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A Review: Proteins Involved in the Major Symptoms of Polycystic Ovarian Syndrome

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Abstract:

Polycystic ovary syndrome (PCOS) is an endocrine, metabolic, reproductive disorder affects around 6.5 - 18% of women at the reproductive age. Since symptoms are not universal in all patients its diagnosis has become more controversial. There are various physical and internal symptoms of PCOS such as irregular menstrual cycles, infertility, obesity, insulin resistance, hirsutism, acne, alopecia. Hyperandrogenism can be regarded as one of the culprits behind all the symptoms, whereas the study of proteins with respect to a symptom is lacking, so the present review is focused on the involvement of some proteins in the pathogenesis of PCOS. So, working in deep with these aspects will be useful in the future to better understand the biochemical, physiological, and immunological aspects and to identify the diagnostic biomarkers of PCOS and for the better therapeutic approach.

Key Words: PCOS, Proteins, Physical symptoms, Internal symptoms.

1. Introduction:

Polycystic ovarian syndrome (PCOS) is a complex, heterogeneous endocrine disorder that affects the women at the reproductive age. The phenotypic features leading to the significant controversy on the diagnostic criteria. Every individual experience variable symptom of PCOS and the diagnosis need to be tailored accordingly. The prevalence rate of PCOS is approximately 4-10% worldwide, but the rate is higher in India that is 20-26% [Chatterjee, 2020]. Oligoanovulation, infertility, metabolic abnormalities, hirsutism, acne, alopecia, obesity/overweight, hyperandrogenism, glucose intolerance, depression and anxiety disorder, endometrial hyperplasia are some of the clinical features of PCOS [Abbott DH 2017, Astapova O 2019]. Apart from these morphological features, alteration in metabolic profiles like insulin resistance is a major symptom of PCOS. Hyperinsulinemia can lead to diabetes mellitus and also high insulin level is responsible for the deposition of fat around the abdomen. Other than these, prolonged PCOS condition may lead to hypertension, cardiovascular issues, dyslipidemia [Haciveliogl S 2013].

In this review article, we have discussed some of the proteins involved in the major symptoms of PCOS. A protein mutation in the PCOS condition is associated with multiple inherited and environmental factors [Panda PK 2016]. Excessive androgen hormone secreted by ovaries or adrenal glands is the main cause of hirsuitism in PCOS [Barbieri RL 2020]. Absence of menstruation in the reproductive age (Amenorrhea) is associated with insulin resistance (IR) and hyperandrogensim [Panidis D 2013]. High levels of androgen, low sex hormone binding globulin (SHBG), insulin-like peptide 3 (INSP3) and antimullerian hormone (AMH) are some of the differently expressed proteins in the menstrual irregularities [Pelusi C 2013]. Hyperandrogenism and oligo-anovulation at the reproductive age may cause infertility in PCOS [Melo AS 2015]. Tumor necrosis factor alpha-induced protein 6 (TNFAIP6); lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1); cluster of differentiation 14(CD14); syndecan-4; and amphiregulin are some of the differently expressed proteins in the infertile condition [Ambekar AS 2015]. Acne is another characteristic of PCOS, which is mainly due to increased testosterone level. Acne severity is associated with the higher concentrations of total testosterone, free testosterone, dehydroepiandrosterone sulfate, and free androgen index (FAI) [Franik G 2018].

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Molecular causes of insulin resistance have been identified as an excessive phosphorylation of serine residues of the insulin receptor and the mutations in insulin receptor substrate-1 (IRS-1) [Pasquali R 2002]. Epiregulin (EREG), inhibin βA, insulysin (IDE), platelet-derived growth factor-D (PDGF-D) and kininogen (KNG1) are the differently expressed proteins with the low level of progesterone in serum of PCOS patient. EREG plays a prominent role in regulating the follicle maturation and ovarian functions. However, EREG and inhibin βA with the low progesterone level may be a novel biomarker for PCOS [Zheng Q 2018]. Elevated insulin like growth factor- 1(IGF-I) may be most common cause of anovulation [Chavarro JE 2008]. Since not much studies have been undertaken on the proteomic aspects of the symptom's, very limited information is available in this area, detailed studies are needed for better understanding of the disease.

