro-inflammatory cytokines and secretes angiotensin II, which increases NADPH oxidase activity. NADPH oxidase is the main pathway for Reactive Oxygen Species (ROS) production in adipocytes[46].

Using microarray expression profiling analysis, Lee *et al.* studied the adipocytes of obese and non-obese subjects[31]. In contrast to non-obese individuals, 52 of 54 inflammatory/immune response genes were upregulated in the adipocytes of obese individuals[31]. Studies have also revealed that PCOS alters the gene expression profile of adipose tissues. Several genes are aberrantly expressed in the omental adipose tissue of women with PCOS[47]. Variations in genes related to immunological response, cell development, metabolic syndrome, lipid metabolism, and insulin signaling have been discovered[47]. Insulin resistance in PCOS may be caused by the dysregulation of factors secreted by hypertrophic adipocytes[41].

Studies have reported that hyperandrogenism increases adipocyte size in the adipose tissue of women with PCOS, which can lead to adipose tissue dysfunction[48]. These findings were supported by studies in rodents, which demonstrated that overexposure to androgens during the early postnatal and peri-puberty stages was linked to hypertrophic adipocytes in subcutaneous and visceral adipose tissue and insulin resistance[49-51]. However, in female sheep and monkeys, prenatal exposure to testosterone has been linked to reduced adipocyte size[52,53]. These contrasting results may be due to the species or nature of the androgens. Human pre-adipocytes have also shown androgen-driven suppression of adipocyte development, and anti-androgenic drugs were able to partially reverse this effect[54]. However, some studies have revealed that the parameters most strongly linked to insulin resistance in women with PCOS are increased adipocyte size, reduced adiponectin levels, and increased waist circumference, but not androgen excess[26].

4. Adiponectin and PCOS

White adipocytes are important secretory cells that release various fatty acids, lipids, and proteins. Leptin and adiponectin are the most significant protein hormones produced and released by adipocytes[55]. Adiponectin is a 224-amino acid protein with a molecular weight of 30 kDa that was first discovered in 1995[56]. It is also known as adipocyte complement-related protein 30 kDa (ACRP30). Women were shown to have significantly higher adiponectin levels than men[57]. Mice also show similar sexual dimorphism[58], wherein tissue adiponectin levels have been reported to rise

early in puberty, which can further increase post-castration in males or ovariectomy in females. Adiponectin expression is inhibited by estrogen *in vitro*. The human adiponectin gene is located on the chromosome 3q27. In a native French cohort, Froguel *et al.* identified a human chromosome 3q27 locus that is associated with diabetes susceptibility[59], and Comuzzie *et al.* showed that this locus is strongly associated with metabolic syndrome in individuals of European descent[60]. Adiponectin is a key factor in regulating insulin sensitivity. Adiponectin promotes beta-oxidation of fatty acids by myocytes, decreases plasma fatty acid levels[61], and inhibits hepatic glucose synthesis[62]. Adiponectin was positively correlated with High-Density Lipoprotein (HDL) and inversely correlated with Body Mass Index (BMI), percentage of body fat, waist-to-hip ratio, glucose, insulin, and triglycerides. Hypoadiponectinemia is closely associated with IR[42,63] and high adiponectin levels are associated with low insulin resistance and a healthy lipid profile[63]. Recombinant adiponectin treatment improves insulin resistance in obese mice with low circulating adiponectin levels[64] and prevents the onset of diet-induced insulin resistance[65]. Circulating adiponectin levels are decreased in obesity[57], T2DM[66] CVD, and hypertension[67].

Increased adiponectin levels have been linked to improved glucose homeostasis, smaller adipocytes, and less visceral fat, all of which have protective functions against metabolic health[25]. Furthermore, increased paternal adiponectin transcription has been shown to protect against adipose tissue dysfunction[25]. In women with PCOS, lowered adiponectin concentrations are closely related to Heart Rate Recovery (HRR) blunt[68]. Adiponectin has been reported to have anti-inflammatory, anti-atherogenic, and insulin-sensitizing activities[42]. Women with PCOS have significantly decreased adiponectin levels[69-72] linked to increased inflammation and higher adipokine levels[73], implying that dyslipidemia is directly associated with inflammation. Women with PCOS have considerably lower Adiponectin/Leptin (A/L) and higher HOMA/Adiponectin (H/A) ratios, respectively[74]. A recent study demonstrated that the A/L ratio is markedly reduced in women with PCOS; however, there is no correlation with BMI or IR[75]. Adiponectin expression is reduced by androgens by reducing their secretion[76]. Although adiponectin does not appear to be directly involved in the pathophysiology of PCOS, it may interact with steroid production or its action in women with PCOS[77]. Adiponectin levels may help identify high-risk for PCOS in women since low adiponectin levels can serve as a predictor of the development of T2DM and CVD in women.

