NTU Journal of Pure Sceinces (2024) 3 (4) : 25-32
DOI: https://doi.org/10.56286/ntujps.v3i4

IRAQI Academic Scientific Journals

ISSN: 2789-1089 EISSN: 2789-1097
NTU Journal of Pure Sciences
Available online at: https://journals.ntu.edu.iq/index.php/NTU-JPS/index

Unraveling Immune Regulatory Mechanisms in PCOS: Role of T Regulatory Cells and Receptors

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Article Informations

Received: 09-02- 2024,
Accepted: 29-09-2024,
Published online: 31-12-2024

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Key Words:
PCOS,
T Regulatory Cells,
Immune Dysregulation,
Chronic Low-grade Inflammation,
Hormonal Imbalances .

A B S T R A C T

Polycystic ovary syndrome (PCOS) is a complex condition influenced by endocrine and immunological abnormalities, including chronic low-grade inflammation. This inflammation involves dysfunctional endotheliocytes, leukocyte accumulation, and pro-inflammatory factor dysregulation. Immune cells and regulatory molecules play a critical role in maintaining metabolic balance and modulating immune responses in PCOS. Hormonal imbalances, such as low progesterone levels due to irregular or absent ovulation, can overstimulate the immune system, leading to autoantibody production. Immune cell dysfunction and cytokine imbalances are also linked to insulin resistance, hyperandrogenism, and obesity, further contributing to inflammation. Obesity in PCOS exacerbates immune dysfunction, creating an inflammatory environment that impacts fertility. Autoimmune diseases may also arise from hormonal disruptions. Studies highlight the role of T regulatory cells (Tregs) and ovarian cytokine imbalances in PCOS pathogenesis, leading to androgen overproduction and ovulation loss. Understanding immune dysregulation in PCOS could identify new therapeutic targets to improve fertility outcomes..

Introduction

Polycystic ovary syndrome (PCOS) affects women in their reproductive years such as periods, excess hair growth acne, and weight gain [1]. It is affected by variables such as low-grade inflammation, hormonal imbalance, insulin resistance, obesity, and hyperandrogenism [2], [3]. Immune system dysfunction may occur as an outcome of obesity, especially in females who suffer from this condition. Imbalances, immune system disorders, genetics, and environmental factors can lead to PCOS [4]. During the study of PCOS, it is critical to keep a healthy balance and regulate immunity because there are indications that immune cells and regulatory molecules are involved in the development of this syndrome [5]. PCOS is a degenerative immune system disease resulting from hormonal imbalance. This affects the system's functioning [6], [7]. The dysfunction of the immune system in PCOS is also related to gut microbiome composition, which could change its functions and result in inflammation [8]. To enhance therapy options, a better understanding of how immunological dysregulation affects PCOS is essential. Immunomodulatory therapies are emerging as dependable therapeutic applications and offer chances to treat patients using some types of immune pathways [9]. An implication for the development of effective treatments for PCOS is that we should develop further knowledge regarding how immune function interplays with other processes in physiology and is related to PCOS in female hosts [10]. PCOS has a firm genetic foundation whereby there are several linked loci and an inheritance pattern that erupts autosomal dominant [11]. PCOS intrinsic nature is genetic work, infertility, and metabolic and reproductive effects that are associated with the condition may be determined by genes [12]. The pathophysiology of PCOS is linked with hormonal components, immunological imbalance, and continued low-grade inflammation [13]. An intricate relationship exists among immune disorders, systemic inflammation, and obesity. Epigenetic programming is also associated with PCOS development [14]. In the first place, it is a combination of genetic predisposition that implies an immunological disbalance and hormonal impact on PCOS along with various epigenetic programming [15], [16]. This study analyze the complex interaction between immunomodulators and other factors that influence PCOS development. It explores the role of immune imbalance in physiological processes. It addresses the debate regarding hormonal imbalances, genetics, and gut microbiome pertinent to immune dysfunction and chronic inflammation in PCOS.

1. Methods

A structured literature review was conducted to explore the role of immune regulatory mechanisms, particularly T regulatory (Treg) cells and receptors, in the pathogenesis of polycystic ovary syndrome (PCOS). Scientific databases, including PubMed, Scopus, and Web of Science, were searched for articles published up to 2024. Studies were included based on their relevance to immune regulation and PCOS-related mechanisms, while non-peer-reviewed articles, irrelevant studies, and those lacking detailed methodologies were excluded. Key data on immune cell dysfunction, cytokine imbalance, and the interaction between immune regulation and hormonal abnormalities were extracted and synthesized into thematic areas. This narrative synthesis highlights the interplay between chronic inflammation, Treg cell activity, and metabolic dysfunction in PCOS, with the aim of identifying potential therapeutic targets.

