

A Review on the Link between Psoriasis Vulgaris and Polycystic Ovary Syndrome

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Abstracts: Psoriasis and polycystic ovary syndrome (PCOS) are both triggered by hormones and chemical messengers. Psoriatic women are also more prone than the general population to PCOS, and both diseases are tightly associated with obesity, insulin resistance, diabetes, and metabolic and cardiovascular alterations. The aim of this paper is to review the current knowledge on the association between psoriasis and PCOS, from immunologic and genetic perspectives.

Keywords: Psoriasis, Polycystic ovary syndrome, Metabolic syndrome, Immunology, Genetic.

INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory disease (IMID) that affects 2% of the general population. It is characterized by silver, scaly plaques on the extensor surfaces of the body, with different clinical manifestations. Genetic factors, immune dysregulation, and environmental factors are thought to be initial factors in the disease [1, 2]. Recent studies have shown that patients with IMIDs have a higher prevalence of comorbidities, including diabetes [3], cardiovascular disease [4], metabolic syndrome [4-6], dyslipidemia [7], and nonalcoholic fatty liver disease [8-10].

Polycystic ovary syndrome (PCOS) is a common disorder in women of reproductive age. Two of the following criteria are sufficient for diagnosis: oligo- or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovaries on ultrasound examination [11]. Similar to psoriasis, the components of metabolic syndrome [12-14], obesity [13], diabetes [15], insulin resistance [16-20], dyslipidemia [21], hypertension [15, 22-23], and coronary artery disease [15] are reported to be closely related to PCOS. Based on these similarities, with the support of the literature, female patients with psoriasis in the reproductive period are thought to have a higher risk of PCOS [24-26].

Although the common pathway that links psoriasis to PCOS is not known exactly, there are studies supporting this relationship. Moro *et al.* [26] first pointed

to the relationship between psoriasis and PCOS, reporting a higher risk of PCOS in about half of female psoriatic patients. Additionally, the women with psoriasis and PCOS had more insulin resistance, more hyperinsulinemia, and lower high-density lipoprotein (HDL) cholesterol levels compared to the patients with psoriasis alone. The etiology of these associations and findings are not clear, but common inflammatory mechanisms may have an influence [24, 26].

Genetic Factors

Although triggering factors, such as streptococcal infections, mechanical and psychological trauma, and psychological stress, play an important role in initiating psoriasis, several studies have shown that there is a strong genetic predisposition involved with this disease. Approximately 35%–90% of patients report a positive family history. The concordance in monozygotic (70%) and dizygotic twins (20%) also supports the strong inherited property of psoriasis [27]. Today, psoriasis is accepted as a multifactorial disease influenced by several genes; thus, the pathogenesis of the disease is thought to result from immune dysregulation based on a genetic background [28-34]. Thirteen main chromosomal loci (PSORS1–13) have been identified as related to psoriasis. In particular, PSORS1 has been determined as the major gene, present in 50% of psoriatic patients. In addition, psoriasis can be defined as a polygenic inherited disease due to gene polymorphisms involved in both the immune system and in keratinocyte biology [35].

PCOS also has an uncertain etiology. Environmental factors, molecular abnormalities, and genetic factors are thought to take part in its

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etiopathogenesis. Familial clustering and twin studies have demonstrated that PCOS is a heritable disease, with up to 70% concordance in monozygotic twins [36]. A genome-wide association study (GWAS) provided evidence of associations between several single nucleotide polymorphisms and PCOS [19-21, 37].

Several PCOS candidate genes are related to steroid hormone biosynthesis and metabolism [38-44], androgen synthesis and metabolism [44-45], and insulin and leptin metabolism.

Psoriasis severity can be affected by female sex hormones and thus influenced by different hormonal phases (for example, puberty, postpartum, and menopause). Androgens are steroid structural hormones responsible for male characteristics. PCOS is a hyperandrogenic disorder, and hence experiments using animal models and cell lines related to androgen biosynthesis and metabolism have been widely performed to understand the molecular mechanisms [46-48]. Recent studies have demonstrated that PCOS is triggered not only by the androgen synthesis pathway, but also by androgen receptor-mediated pathways [44-46]. Udhane *et al.* [48] showed that retinoic acid receptor beta (RARβ) enhanced androgen biosynthesis by stimulation of the genes responsible for androgen production (StAR, CYP17A1, HSD3B2). Retinoid acid derivatives (etretinate and its active metabolite, acitretin) are steroid structures used for the treatment of psoriasis. Thus, genetic and epigenetic variations in steroid and androgen synthesis pathways may trigger both psoriasis and PCOS [44].

Adipose tissue is an endocrine organ that affects the metabolism via secreted cytokines and hormones. Both psoriasis and PCOS patients are more prone to developing obesity, and it is speculated that adipose tissue delivers cytokines that trigger PCOS in psoriatic patients, or vice versa. The phenotypic features of PCOS are associated with hyperinsulinemia as a result of insulin resistance [49] due to insulin secretion effects on ovarian androgen hypersecretion [50]. Recent studies have demonstrated that tandem repeat variations in the insulin gene (INS) [51-52], as well as single nucleotide polymorphisms in the insulin receptor (INSR) gene [19-20], are associated with PCOS. In addition, genetic alterations in insulin-mediated pathways cause insulin resistance, obesity, and metabolic and cardiovascular disease both in patients with psoriasis and in those with PCOS. The FTO and MC4R genes are related to obesity, pointing to their association with PCOS [53-55]. Fatty acid desaturase

genes (FADS) were also found to be related to both dyslipidemia and PCOS [21].