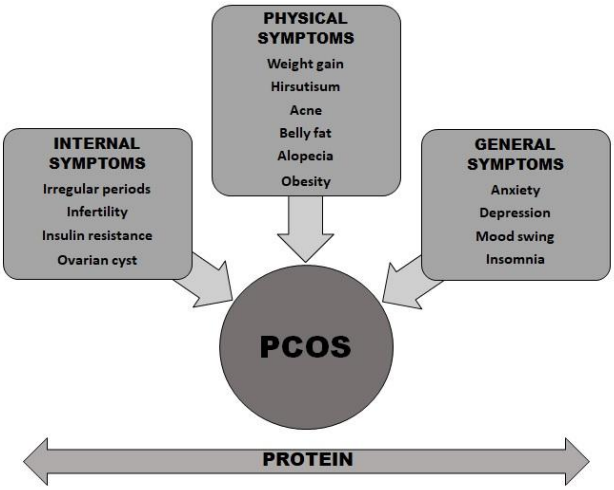

Fig. 1 Schematic diagram showing the involvement of protein in the major symptoms of PCOS.

1.1 Hirsutism

Hirsutism is the condition of excessive hair growth on the face and other body parts of the body in women [Mara Spritzer P 2016]. Around 75% of PCOS patients shows symptoms of hirsutism [Sardana K 2016]. Ferriman-Gallwey (FG) is a measure to grade the hirsutism [Hacivelioglu S 2013]. Hirsutism is mainly due to hyperandrogenism. Androstenedione, testosterone, DHT (dihydrotestosterone), Androstenediol, DHEA (dehydroepiandrosterone), DHEA-S are some of the androgen hormones. Elevated androgens have a role in hirsutism. Elevated serum androstenedione may worsen the PCOS features and could be a valuable marker of biochemical hyperandrogenemia [Georgopoulos NA 2014]. Literature shows that independently elevated androstenedione does not harm PCOS further, a higher androstenedione/free testosterone-ratio was independently associated with a beneficial metabolic profile [Lerchbaum E 2014]. Free testosterone, total testosterone, free DHT, and the ratio of total testosterone and DHT ratio are significantly higher when compare to control. Whereas no difference was found between the total DHT level in PCOS and control [Münzker J 2015]. Androstenediol, showed elevation in the serum of PCOS women when compared to the control [Lobo RA 1983]. However, it is found that androstenediol is a molecule that could be involved in PCOS by stimulating cell proliferation [Plaza-Parrochia F 2014]. Recent literature shows that DHEA inhibited the proliferation and promoted the apoptosis of ovarian granulosa cells through down regulating the expression of inflammatory cytokine IFN- γ (Interferon gamma) and may serve as a potential inflammatory biomarker for PCOS detection [Li Y 2019]. Several studies support the significant higher levels of serum DHEAS in PCOS [Mardanian F 2011]. Hirsutism is also associated with lower psychological quality of life [Chaudhari AP 2018]. The link between circulating androgen and hirsutism with higher levels of PSA (Prostate-specific antigen) was observed in PCOS [Mardanian F 2011, Wu ZH 2019]. Serum complexed PSA (cPSA) and free PSA (fPSA) were three times more than that of control when compared to PCOS. These are the novel biomarkers for hyperandrogenism in PCOS which can be the regulator for the disease condition [Diamandis EP 2017]. The detailed role of PSA can benefit the clinical diagnosis of PCOS. Recent literature on proteomic profiles in hyperandrogenism syndrome spots 6 proteins differently expressed in T lymphocyte cells of PCOS compared to healthy control. Out of these 6 proteins 4 were down-regulated, such as Cathepsin D involved in apoptosis, proliferation, and angiogenesis process [Liaudet-Coopman E 2016]. Raf kinase inhibitor protein invoved in several signalling cascades, can inhibit activation of nuclear factor kB (NF-ϰB) [Yeung KC 2001]. Mitochondrial Three-hydroxyisobutyrate dehydrogenase and protein disulfide-isomerase A3 are both involved in insulin resistance and adipocyte differentiation [Misiti S 2010]. On the other hand, some proteins involved in insulin metabolism called superoxide dismutase [Miller AF 2004] and platelet basic protein were down-regulated [Misiti S 2010].

Since hyperandrogenism is the main cause of hirsutism the further detailed work on these expressed proteins may benefit the treatment procedure of hirsutism as well as PCOS. Symptoms of hirsutism vary among the races. It is found mild or absence of hirsute in South Asian and Scandinavian origin, but Middle Eastern and Mediterranean origin patients are more affected by hirsutism [Patel S 2018].