2. Pathophysiology of PCOS

The pathophysiology of PCOS is intricate as it involves the interplay of various factors. It can be better understood by examining the primary abnormalities and their interactions. PCOS is a condition that results from a combination of genetic and epigenetic changes, abnormalities in the ovaries, changes in the production of hormones, variations in the nervous and endocrine systems, and modifications in the metabolism. It is also influenced by factors such as inflammation, food, physical activity, and exposure to substances that disturb the endocrine system [17]. Figure 1, shows women with PCOS experience irregularities in their ovarian function, characterized by excessive release of androgens and dysfunction in ovulation, leading to the development of polycystic ovarian morphology (PCOM). The excessive production of androgens is a result of malfunctioning theca cells and/or the hypothalamus-pituitary-ovarian axis. Hyperandrogenism, on the other hand, disrupts the normal pulsation of Gonadotropin-releasing hormone (GnRH) and the secretion of gonadotropins due to irregular feedback from progesterone and estrogen. Patients with PCOS exhibit atypical secretion of gonadotropins, specifically a high ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH). This hormonal imbalance leads to malfunction in the ovaries, resulting in excessive production of androgens. Moreover, the elevated levels of anti-Müllerian hormone (AMH) produced by the pre-antral follicles that gather in the ovaries of women with PCOS worsen the dysfunction of the ovaries by negatively impacting the follicular microenvironment or the pulsation of GnRH. Hyperandrogenism is exacerbated by hyperinsulinemia, which occurs as a result of insulin resistance. Hyperinsulinemia stimulates theca cells to secrete more androgens and inhibits the liver's production of sex hormone-binding globulin (SHBG). This leads to an increase in the amount

of bioactive-free testosterone in the bloodstream. Insulin resistance arises in tissues like the liver and muscle and is linked to visceral adiposity and dysfunctional adipocytes, which are worsened by hyperandrogenism [18].