Genes related to skin properties have also been analyzed in order to understand the mechanisms of psoriasis and PCOS. Li *et al.* [56] reported that the MTNR1B gene is related to type 2 diabetes mellitus, but not to PCOS susceptibility.

The Role of Inflammation

According to current studies, the main factor in the initiation of psoriasis is the cooperation of T cells, dendritic cells, and keratinocytes in the lesion area on the skin. T cells that are activated in psoriatic plaques are divided into two groups, Th1 (T helper) and Th2, depending on the cytokines they produce. Th1 is responsible for the production of inflammatory cytokines, while Th2 is responsible for non-inflammatory cytokines [57]. Interleukin (IL)-23 and IL-12, released from myeloid dendritic cells, activate T cells and lead to production of IL-17, IL-22, interferon (IFN)- γ , and tumor necrosis factor (TNF). IL-23, TNF, and IL-17 seem to be the key factors in psoriasis [58-60].

The primary reason for abnormal keratinocyte differentiation caused by keratinocyte hyperproliferation is that several cytokines and chemokines are secreted by antigen-presenting cells [61]. Cytokines such as IL-6, IL-8, IL-18, IL-20, transforming growth factor (TGF)- α , TGF- β , and amphiregulin (keratinocyte autocrine factor), secreted by keratinocytes, contribute to the course of psoriatic inflammation [62]. IFN- γ is a soluble cytokine with antiviral, immune regulatory, and antineoplastic effects. It has been identified at high levels in psoriatic patients, and correlates with the severity of disease [63].

PCOS is currently accepted as a pro-inflammatory condition that induces low-grade inflammation. It results from ovarian dysfunction and fibrosis. IL-6 levels are elevated in women with PCOS, yet the association with genetic variations in IL-6 and PCOS is controversial [64-66]. The association of the IL-6 pathway and PCOS susceptibility may be related to testosterone-mediated IL-6 expression [67].

TNF- α is a pro-inflammatory cytokine with a polypeptide structure, located at 6p21.3. It is multifunctional protein that affects lipid metabolism, insulin resistance, and endothelial function. Hence, pro-inflammatory genotypes, such as encoding TNF- α and type 2 TNF receptors, play a role in the inflammatory

course of psoriasis and PCOS [64, 68-69], and TNF can trigger both PCOS [70] and psoriasis [62, 71-72]. In addition, TNF- α targeting may be useful for treating both PCOS [73] and psoriasis [74-76].

Associations With Other Diseases

Psoriasis is regarded as a systemic condition, mainly because it is a chronic inflammatory disease strongly associated with metabolic and cardiovascular diseases. In recent years, several studies have reported a relationship between psoriasis and diabetes [77-79]. Additionally, studies investigating the link between cardiovascular disease and psoriasis have pointed to an increased risk for cardiovascular morbidity and mortality, and revealed that myocardial infarction is three times more common in psoriasis patients compared to the general population [80]. On the basis of the diseases accompanying psoriasis, metabolic pathways are the key factors in which cytokines play a role as mediator substances causing chronic inflammatory reactions. By causing inflammatory reactions, cytokines increase the risk of atherosclerosis and insulin resistance and ultimately lead to hypertension and type 2 diabetes mellitus [81].

Psoriatic arthritis is a seronegative arthritis that occurs as a complication of psoriasis, with increased TNF- α production in the skin lesions and synovium of psoriatic patients during the cutaneous inflammation phase of the disease [82-83]. Similar to psoriasis, women with PCOS have a higher risk of metabolic disorders, such as obesity, dyslipidemia, diabetes mellitus, and insulin resistance [84].

DISCUSSION

Psoriasis is a common immune-mediated skin disease, and PCOS is a common endocrine disorder in women of reproductive age. Although the clinical features of each disease are very different, the genetic background, chronic inflammatory process, and relationship to other metabolic disorders may all be signs of a link between PCOS and psoriasis. The association between the two diseases is not exactly known, but in recent studies, the prevalence of PCOS in patients with psoriasis has been found to be markedly higher than in the normal population. Furthermore, skin lesions are more exacerbated and the risk of insulin resistance, hyperinsulinemia, and low HDL levels are markedly higher when these two disorders coexist [14-16]. Various inflammatory markers, such as TNF- α , IFN- γ , IL-1, and IL-6, can

have similar functions in the processes of both PCOS and psoriasis. Moro *et al.* suggested that anovulation, hyperandrogenism, and hyperinsulinemia contribute to the inflammatory process and worsen the features of psoriasis [24]. Consistent with this study, de Simone *et al.* [25] determined that the prevalence of PCOS was markedly higher in reproductive-age women with psoriasis, and this group was also at a higher risk of insulin resistance, high triglycerides, low HDL cholesterol, and more severe skin lesions [15]. Additionally, Bommsma *et al.* [85] reported poor pregnancy outcomes in women with PCOS, and due to these data, de Simone *et al.* [25] pointed to the probability of an important impact of psoriasis on the course of pregnancy, as well as the role of PCOS contributing to these effects.

CONCLUSION

PCOS is common in patients with psoriasis, and it has a negative impact on the clinical course of the disease. Genetic and inflammatory factors, and accompanying metabolic disorders, may contribute to this mechanism. Further studies are needed to clarify the exact etiology of PCOS, which will lead to a common treatment approach and better outcomes.

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