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

Selda Isik[1], Meliha Merve Hiz[2], Sevilay Kilic[1] and Ayse Nur Cakir Gungor[3,*]

[1]*Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Dermatology*

[2]*Canakkale Onsekiz Mart University, Faculty of Science and Arts, Department of Biology*

[3]*Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Obstetrics and Gynecology*

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

*Address correspondence to this author at the Canakkale Onsekiz Mart University, Faculty of Medicine, Department of Obstetrics and Gynecology;
Tel: +902862635950; Fax: +902862635957;
E-mail: dr_aysecakir@hotmail.com

E-ISSN: 2408-9761/16

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 (RARB) 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 resoluble 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.

REFERENCES

[1] Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol 2001; 26: 314-20. http://dx.doi.org/10.1046/j.1365-2230.2001.00832.x

[2] Ogretmen Z, Hiz MM, Silan F, Uludag A, Ozdemirc O. Association of endothelial nitric oxide synthase Glu298Asp gene polymorphism in psoriasis cases with hypertension. Ann Saudi Med 2014; 34: 340-5.

[3] Armesto S, Santos-Juanes J, Galache-Osuna C, Martinez-Camblor P, Coto E, Coto-Segura P. Psoriasis and Type 2 Diabetes Risk Among Psoriatic Patients in a Spanish Population. Australas J Dermatol 2012; 53: 128-30. http://dx.doi.org/10.1111/j.1440-0960.2011.00802.x

[4] Meziane M, Kelati A, Najdi A, Berraho A, Nejjari C, Mernissi FZ. Metabolic syndrome in Moroccan patients with psoriasis. Int J Dermatol 2015: doi: 10.1111/ijd.12623. [Epub ahead of print]. http://dx.doi.org/10.1111/ijd.12623

[5] Owczarczyk-Saczonek AB, Nowicki R. The association between smoking and the prevalence of metabolic syndrome and itcomponents in patients with psoriasis aged 30 to 49 years. Postepy Dermatol Alergol 2015; 2: 331-6. http://dx.doi.org/10.5114/pdia.2015.54743

[6] Itani S, Arabi A, Harb D, Hamzeh D, Kibbi AG. High prevalence of metabolic syndrome in patients with psoriasis in Lebanon: a prospective study. Int J Dermatol 2016; doi: 10.1111/ijd.12811. [Epub ahead of print]. http://dx.doi.org/10.1111/ijd.12811

[7] Coban M, Tasli L, Turgut S, Özkan S, Tunç Ata M, Akın F. Association of Adipokines, Insulin Resistance, Hypertension and Dyslipidemia in Patients with Psoriasis Vulgaris. Ann Dermatol 2016; 28: 74-9. http://dx.doi.org/10.5021/ad.2016.28.1.74

[8] Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2015; 29: 656-62. http://dx.doi.org/10.1111/jdv.12847

[9] Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between Non-Alcoholic Fatty Liver Disease and Psoriasis: A Novel Hepato-Dermal Axis? Int J Mol Sci 2016; [Epub ahead of print]. http://dx.doi.org/10.3390/ijms17020217

[10] Roberts KK, Cochet AE, Lamb PB, Brown PJ, Battafarano DF, Brunt EM *et al*. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. Pharmacol Ther 2015; 41: 293-300. http://dx.doi.org/10.1111/apt.13042

[11] Bachanek M, Abdalla N. Value of ultrasonography in the diagnosis of polycystic ovary syndrome - literature review. J Ultrason 2015; 63: 410-22. http://dx.doi.org/10.15557/JoU.2015.0038

[12] Indhavivadhana S, Wongwananuruk T, Rattanachaiyanont M, Techatraisak K, Leerasiri P, Tanmahasamut P *et al*. Prevalence of metabolic syndrome in reproductive-aged polycystic ovary syndrome Thai women. Med Assoc Thai 2010; 93: 653-60.

[13] Sharma S, Majumdar A. Prevalence of metabolic syndrome in relation to body mass index and polycystic ovarian syndrome in Indian women. J Hum Reprod Sci 2015; 8: 202-8.