In some studies, adiponectin secretion was shown to be independent of BMI or IR. As both lean and obese women with PCOS have abnormal adipose tissue morphology independent of BMI or IR, there seems to be another factor(s) influencing adipose tissue biology in PCOS. *In vitro* studies have demonstrated that differentiated pre-adipocytes and human adipocytes express LHCGR mRNA. Furthermore, fully differentiated adipocytes had a three-fold higher level of LHCGR mRNA than confluent or early differentiating preadipocytes. Thus, human preadipocytes are directly influenced by hCG *in vitro*, which affects their ability to proliferate and differentiate[78]. As LH levels are higher in women with PCOS, there may be a possible link between higher LH levels and adipose tissue dysfunction in PCOS [Figure 3].

Additionally, higher LH levels, and a high LH: FSH ratio may contribute to the hyperandrogenism associated with adipose dysfunction in PCOS. Androgens influence adipocyte size and activity. Hyperandrogenism has been linked to lower adiponectin levels, leading to insulin resistance, as adiponectin is an insulin sensitizer[69]. In women with PCOS, increased adipocyte size and decreased adiponectin levels are characteristics most closely linked to insulin resistance[26]. Adiponectin overexpression is linked to reduced adipocyte size, increased mitochondrial density in adipocytes, and the transcriptional upregulation of factors involved in lipid storage[79,80].

5. Role of Other Adipocytokines in PCOS

Adipokines, also known as adipocytokines, are a class of bioactive proteins and immunological agents secreted by the adipose tissue. Adipokines play crucial roles in the regulation of glucose and lipid metabolism, energy homeostasis, insulin sensitivity, immunity, and inflammation. Adipokines are categorized as inflammatory or anti-inflammatory. The adipokines that are increased in obese individuals are classified as inflammatory adipokines. Numerous studies have demonstrated the role of adipokines in the pathophysiology of PCOS. Altered adipokine secretion leads to IR in obese individuals, and IR may be an important link between adipokines and polycystic ovaries. A study conducted by Mahde *et al.* revealed that IL-6, IL-18, TNF-α, RBP-4, Resistin, leptin, insulin, LH, testosterone, and free testosterone levels were elevated in women with PCOS[81]. Another study conducted on the Indian population by Ram *et*