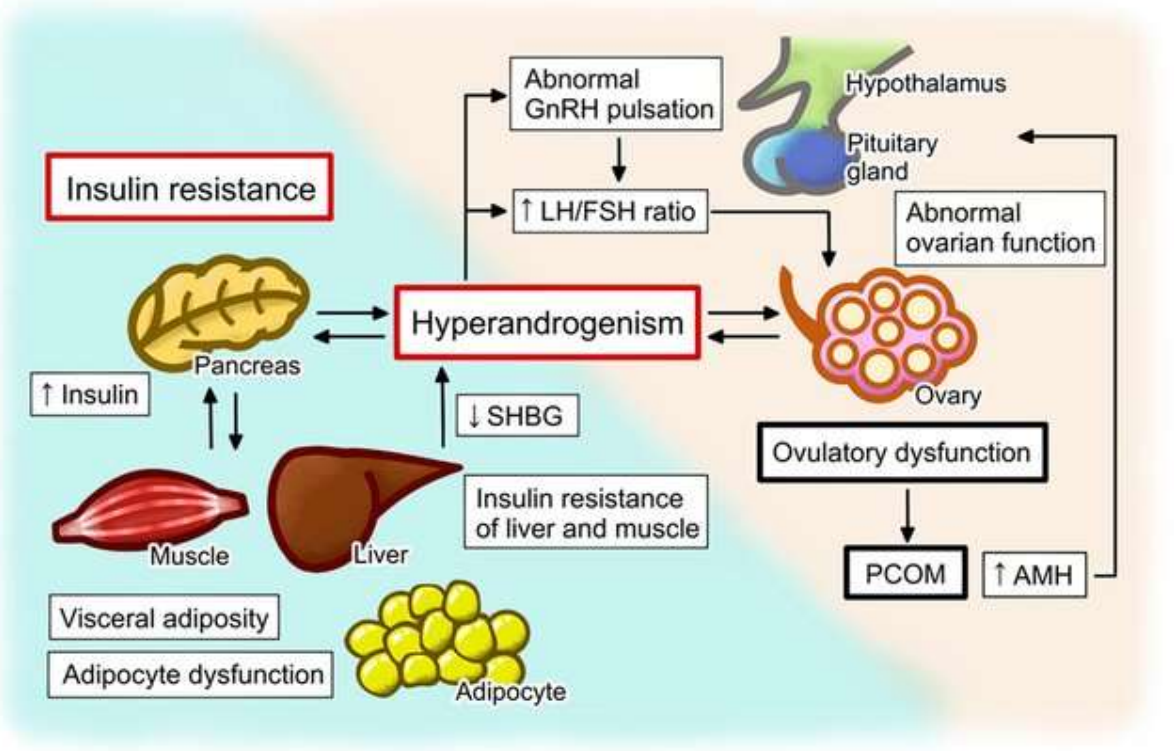

Figure 1. The pathophysiology of polycystic ovary syndrome (PCOS) is caused by androgen hypersecretion and ovulatory disruption. Hyperandrogenism impacts GnRH pulsation and gonadotropin secretion via progesterone and estrogen feedback, while theca cell and hypothalamus-pituitary-ovarian axis failure produces androgen hypersecretion PCOS patients' high LH/FSH ratio causes ovarian dysfunction and androgen hypersecretion. In patients with PCOS, high AMH levels from pre-/small antral follicles impair the follicular microenvironment and/or GnRH pulsation, exacerbating ovarian dysfunction Insulin resistance and hyperinsulinemia aggravate hyperandrogenism. Theca cells release more androgen and hyperinsulinemia inhibits hepatic SHBG production, elevating blood bioactive free testosterone. Due to liver and muscle insulin resistance, hyperandrogenism causes visceral obesity and adipocyte dysfunction. [18].

3. Immune Dysregulation in PCOS

3.1. PCOS Development Evidence Immune Involvement

The primary relationship between immune dysregulation and chronic low-grade inflammation in PCOS is mediated by visceral fat accumulation along with hyperandrogenemia [11]. High levels of circulating inflammatory markers suggest the key role that immune cells and molecules play in PCOS progression. Furthermore, the immune factors to the follicular microenvironment may also trigger insulin resistance and change ovarian phenotype [6]. The condition also has a connection with autoimmune thyroiditis, which points to an affiliation between immune dysregulation and PCOS. Understanding these immunoregulatory mechanisms is essential for the development of precise therapeutic approaches to control PCOS signs [19,20]. Figure one demonstrates how visceral adipocytes can impact insulin activity, resulting in issues such as impaired glucose tolerance, hyperinsulinemia, and insulin resistance [20]. Hyperinsulinemia imitates the trophic effect of LH on theca cells, leading to an increase in androgen production. Finally, adipose tissue contains a significant amount of immune cells (macrophages, monocytes) that release cytokines interleukin -6 (IL-6), Tumor necrosis factor-alpha (TNF-α), interleukin -6 (IL-1), and Monocyte chemoattractant protein-1 (MCP-1) linked to the inflammatory process in PCOS [20]. Also, IL-6 contributes to the regulation of immune response [21]. The shift of visceral adipose macrophages from M2 to M1 (M1 macrophages are mainly involved in pro-inflammatory responses and M2 macrophages are mainly involved in anti-inflammatory responses) amplifies the release of proinflammatory cytokines from adipocytes. There are certain abnormalities in peripheral immune cells, such as a bias towards Type 1 and 17 T helper (Th1 and Th17) cells, a reduction in T Regulatory Cells (Treg) cells, and an elevation in Natural killer (NK) cells. It is worth mentioning that patients with PCOS exhibit increased levels of IL-1 and IL-18 in their follicular fluid and serum, this is accompanied by the activation of the Nuclear factor kappa-light-chain-enhancer of activated B (NF-κB) pathway and the formation of NLR family pyrin domain containing 3 (NLRP3) inflammasome in ovarian granulosa cells. Ovarian pathology is characterized by changes

in steroidogenesis, increased levels of androgens, apoptosis of granulosa cells and luteal cells, halted development of follicles, defects in chromosomal maturation of oocytes, and reduced quality of oocytes [16,22]. The subfertility associated with PCOS is caused by impaired NK cell recruitment, disrupted cellular and cytokine pathways involved in implantation, altered oocyte quality, and anovulation [20].