[14] Ovalle F, Azziz R. Insulin resistance, polycystic ovary syndrome, and type 2 diabetes mellitus. Fertil Steril 2002; 77: 1095-105. http://dx.doi.org/10.1016/S0015-0282(02)03111-4

[15] Nasrat H, , Patra SK, Goswami B, Jain A, Raghunandan C. Study of Association of Leptin and Insulin Resistance Markers in Patients of PCOS. Indian J Clin Biochem 2016; 1:104-7. http://dx.doi.org/10.1007/s12291-015-0499-8

[16] Wongwananuruk T, Rattanachaiyanont M, Indhavivadhana S, Leerasiri P, Techatraisak K, Tanmahasamut P *et al*. Prevalence and clinical predictors of insulin resistance in reproductive-aged thai women with polycystic ovary syndrome. Int J Endocrinol 2012; 2012: 529184.

[17] Zhu Q, Zhou H, Zhang A, Gao R, Yang S, Zhao C *et al*. Serum LBP Is Associated with Insulin Resistance in Women with PCOS, Plos One. 2016; 11:e0145337. http://dx.doi.org/10.1371/journal.pone.0145337

[18] Paul C, Laganà AS, Maniglio P, Triolo O, Brady DM. Inositol's and other nutraceuticals' synergistic actions counteract insulin resistance in polycystic ovarian syndrome and metabolic syndrome: state-of-the-art and future perspectives. Gynecol Endocrinol 2016; [Epub ahead of print]. http://dx.doi.org/10.3109/09513590.2016.1144741

[19] Du J, Wang Z, Zhang J, Jia L, Zhang F, Shi Y *et al*. Association between single nucleotide polymorphism of rs2252673 of INSR gene and polycystic ovarian syndrome. Zhonghua Fu Chan Ke Za Zhi 2014; 49: 919-24.

[20] Du J, Wang J, Sun X, Xu X, Zhang F, Wang B *et al*. Family-based analysis of INSR polymorphisms in Chinese PCOS. Reprod Biomed Online 2015; 2: 239-44.

[21] Tian Y, Zhang W, Zhao S, Sun Y, Bian Y, Chen T *et al*. FADS1-FADS2 gene cluster confers risk to polycystic ovary syndrome. Sci Rep. 2016; 6:21195. http://dx.doi.org/10.1038/srep21195

[22] Hoang V, Bi J, Mohankumar SM, Vyas AK. Liraglutide improves hypertension and metabolic perturbation in a rat model of polycystic ovarian syndrome. PLoS One 2015; 10: e0126119. http://dx.doi.org/10.1371/journal.pone.0126119

[23] Kiałka M, Milewicz T, Klocek M. Blood pressure and polycystic ovary syndrome (PCOS). Przegl Lek 2015; 72: 309-12.

[24] Moro F, Tropea A, Scarinci E, Federico A, De Simone C, Caldarola G *et al*. Psoriasis and polycystic ovary syndrome: a new link in different phenotypes. Eur J Obstet Gynecol Reprod Biol 2015; 191:101-5. http://dx.doi.org/10.1016/j.ejogrb.2015.06.002

[25] De Simone C, Caldarola G, Corbeddu M, Moro F, Tropea A, Moretta G, Apa R. A possible role of polycystic ovary syndrome for pregnancy complications in women with psoriasis. Drug Dev Res 2014; 75; Suppl 1: S64-6 http://dx.doi.org/10.1002/ddr.21199

[26] Moro F, De Simone C, Morciano A, Tropea A, Sagnella F, Palla C *et al*. Psoriatic patients have an increased risk of polycystic ovary syndrome: results of a cross-sectional analysis. Fertil Steril 2013; 99: 936-42. http://dx.doi.org/10.1016/j.fertnstert.2012.10.040

[27] Pedersen OB, Svendsen AJ, Ejstrup L, Skytthe A, Junker P. On the heritability of psoriatic arthritis. Disease concordance among monozygotic and dizygotic twins. Ann Rheum Dis 2008; 67: 1417-21. http://dx.doi.org/10.1136/ard.2007.078428