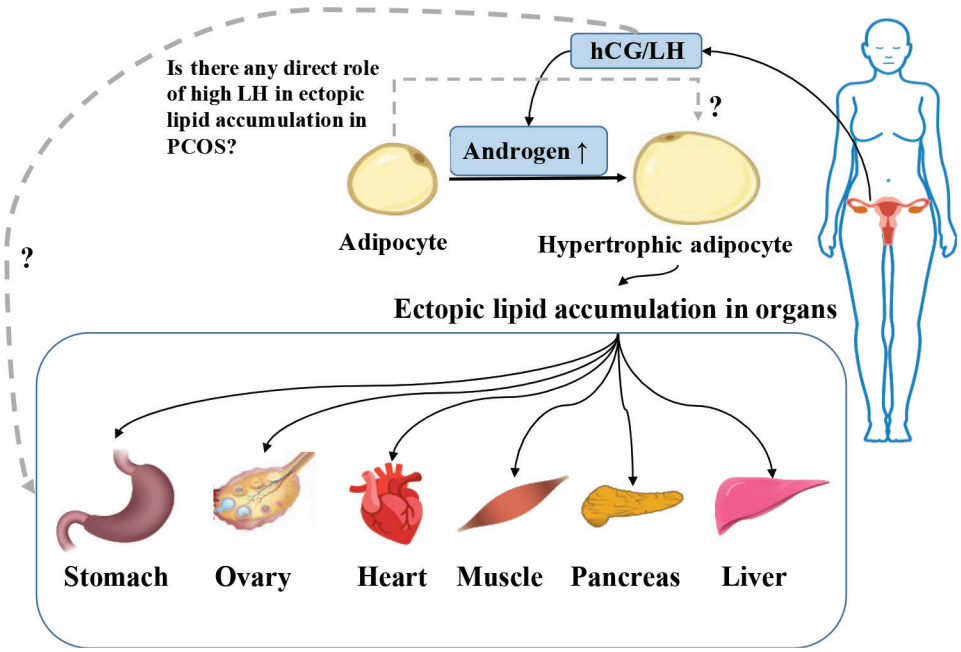

Figure 3. Hyperandrogenism is linked to adipose tissue dysfunction, leading to hypertrophic adipocytes and decreased adiponectin secretion, which leads to ectopic lipid accumulation. Here, we illustrated the possible direct role of hCG/LH in abnormal adipose tissue morphology and adipose tissue dysfunction in PCOS.

al. revealed that underweight, overweight, obese, and morbidly obese PCOS women had elevated serum leptin and serum TNF-α, IL-6, and IL-8 levels compared to women with normal weight and underweight non-PCOS. Leptin plays a key role in regulating female reproduction, and leptin resistance in underweight and obese women with PCOS may be caused by impaired leptin expression in ovaries. Elevated TNF-α, IL-6, and IL-8 levels are strongly correlated with Insulin resistance[82]. Studies have demonstrated that TNF-α induces IR in animal models and cultured cells. Expression of TNF-α is also significantly elevated in the adipose tissue of obese human patients, which is strongly associated with hyperinsulinemia[29]. Hence, overproduction of TNF-α by adipose tissue contributes to insulin resistance. A recent study shows that both normal-weight and obese PCOS women have lower plasma omentin-1 levels than non-PCOS women[83]. Omentin-1 is a novel adipokine produced by the visceral white adipose tissue. It has anti-inflammatory, anti-obesity, and antidiabetic effects[84]. Apelin is an adipokine that contributes to the endocrine regulation of glucose metabolism. There are conflicting reports on serum apelin levels in women with PCOS. Apelin might be a contributing factor in the development of PCOS[85]. Chemerin is an adipokine that induces insulin resistance and modulates adipogenesis and adipocyte metabolism. Women with PCOS have elevated chemerin levels compared with controls[86]. Retinol-Binding Protein 4 (RBP4) is secreted by adipocytes, hepatocytes, and macrophages. A study revealed that women with PCOS in Asia have elevated RBP4 levels compared with controls[87]. Visfatin is primarily expressed in human visceral fat, bone marrow, the liver, and muscles. There are conflicting studies on visfatin levels and expression in women with PCOS. Most studies have revealed higher visfatin levels in the ovary[88]. Visceral adipose tissue-derived serpin (Vaspin) is a member of the serine protease inhibitor family and is secreted mainly by visceral and subcutaneous adipose tissues. Vaspin expression is strongly associated with lipid metabolism and IR. Numerous studies have demonstrated that women with PCOS have higher vaspin levels which contributes to IR[88]. Lipocalin 2 is a novel adipokine majorly expressed in white adipose tissue. There are conflicting studies on lipocalin 2 levels in women with PCOS. Some studies have demonstrated that women have higher lipocalin 2 levels, some suggest that lipocalin 2 levels are lower in women with PCOS than in controls, while others have shown no significant difference between women with PCOS and controls[88].

Several studies have revealed a strong association between adipose tissue dysfunction, altered adipokine secretion, and PCOS in the Indian population. A study

conducted by Nambiar *et al*. in a south Indian population demonstrated that women with PCOS have lower adiponectin levels and higher resistin levels than controls. They also suggested that serum adiponectin levels might be a potential indicator of abdominal fat in PCOS[89]. IL-6 regulates ovarian steroid synthesis, follicular maturation, fertilization, and implantation. The human IL-6 gene is situated at the 7p21-24 locus and has an upstream promoter of 303 bp. The IL-6 promoter's transcription rate is influenced by frequent G/C Single Nucleotide Polymorphisms (SNP) at np -174. A study conducted by Tumu *et al*., for the first time, revealed a strong association between IL-6–174G/C SNP and PCOS in South Indian women. Compared to controls, there was a substantial increase in the G/G genotype frequency, indicating that the "G" allele may be regarded as a risk factor for PCOS. Thus, the IL-6 gene can be considered a potential candidate for PCOS treatment[90]. As mentioned earlier, Ram *et al*. concluded that leptin, TNF-α, IL-6, and IL-8 levels are elevated in South Indian PCOS subjects compared with controls[82].