1.2 Irregular Menstrual Cycles (Amenorrhea/Oligomenorrhea/Polymenorrhea)

One of the defining characteristics of PCOS is anovulation or oligoovulation (infrequent or irregular ovulation) [Harris HR 2017]. The menstrual disturbance doesn't appear in all PCOS woman but approximately 85-90% of women with oligomenorrhea are ended up with PCOS. Along with PCOS, body size, alcohol intake, smoking, physical activities are some factors that may responsible for the anovulation or oligoovulation condition [Harris HR 2017]. As per the study obesity is one of the causes of irregular menstruation and even some evidence showed that 5-10% weight loss improved the ovulation and cycle regularity. Literature has shown varieties of causes behind this, in few studies high level of androgen and low level of sex hormone-binding globulin (SHBG), contributes to the irregular menstrual cycles in PCOS [Harris HR 2017]. Follicle stimulating hormone (FSH) may have a stronger effect on ovulation dysfunction [Catteau-Jonard S, 2019]. Insulin like peptide 3(INSL-3) and Anti Mullerian Hormone (AMH) levels were significantly increased and correlated with irregular menstrual cycles in PCOS women, which may affect the function of the granulose cells by producing higher androgen which is responsible for anovulation [Pelusi C 2013]. Elevated levels of serum estradiol (E2) were observed since estradiol is the hormone produced by the ovary and dysfunction of the ovary may be due to this variation [Çınar M, 2016, Abbott DH 2017].

1.3 Infertility

Infertility is one of the conditions linked to polycystic ovarian syndrome (PCOS). It is the condition where couples are not able to conceive because of some medical condition. One in seven couples is getting affected by infertility and the number is increasing day by day. There is a significant proportion of these cases are directly or indirectly linked to obesity [Talmor A, 2015]. Literature has shed a light on intramolecular chemicals with infertility. Sirtuin 1(SIRT1) is a protein it has a role to regulate proliferation and apoptosis in granulosa cells. Biochemical modulation that is downregulation of SIRT1 is associated with the physiological or pathological reduction of ovarian function; whereas some studies have shown the increased activity of SIRT1 may have the ability to ameliorate fertility in PCOS [Tatone C 2018]. INSL3 is another protein involved in the internal fertilization, loss of INSL3 and its receptor in females' leads to partial infertility with reduced follicle numbers, ovulation, and litter size in knockout mice [Ivell R 2018]. Excess of androgen also leads to the dysfunction of follicle development and anovulatory infertility that is PCOS [Astapova O 2019]. Bisphenol A is a chemical which is widely used in plastic production, whereas food is in direct contact with these chemical as it is used in the inner coating of cans and jars. Due to its phenolic structure, BPA has been shown to interact with estrogen receptors (ER) dependent signaling pathways. Therefore, BPA has been shown to play a role in the pathogenesis of several endocrine disorders including female and male infertility, metabolic disorders including polycystic ovary syndrome (PCOS) [Konieczna A 2015]. In PCOS women's infertility is associated with anxiety [Chaudhari AP 2018]. In recent years association of vitamin D has been seen with metabolic disorders such as PCOS. The vitamin D receptor (VDR) is expressed throughout the central and peripheral organs of reproduction. Both in animal and human studies, there is evidence for the role of vitamin D in PCOS [Nandi A 2016]. Higher oxidative stress is noticed in the infertile PCOS patient [Özer A 2016]. PCOS women showed some differently expressed proteins which are involved in the function of follicular maturation and ovulation. They are tumor necrosis factor, alpha-induced protein 6 (TNFAIP6); lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1); cluster of differentiation 14 (CD14), syndecan-4; and amphiregulin. The amphiregulin may impair cumulus oocyte complex (COC) matrix expansion in PCOS. downregulation of α-1-microglobulin/bikunin precursor (AMBP), TNFAIP6 leads to infertility due to disrupt in proper expansion of COC matrix. Anticoagulant heparan sulfate proteoglycans (HSPG) which is essential in focal adhesion also found down regulated in PCOS [Ambekar AS 2015]. Some proteins involved in the different processes of follicular development found to be deregulated in PCOS are heparan sulfate proteoglycan 2, α-induced protein 6, plasminogen, and lymphatic vessel endothelial hyaluronan receptor 1[Ambekar AS 2015]. So further work on all these differentially expressed proteins may be helpful to understand the ovarian physiology in more detail.

1.4 Acne

Acne Vulgaris is a chronic inflammatory disease. It has been associated with hyperandrogenism [Sharma S, 2019]. One of the important etiological factors for acne is the sebaceous gland activity that is androgen-dependent [Timpatanapong P 1997]. The influence of hormones, growth factors, prostaglandins, leukotrienes, and neuropeptides have a role in the pathology of acne [H P M Gollnick 2015].