[28] Pietrzak AT, Zalewska A, Chodorowska G, Krasowska D, Michalak-Stoma A, Nockowski P *et al*. Cytokines and Anticytokines in Psoriasis. Clinica Chimica Acta 2008; 394: 7-21. http://dx.doi.org/10.1016/j.cca.2008.04.005

[29] 29.Ammar M, Souissi-Bouchlaka C, Gati A, Zaraa I, Bouhaha R, Kouidhi S *et al*. Psoriasis: physiopathology and immunogenetics Pathol Biol 2014; 62: 10-23. http://dx.doi.org/10.1016/j.patbio.2013.07.014

[30] Harden JL, Krueger JG, Bowcock AM. The immunogenetics of Psoriasis: A comprehensive review. J Autoimmun 2015; 64: 66-73. http://dx.doi.org/10.1016/j.jaut.2015.07.008

[31] Ghoreschi K, Röcken M. Immunopathogenesis of psoriasis. J Dtsch Dermatol Ges 2003; 1:524-32. http://dx.doi.org/10.1046/j.1610-0387.2003.03010.x

[32] Bowcock AM, Krueger JG. Getting under the skin: the immunogenetics of psoriasis. Nat Rev Immunol 2005; 9: 699-711. http://dx.doi.org/10.1038/nri1689

[33] Chamian F, Krueger JG. Psoriasis vulgaris: an interplay of T lymphocytes, dendritic cells, and inflammatory cytokines in pathogenesis. Curr Opin Rheumatol 2004; 16: 331-7. http://dx.doi.org/10.1097/01.bor.0000129715.35024.50

[34] Holm S, Sanchez F, Carlén L, Mallbris L, Ståhle M, O'Brien K. HLA-Cw*0602 Associates More Strongly to Psoriasis in the Swedish Population Than Variants of the Novel 6p21.3 Gene PSORS1C3. Acta Derm Venereol 2005; 85: 2-8. http://dx.doi.org/10.1080/00015550410023527

[35] Puig L, Julia A, Marsal S. The pathogenesis and genetics of psoriasis. Actas Dermosifiliogr 2014; 105: 535-5. http://dx.doi.org/10.1016/j.ad.2012.11.006

[36] Vink JM, Sadrzadeh S, Lambalk CB, Boomsma DI. Heritability of polycystic ovary syndrome (PCOS) in a Dutch twin-family study. J Clin Endocrinol Metab 2005; 91: 2100-4. http://dx.doi.org/10.1210/jc.2005-1494

[37] McAllister JM, Legro RS, Modi BP, Strauss JF. Functional genomics of PCOS: from GWAS to molecular mechanisms. Trends Endocrinol Metab 2015; 3: 118-24. http://dx.doi.org/10.1016/j.tem.2014.12.004

[38] Gharani N, Waterworth DM, Batty S, White D, Gilling-Smith C, Conway GS *et al*. Association of the steroid synthesis gene CYP11a with polycystic ovary syndrome and hyperandrogenism. Hum Mol Genet 1997; 3: 397-402. http://dx.doi.org/10.1093/hmg/6.3.397

[39] Pérez MS, Cerrone GE, Benencia H, Márquez N, De Piano E, Frechtel GD. Polymorphism in CYP11alpha and CYP17 genes and the etiology of hyperandrogenism in patients with polycystic ovary syndrome. Medicina (B Aires) 2008; 68: 129-34.

[40] Strauss JF. Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome. Ann N Y Acad Sci 2003; 997: 42-8. http://dx.doi.org/10.1196/annals.1290.005

[41] Tan L, Zhu G. J Role of the pentanucleotide (tttta)n polymorphisms of Cyp11alpha gene in the pathogenesis of hyperandrogenism in Chinese women with polycystic ovary syndrome. Huazhong Univ Sci Technolog Med Sci 2005; 25: 212-4. http://dx.doi.org/10.1007/BF02873580

[42] Fan W, Li S, Chen Q, Huang Z. Association between the (TAAAA)n SHBG polymorphism and PCOS: a systematic review and meta-analysis. Gynecol Endocrinol 2013; 7: 645-50. http://dx.doi.org/10.3109/09513590.2013.797394

[43] Chen C, Smothers J, Lange A, Nestler JE, Strauss Iii JF, Wickham Iii EP. Sex hormone-binding globulin genetic variation: associations with type 2 diabetes mellitus and polycystic ovary syndrome. Minerva Endocrinol 2013; 4: 271-80.