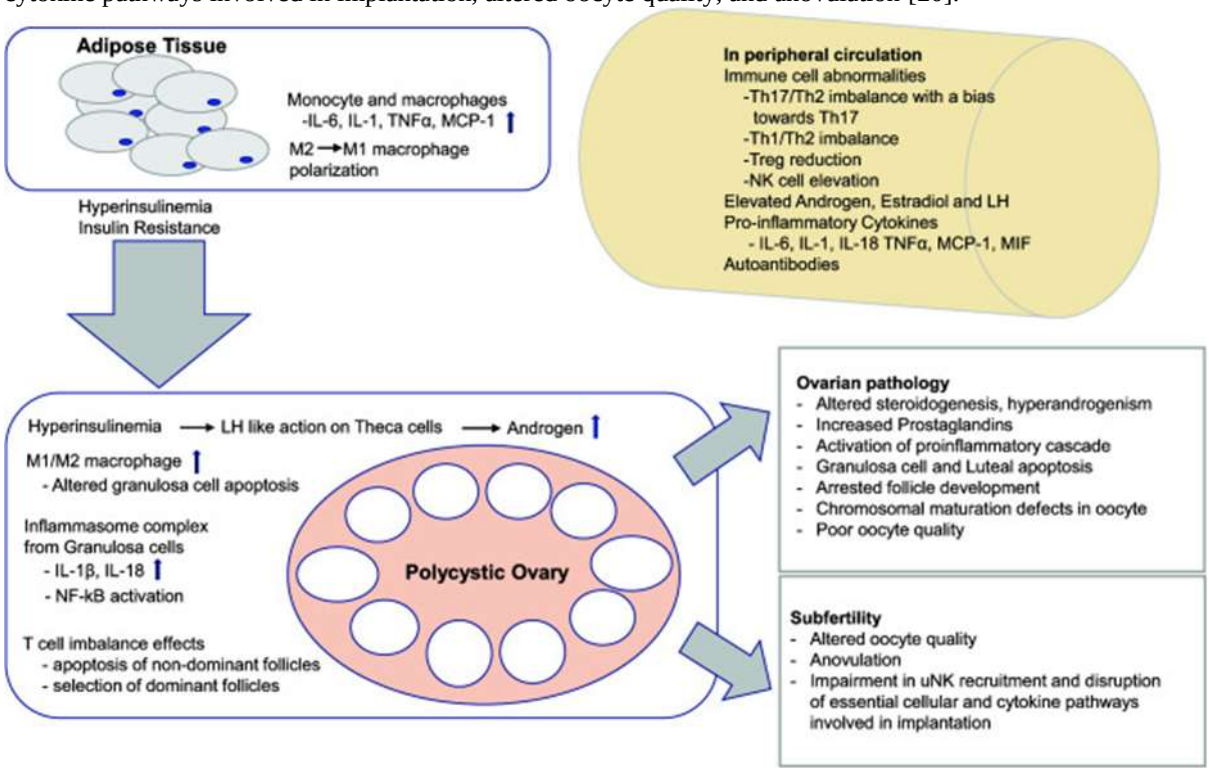

Figure 2. Visceral adipocyte insulin activity decreases glucose tolerance, raises insulin, and promotes insulin resistance. High insulin increases trophic LH-like theca cell androgen. Finally, fat tissue macrophages and monocytes release PCOS-inflamming cytokines. IL-6, TNF-α, IL-1, and MCP-1 are cytokines. Adipocytes release more proinflammatory cytokines when visceral adipose macrophages polarize from M2 to M1 (M1s are pro-inflammatory, M2s are anti-inflammatory). Ovarian granulosa cells in PCOS patients with NF-κB pathway activation and NLRP3 inflammasome production show abnormal peripheral immune cells, including Th1 and Th17 bias, reduced Tregs, and increased NK These cells also show elevated IL-1β and IL-18 levels. The ovarian disease causes steroidogenesis alterations, hyperandrogenism, granulosa cell and luteal mortality, chromosomal maturation difficulties, low oocyte quality, and delayed follicular development [PCOS reduces NK cell recruitment and cellular and cytokine pathways involved in implantation, oocyte quality, and anovulation, causing subfertility. [20]