The most common cause of acne in women is PCOS [Uysal G, 2017]. Around 45.7% of PCOS patients suffer from acne [Sardana K, 2016]. Global Acne Grading System (GAGS) score is used to quantify the severity of acne in PCOS patients [Hacivelioglu S 2013]. According to the literature, acne severity is associated with the higher concentrations of total testosterone, free testosterone, dehydroepiandrosterone sulfate, and free androgen index (FAI) value but it is not affected by the higher concentrations of androstenedione [Franik G 2018]. Patients with moderate to severe acne and particularly, it is resistant to conventional therapies or recurrence after treatment with isotretinoin should be considered for androgen access [Lause M 2017]. Genetic phenotypes and environmental factors may also have a role in the severity of acne. In PCOS acne is associated with depression [Suggs A 2018]. Prospectively designed studies with AMH can be a tool to diagnose persistent acne in PCOS patients [Sardana K 2016]. Even higher levels of prolactin and LH: FSH ratio was observed in the serum of PCOS patient with acne [Timpatanapong P 1997]. A significant difference was found in the free androgen index (FAI), body mass index (BMI), and SHBG between the PCOS with acne and PCOS without acne group [Feng JG 2018].

1.5 Insulin Resistant

It is the most significant feature of PCOS. IR has been observed in 70-80% of obese and 20-25% of lean PCOS [Belani M 2018]. The standard method to measure insulin sensitivity is the hyperinsulinemic-euglycemic glucose clamp technique, but Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Quantitative insulin sensitivity check index (QUICKI) are the most used methods in the scientific literature [Polak K 2017]. Decrease in insulin signaling proteins INSR β, PI (3)K, pIRS-1, pAkt, related to insulin and lipid metabolism in PCOS-IR group as against PCOS-NIR (non-insulin resistant) group, whereas in steroidogenesis P38 mitogen activated protein kinase (MAPK), P44/42 MAPK (Erk1/2), protein kinase C zeta (PKCζ), peroxisome proliferator activated receptor gamma (PPARG) showed increased metabolic changes in both PCOS-IR and PCOS-NIR group. This observation says that individuals may lead to hyperandrogenemia in the PCOS-IR group and co intrinsic ovarian defects in the PCOS-NIR group leading to the follicular arrest, poor oocyte growth as well as quality in luteinized granulose cells. Increased testosterone and decreased progesterone in the follicular fluid of the PCOS-IR group were also noticed [Belani M 2018]. Strong involvement of some proteins, adipocytokines (adiponectin, visfatin, vaspin, and apelin), copeptin, irisin, Plasminogen activator inhibitor-1(PAI-1), and zonulin have been seen. Decreased adiponectin level and increased visfatin level, apelin level speculating that adipocytokines can be used as a specific marker in insulin resistance PCOS condition. There is even high level of serum vaspin was noted in the insulin resistance PCOS group [Polak K 2017]. Decreased kisspeptin level was observed in insulin resistance PCOS whereas small number of controls was involved in the study so couldn't definite the conclusion [Polak K 2017]. Other studies on kisspeptin can be used as a marker for hyperandrogenism since further studies are needed to explain its metabolic consequences in PCOS. In obese PCOS-IR women, a high level of copeptin was observed. Increased serum irisin levels were observed in the insulin resistance PCOS women. A significant correlation between gherlin and insulin resistance was found in PCOS women. Tarkun et al, suggested that PAI-1 is the strong biomarker indicating insulin resistance with high accuracy to predict IR in PCOS [Polak K 2017]. Zonulin is a eukaryotic protein that increases the level of zonulin, which was associated with insulin resistance PCOS. Since much work is not done on this protein, it is necessary to carry out more work on this area to know the role of zonulin and alterations of intestinal permeability in PCOS physiopathology [Polak K 2017]. Leptin-adiponectin ratio (L:A) has been suggested as the potential biomarker for insulin resistance in PCOS [Gupta V 2017]. Inflammation in the PCOS induces leukocyte-endothelium interactions thus proinflammatory cytokines interleukin-6(IL-6), tumor necrosis factor (TNF-α) and adhesion molecules such as E-selectin, Intercellular Adhesion Molecule 1(ICAM-1) and Vascular cell adhesion protein 1 (VCAM-1) increases in insulin resistance PCOS women. Along with these metabolic and anthropometric parameters, total and mitochondrial reactive oxygen species (ROS) production, myeloperoxidase (MPO) levels, interactions between human umbilical vein endothelial cells, and leukocytes were found increased in general PCOS patients and with insulin resistance PCOS [Victor VM 2016]. The abnormal level of adipose-specific cytokines, leptin, adiponectin (APN), resistin, visfatin and omentin, and the non-adipose-specific cytokines such as retinol-binding protein-4 (RBP4), lipocalin-2 (LCN2), chemerin, IL6, interleukin 1β (IL1β), and TNFα are strongly associated with insulin resistance PCOS [Silvestris 2018].