[44] Walters KA. Androgens in polycyctic ovary syndrome: lessons from experimental models. Curr Opin Endocriol Diabetes Obes 2016; [Epub ahead of print].

[45] Zhang T, Liang W, Fang M, Yu J, Ni Y, Li Z. Association of the CAG repeat polymorphisms in androgen receptor gene with polycystic ovary syndrome: a systemic review and meta-analysis. Gene 2013; 524: 161-7. http://dx.doi.org/10.1016/j.gene.2013.04.040

[46] Udhane SS, Flück CE. Regulation of human (adrenal) androgen biosynthesis -New insights from novel thoughtput technology studies. Biochem Pharmacol 2016; 102: 20-33. http://dx.doi.org/10.1016/j.bcp.2015.10.010

[47] Kempna P, Marti N, Udhane S, Flück CE. Regulation of androgen biosynthesis -A short review and preliminary results from the hyperandrogenic stravation NCI-H295R cell model. Mol Cell Endocrinol 2015; 408: 124-32. http://dx.doi.org/10.1016/j.mce.2014.12.015

[48] Udhane SS, Pandey AV, Hofer G, Mullis PE, Flück CE. Retinoic acid receptor beta and angiopoietin like protein 1 are involved in the regulation of human androgen biosynthesis. Sci. Rep 2015; 5: 10132. http://dx.doi.org/10.1038/srep10132

[49] Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genet,c syndrome in severe insulin resistance. Endocr Rev 2011; 32: 498-514. http://dx.doi.org/10.1210/er.2010-0020

[50] Tosi F, Negri C, Perrone F, Dorrizzi R, Castello R Bonora E, *et al*. Hyperinsulinemia amplifies GnRH agonist stimulated ovarian steroid secretion in women with polycyctic ovary syndrome. J Clin Endocrinol Metab 2012; 97: 1712-9. http://dx.doi.org/10.1210/jc.2011-293951.

[51] Yun YH, Gu BH, Kang YB, Choi BC, Song S, Baek KH. Association between INS-VNTR polymorphism and plycyctic ovary syndrome in a Korean population. Gynecol Endrocriniol 2012; 7: 525-8. http://dx.doi.org/10.3109/09513590.2011.650658

[52] Yan MS, Liang GY, Xia BR, Liu DY, Kong D, Jin XM. Association of insulin gene variable number of tandem repeats regulatory polymorphism with polycyctic ovary syndrome. Hum Immınol 2014; 75: 1047-52. http://dx.doi.org/10.1016/j.humimm.2014.09.001

[53] Ramos RB, Spitzer PM. FTO gene variants are not associate with polycyctic ovary syndrome in women from Sourthern Brazil. Gene, 2015; 560: 25-9. http://dx.doi.org/10.1016/j.gene.2015.01.012

[54] Song do K, Lee H, Oh JY, Hong YS, Sung YA. FTO gene variants are associated with PCOS suspectibility and hyperandrogenemia in Young Korean Women. Diabetes Metab 2014; 38: 302-10. http://dx.doi.org/10.4093/dmj.2014.38.4.302

[55] Yuan H, Zhu G, Wang F, Wang X, Guo H, Shen M. Interaction between commmon variants of FTO and MC4R is associated with risk of PCOS. Endocrinol 2015; 13: 55.

[56] Li C, Shi Y, You L, Wang L, Chen ZJ. Association of rs10830963 and rs10830962 SNPs in the melatonin receptor (MTNR1B) gene among Han Chinese women with polycystic ovary syndrome. Molecular human reproduction 17, 2011; 3: 193-198. http://dx.doi.org/10.1093/molehr/gaq087

[57] Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two Types of Murine Helper T Cell Clones I. Definition According to Profiles of Lymphokine Activities and Secreted Proteins. Immunol 1986; 136: 2348-57.

[58] Di Meglio P. The Role of IL-23 in The Immunopathogenesis of Psoriasis. F1000 Biol Rep 2010; 24; 2. pii: 40.