3.2. Types of immune cells implicated in PCOS

The pathogenesis of PCOS has generated increasing interest in the role played by immune cells in inducing as well as promoting this disease. Studies suggest that many immune cells with T lymphocytes, NK cells, and B cells are related to the pathogenesis of PCOS [23]. In the Woman with PCOS, studies have indicated that there is an imbalance in leukocyte subsets which includes lymphocytes and neutrophils [24]. Furthermore, there is an increase in the number of NK cells found to be circulating among those with PCOS. Endometrial NK cell dysfunction has also been associated with subfertility in women suffering from PCOS, emphasizing the adverse implications for reproductive performance. The presence of CD68+ macrophages and CD163+ M2 macrophage infiltration in endometrial samples from PCOS infertile individuals suggests a disturbance of suitable populations, which may result in reproductive issues [20]. The fact that many immune cells are defined additionally highlights the relatively complicated association between immunoregulation and the pathophysiology of PCOS. This, therefore, shows that these results may be useful for determining some of the immunological reactions to PCOS targeted at treatment [25].

3.3. Highlighting immune regulatory mechanisms

Many women of reproductive age suffer from polycystic ovarian syndrome disease, a chronic condition that presents with the phenomenon of polycystic morphology and has hormonal imbalances [11]. Our deeper understanding of the underlying complex relationship between PCOS and immune system dysfunction provides further insight into how this disease develops. PCOS is a condition that involves hormonal imbalance and hyperandrogenism that can cause monocyte infiltration into the ovary. This leads to the liberation of

inflammatmatic factors which cause chronic ovarian tissues' inflammation. Scientists found that PCOS women had much higher levels of inflammatory factors in their peripheral blood as compared to non-PCOS individuals [12]. Low-grade chronic inflammation that results from low activity of immune cells could lead to dysfunction or imbalance in the factors related to immunity, which is associated with PCOS. This form of inflammation is mainly caused by the stored visceral fat that generates various cytokines. Moreover, the gut microbiome is crucial to immune dysregulation in PCOS and affects female follicular growth and ovulation [8]. It has been suggested that the composition of gut microbiota plays a role in pathological features in PCOS [26]. Generally, immune regulation can be considered a major player in PCOS development based on significant evidence. It is hoped that the knowledge about these mechanisms will reveal new ways of therapy methods to deal with immune deregulation observed in this intricate endocrine disorder [27].

4. T Regulatory Cells (Tregs) in PCOS

4.1. Introduction to Tregs and their role in immune tolerance

The study of PCOS highlights Tregs as a major research direction because they support immune tolerance and suppress autoimmunity [11]. Studies revealed varying results on the prevalence of Treg cells in PCOS women; hence, additional research is required to understand their specific activity. Other immune cells including CD4 +CD28 null cytotoxic T lymphocytes have been associated with PCOS and further contribute to augmented inflammation [23]. It was shown that Treg changes were associated with unfavorable outcomes of pregnancy and autoimmune disorders related to PCOS pointing out the share they may have in these complications. In summary, the specific role of Tregs in PCOS is not clear but there are indications that alteration to cellular populations impacts immunological dysfunction and chronic inflammation observed among patients [20].

4.2. Evidence linking Tregs to PCOS pathogenesis

Several studies have indicated the importance of T regulatory (Treg) cells in polycystic ovary syndrome (PCOS) [11]. These immune functions are essential for the maintenance of immunological homeostasis and control of inflammation. Studies have demonstrated that the number of Tregs in peripheral blood decreases among PCOS patients, leading to an increase in Th17/Treg ratio associated with autoimmune and inflammatory diseases [28]. This disparity leads to a lesser secreted amount of anti-inflammatory agents alongside the more presented autoreactive antibodies' contribution to chronic inflammation. In addition, an increased ratio of pro- and anti-inflammatory T lymphocytes and the respective cytokines further aggravates chronic inflammation in PCOS [28]. Certainly, the interplay between different groups of CD4+T cells, including Tregs is very dynamic as studies illustrate that there are reduced numbers of Treg in PCOS women compared to those observed in the control group [29]. Such an imbalance may be a very important feature in the development of PCOS. There is also evidence for considerable immune system regulation impairment among PCOS patients in women, including an increase in circulating CD4+ T-lymphocytes and a cytokines imbalance caused by pro-antiproinflammatory T-lymphocytes [23]. In general, many studies have suggested that Tregs are associated with the pathogenesis of PCOS by emphasizing their role in maintaining homeostasis and regulation of inflammation. Reduction of Tregs results in the impairment of pro- and anti-inflammatory responses, which is reflected in chronic inflammation associated with PCOS [20].