1.6 Alopecia

Alopecia is a condition of hair loss it is one of the symptoms of PCOS. Ludwig classification is a measure used to grade the alopecia [Hacivelioglu S 2013]. Alopecia is associated with hyperandrogenism, in PCOS, elevation in luteinizing hormone (LH) and insulin contributes to the excess of androgen [Lause M 2017]. Hair thinning results from the effects of the testosterone metabolite dihydrotestosterone on androgen-sensitive hair follicles. Alopecia in PCOS women can appear either male pattern baldness, with both front temporal and vertex recession which is less common in PCOS or in a female pattern that is dominant in PCOS with hair loss predominantly located in the central scalp with preservation of the frontal hairline [Housman E 2014].

Since the female pattern is dominant, it needs to focus more on androgen linked pathogenesis which is not clear. Some studies reports, pathogenesis might be linked to oestrogens which appear to have an inhibitory effect on hair growth-inducing catagen and arresting the follicles in telogen in animal models [Ohnemus U 2005]. Even though the pathogenesis of female pattern is less clear, around 20% of the patient's reports have shown the relative increase in androgen hormones is a cause for female pattern hair loss in PCOS [Rossi A, 2019]. It is noted that alopecia is associated with other clinical hyperandrogenism but not with greater risk of biochemical hyperandrogenemia or metabolic dysfunction than with PCOS alone [Quinn M 2014]. Female androgenetic alopecia can have a significant impact on physiological status like anxiety and depression [Starace M 2019]. The treatment pattern includes the assessment of androgen and the hormonal imbalance like prolactin, zinc, thyroid hormones, iron, and vitamin D. Even the ferritin level was found lowest in the severe hair loss patients [Carmina E, 2019].

1.7 Obesity

Obesity is a major global pandemic. Obesity and overweight involve an abnormal and excessive fat accumulation that negatively affects health status. According to the World Health Organization (WHO), if BMI is equal or greater than 25 kg/m^2 is considered overweight, whereas the BMI higher than 30 kg/m^2 defines obesity [Silvestris E 2018]. It is found that obesity has a biochemical effect on fertility thus contributes to varying degrees with insulin resistance, metabolic syndrome like PCOS. Obesity shows profound effects on sex hormone secretion and metabolism. With increasing adiposity, there is an increase in peripheral aromatization of androgens to oestrogens with a concurrent decrease in the hepatic synthesis of SHBG. This increases free oestradiol and testosterone levels. This is further exacerbated by associated hyperinsulinemia resulting in a further decrease of SHBG and stimulation of ovarian androgen production. The resultant hypersecretion of LH and the increased androgen to oestrogen ratio and the overall altered endocrine milieu in turn leads to impaired folliculogenesis and follicular atresia [Talmor A 2016]. Aadipokines like leptin, adiponectin, resistin visfatin, omentin, and chemerin affect the fertility of obese women [Silvestris E 2018]. The higher level of resistin, leptin, irisin, and copeptin was observed in the obese PCOS group in comparison with the healthy control. Ghrelin is a multifunctional peptide hormone secreted principally in the stomach. Gherlin is strongly correlated with obesity but further studies are needed to elucidate the relationship between gherlin level and PCOS. Significantly increased level of zonulin was noticed in the serum of obese PCOS women [Polak K 2017]. From the literature, it is found that the levels of cytokines like IL-27, IL-35, and IL-37 with anti-inflammatory properties were significantly lower, and levels of a-1 acid glycoprotein were significantly higher in obese PCOS patients than lean PCOS patients [Nehir Aytan A 2016]. However, there are no conclusive studies on the importance of different proteins and cytokines in this area have been done.

2. Conclusion

Mechanism and genetics behind the PCOS are not completely successful to reveal the etiology. Computational tools may be helpful in finding the cause of this syndrome using different structural aspects to dig out the different proteins responsible for etiology. Since most of the symptoms are associated with hyperandrogenism, increased androgen level is a culprit of this metabolic disorder. So, elucidating the important proteins responsible will be useful to focus on the therapeutic aspect of this disease.

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