[59] Kurzeja M, Rudnicka L, Olszewska M. New Interleukin-23 Pathway Inhibitors in Dermatology: Ustekinumab, Briakinumab, and Secukinumab. Am J Clin Dermatol 2011; 12: 113-25. http://dx.doi.org/10.2165/11538950-000000000-00000

[60] Campa M, Mansouri B, Warren R, Menter A. A Review of Biologic Therapies Targeting IL-23 and IL-17 for Use in Moderate-to-Severe Plaque Psoriasis. Dermatol Ther (Heidelb) 2015. [Epub ahead of print].

[61] 61. Chamian F, Krueger JG. Psoriasis Vulgaris: an Interplay of T Lymphocytes, Dendritic Cells, and Inflammatory Cytokines in Pathogenesis. Curr Opin Rheumatol 2004; 16: 331-7. http://dx.doi.org/10.1097/01.bor.0000129715.35024.50

[62] Serum Levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in Patients With Active Psoriasis And Correlation With Disease Severity. Arican O, Aral M, Sasmaz S, ve Ciragil P. Mediators Inflamm. 2005; 5: 273-9.

[63] Lew W, Bowcock AM, Krueger JG. Psoriasis Vulgaris: Cutaneous Lymphoid Tissue Supports T-Cell Activation and 'Type 1' Inflammatory Gene Expression. Trends Immunol 2004; 25: 295-305. http://dx.doi.org/10.1016/j.it.2004.03.006

[64] Escobar-Morreale HF, Calvo RM, Villuendas G, Sancho J, San Millan JL. Association of polymorphisms in the interleukin 6 receptor complex with obesity and hyperandrogenism. Obes Res 2003; 11: 987-96. http://dx.doi.org/10.1038/oby.2003.136

[65] Peng Z, Sun Y, Lv X, Zhang H, Liu C, Dai S. Interleulin 6 leveles in women with polycyctic ovary syndrome: A systematic review and Meta Analysis. Plos One 2016; 11: e0148531. http://dx.doi.org/10.1371/journal.pone.0148531

[66] Wang Q, Tong X, Ji Y, Li H, Lu W, Song Z. Meta analyses of the correlation between IL-6 -174G/C polymorphism and polycyctic ovarian syndrome. J Obstet Gynaecol Res 2015; 41: 1087-92. http://dx.doi.org/10.1111/jog.12682

[67] Su C, Chen M, Huang H, Lin J. Testosterone enhances lipopolysaccharide-induced interleukin 6 and macrophage chemotactic protein 1 expression by activating the extracellular signal regulated kinase 1/2/nuclear factor kB signaling pathway in 3T3--L1 Adipocytes. Mol Med Rep 2015; 12: 679-704.

[68] Peral B, San Millan JL, Castello R, Moghetti P, Escobar-Morreale HF. The methionine 196 arginine polymorphism in exon 6 of the TNF receptor 2 gene (TNFRSF1B) is associated with the polycystic ovary syndrome and hyperandrogenism. J Clin Endocrinol Metab 2002; 39: 77-83. http://dx.doi.org/10.1210/jcem.87.8.8715

[69] Wu H, Yu K, YAng Z. Association between TNF-a and interleukin gene polymmorphism with polycyctic ovary syndrome: a systematiic review and meta analysis. J Assist Reprod Genet 2015; 32: 625-34. http://dx.doi.org/10.1007/s10815-015-0449-7

[70] Deepika MLN, Reddy KR, Yashwant A, Usha Rani V, Prassanna Latha K, Jahan P. TNF-a haplotype associated with polycyctic ovary syndrome - a South Indian study. . J Assist Reprod Genet 2013; 30: 1493-503. http://dx.doi.org/10.1007/s10815-013-0080-4

[71] Hohler T, Grossmann S, Stradmann-Bellinghausen B, Kaluza W, Reuss E, de Vlam K *et al*. Differential association of polymorphisms in the TNFalpha region with psoriatic arthritis but not psoriasis. Ann. Rheum Dis 2002; 61: 213-8. http://dx.doi.org/10.1136/ard.61.3.213