6. Novel Therapies Targeting Adipocytokines for PCOS and Related Disorders

New drugs with therapeutic potential have been developed to target adipokines for PCOS treatment. Recombinant proteins, peptides, and therapeutic antibodies have been used in adipokine-targeting protein therapies. With encouraging results in murine models, anti-TNF-α therapy has been proposed as a potential treatment for PCOS[91]. Osmotin is an antifungal stress-responsive protein that is similar to adiponectin in terms of structure and functionality. Osmotin was identified as a mammalian adiponectin homolog by a variety of *in vitro* and *in vivo* studies. In ob/ob and db/db mice, osmotin prevents Non-Alcoholic Fatty Liver Disease (NAFLD)[92]. Apelin agonists and antagonists both have a positive impact, and further research is needed to fully understand the potential of recently developed therapeutic biologics that target apelin[92]. The anti-ChemR23 nanobodies CA4910 and CA5183, have been developed as new functional antibodies that target the chemerin receptor. CA4910 and CA5183 may represent novel strategies for investigating the involvement of the chemerin/ChemR23 system in the emergence of PCOS and related disorders[92]. Although only a few monoclonal antibody medications that target adipokines have been investigated in PCOS preclinical models, they have already demonstrated tentative therapeutic results in a number of diseases[92]. Adipokine receptor agonists are mostly used to treat diabetes-associated conditions. PCOS is often associated with diabetes. Therefore, these agonists may help with PCOS symptoms. An oral drug called AdipoRon stimulates AdipoR1 and AdipoR2 expression in skeletal muscle and the liver, and the effects of AdipoRon are highly similar to those of adiponectin. AdipoRon treatment reduced IR and glucose intolerance in wild-type mice fed a high-fat diet. Additionally, in mice treated with corticosterone, AdipoRon reverses abdominal adiposity, hyperleptinemia, and hyperinsulinemia[92]. Adipo anti-inflammation agonist (AdipoAI) is a newly discovered and powerful AdipoR agonist. AdipoAI is structurally similar to AdipoRon and has potent anti-inflammatory effects in animal models of diet-induced obesity and Lipopolysaccharide (LPS)-induced septic shock[92]. Novel drugs that target adipokines may open new therapeutic possibilities for PCOS.

7. Summary

Adipose tissue dysfunction is a crucial factor in PCOS, and both lean and obese women with PCOS have abnormal adipose tissue morphology. In PCOS, adipokine, cytokine, and chemoattractant protein secretion are enhanced in a pro-inflammatory manner, resulting in lower insulin sensitivity via altered glucose transporters, and thus decreased glucose absorption. Considering the intricate metabolic environment associated with PCOS, including hyperandrogenism, hyperinsulinemia, central adiposity, and chronic low-grade inflammation, it is challenging to identify the factors (s) that cause adipose tissue dysfunction. Adiponectin and adipocyte size are the strongest predictors of insulin resistance in women with PCOS. Understanding whether high LH levels cause metabolic defects and adipose tissue dysfunction in PCOS would help diagnose or treat the metabolic complications associated with this reproductive disease.

8. Abbreviations

ACRP30, Adipocyte Complement-Related Protein 30 kDa; BMI, Body mass index; CD36, Cluster of differentiation 36/ Fatty acid translocase; CVD, Cardiovascular diseases;

FF, Follicular fluid; GLUT 4, Glucose transporter type 4; GSK3β, Glycogen synthase kinase-3 β; HDL, High-density lipoprotein; HRR, Heart rate recovery; HSL, Hormone-sensitive lipase; IL-6, Interleukin 6; IGT, Impaired glucose tolerance; IR, Insulin resistance; LH, Luteinizing hormone; LPL, Lipoprotein lipase; MNC, Mononuclear cell; NADPH, Nicotinamide adenine dinucleotide phosphate; NAFLD, Nonalcoholic fatty liver disease; ROS, Reactive oxygen species; SHBG, Sex hormone binding globulin; SNP, Single nucleotide polymorphism; T2DM; Type 2 diabetes mellitus; TG, Triglycerides; TNF α, Tumor necrosis factor α; VLDL, Very-low-density lipoprotein.

9. References

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