[72] Reich K, Huffmeier U, Konig IR, Lascorz J, Lohmann J, Wendler J *et al*. TNF polymorphisms in psoriasis: association of psoriatic arthritis with the promoter polymorphism TNF*-857 independent of the PSORS1 risk allele. Arthritis Rheum 2007; 56: 2056-64. http://dx.doi.org/10.1002/art.22590

[73] Rezvanfar MA, Saeedi S, Mansoori P, Saadat S, Goosheh M, Shojaei Saadi HA *et al*. Dual targetting of TNF-a and free radical toxic stress as a promising strategy to manage experimental polycyctic ovary. Pharm Biol 2016; 54: 80-90. http://dx.doi.org/10.3109/13880209.2015.1014922

[74] Pirowska MM, Goździalska A, Lipko-Godlewska S, Obtułowicz A, Sułowicz J, Podolec K *et al*., Autoimmunogenicity during anti-TNF therapy in patients with psoriasis and psoriatic arthritis. Postep Derm Alergol 2015, XXXII (4): 250-54. http://dx.doi.org/10.5114/pdia.2015.53320

[75] Tobin AM, Kirby B. TNF Alpha Inhibitors in the Treatment of Psoriasis and Psoriatic Arthritis. Bio Drugs 2005; 19: 47-57. http://dx.doi.org/10.2165/00063030-200519010-00006

[76] Victor FC, Gottlieb AB. TNF-alpha and Apoptosis: Implications for the Pathogenesis and Treatment of Psoriasis. J Drugs Dermatol 2002; 1: 264-75.

[77] Brauchli YB, Jick SS, Meier CR. Psoriasis and the risk of Incident Diabetes Mellitus: a Population-Based Study. Br J Dermatol 2008; 159: 1331-7. http://dx.doi.org/10.1111/j.1365-2133.2008.08814.x

[78] Cohen AD, Dreiher J, Shapiro Y, Vidavsky L, Vardy DA, Davidovici B. *et al*. Psoriasis and Diabetes: a Population-Based Cross-Sectional Study. J Eur Acad Dermatol Venereol 2008; 22: 585-89. http://dx.doi.org/10.1111/j.1468-3083.2008.02636.x

[79] Qureshi AA, Choi HC, Choi AR, Curhan GC. Psoriasis and the Risk of Diabetes and Hypertension: A Prospective Study of US Female Nurses. Arch Dermatol 2009; 145:379-82. http://dx.doi.org/10.1001/archdermatol.2009.48

[80] Ghazizadeh R, Shimizu H, Tosa M, Ghazizadeh M. Pathogenic Mechanisms Shared between Psoriasis and Cardiovascular Disease. Int J Med Sci 2010; 5: 284-89. http://dx.doi.org/10.7150/ijms.7.284

[81] Shapiro J, Cohen AD, David M, Hodak E, Chodik G, Viner A *et al*. The Association Between Psoriasis,Diabetes Mellitus, and Atherosclerosis in Israel: A Case-Control 2007; 56: 629-34.

[82] Tobin AM, Kirby B. TNF Alpha Inhibitors in the Treatment of Psoriasis and Psoriatic Arthritis. Bio Drugs 2005; 19: 47-57. http://dx.doi.org/10.2165/00063030-200519010-00006

[83] Murdoch N, Navsaria H, Blackwell F, Trousdale J, Leigh I. Tumour Necrosis Factor and Psoriasis. Br J Dermatol 2006; 119: supp33: 46. http://dx.doi.org/10.1111/j.1365-2133.1988.tb05383.x

[84] Madani T, Hosseini R, Ramezanali F, Khalili G, Jahangiri N, Ahmadi J *et al*. Metabolic syndrome in infertile women with polycystic ovarian syndrome. Arch Endocrinol Metab. 2016; pii: S2359-39972016005002107.

[85] Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. Hum Reprod Update 2006; 12: 673-83. http://dx.doi.org/10.1093/humupd/dml036

Received on 06-03-2016 Accepted on 25-03-2016 Published on 31-03-2016

http://dx.doi.org/10.15379/2408-9761.2016.03.01.02