4.3. Mechanisms by which Tregs may influence PCOS development

The T regulatory (Treg) cells are pivotal in the onset of polycystic ovary syndrome. In PCOS patients, their depletion has been associated with an imbalance in the Th17/Treg ratio and autoimmune or inflammatory diseases. Differentiation between pro-inflammatory Th17 cells and anti-inflammatory Tregs is suggested in the genesis of PCOS, which leads to persisting inflammation. T lymphocyte population dysregulation and the interaction among various subgroups of CD4+T cells may also be involved in PCOS development [30]. Research illustrates that the loss of adaptive immunity and regulatory T-cell activity is a cause of PCOS pathogenesis, perpetuating chronic low-grade inflammation with hormonal imbalance, ovarian dysfunction, and impaired immune homeostasis in the ovary. Malfunctioning Tregs may modulate systemic inflammatory balance [29,31]. As such, Tregs play an important role in immune imbalance PCOS affecting inflammation, ovarian function, and whole-body homeostasis. The elucidation of how Tregs affect PCOS development is essential for finding effective therapeutic targets that will lead to balancing out immunity and relieving signs that arise from this multifaceted condition [32].

5. Regulatory Receptors in PCOS

4.1. Programmed Cell Death Protein 1 (PD-1) and its role in immune regulation

PD-1 which is a protein that can induce cell death has been determined to be an essential part of the PCOS immune imbalances [32]. PD-1 also contributes to the pathogenesis of autoimmune diseases such as Systemic lupus erythematosus (SLE) [33]. The levels of PD-1 in CD4+ and CD8+ T cells from patients with PCOS suffering from infertility have been shown to increase significantly. The expression of PD-1 on these T cells was determined to be positively associated with estradiol levels in serum and negatively related to interferon (IFN – γ) This supports that PD-1 may be involved in T cell impairment potentially contributing to the mechanism of PCOS [1]. Additionally, there are studies suggestive of a strong association between PD-1 and programmed cell death I polymorphisms and PCOS [34]. It has been suggested that PD-1/PD-L1 immune checkpoint pathways regulate the cytotoxic activity of decidua CD8+ T cells and maternal immunotolerance at the maternofetal interface [35]. However, one thing worth noting is that the immune dysregulation in PCOS goes beyond T cell dysfunction and covers other immunological factors including B-cells, NK cells, macrophages as well as IFN-γ, IL1 7A plus IL10. Hormonal factors worsen the immune imbalance that characterizes PCOS [36,37]. In general, knowing the function of PD-1 and other immune factors in PCOS pathogenesis provides a better understanding of possible treatment approaches that might disrupt immunological abnormalities helping manage symptoms characteristic of this complex syndrome [4].

4.2. Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and its significance in PCOS

PCOS implies immune dysregulation that has been revealed by research to be a function of CTLA-4 [20]. CTLA-4, a Treg surface protein is required for the immune tolerance function. It is associated with several autoimmune conditions including type 1 diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, breast cancer, and thyroid disease among others [20,38,39]. T cell immunity is regulated by CTLA-4, as it competitively binds CD80 and CDCD86 to inhibit immune responses that remain essential for the preservation of tolerance [20]. Several studies prove that people suffering from PCOS have a higher rate of inflammatory markers, pro-inflammatory cytokines, and altered immune cells indicating the connection between some immune factors to ovulatory dysfunction. Moreover, the occurrence of CD4+CD28 null T cytotoxic cells – a cell phenotype indicative of proinflammatory functions - is raised in PCOS. These cells are cytokine producers which include IFN-, TNF-, IL-18, and IL-2, all of which have also been identified as risk factors for cardiovascular disease [40,41]. The importance of CTLA-4 in PCOS is more than simply an immune tolerance preservation function. It may help to understand the inflammatory mechanisms underlying PCOS development. As such, deepening the understanding of this relationship between CTLA-4 and immune dysfunction in PCOS is essential for developing precision treatment methods that address singularly targeted mechanisms to adequately control symptoms [12].

4.3. The Transforming Growth Factor Beta (TGF-β) pathway, especially its involvement in PCOS and immune regulation.

TGF-β pathway in immunological modulation and the etiology of PCOS is increasingly recognized. Multi-role cytokine TGF-β participates in several key functions that include immune system control and regulation of cell proliferation, differentiation, and death [42]. TGF-β also contributes to the pathogenesis of Osteoarthritis, gastric and colorectal cancer, and asthma [43–45]. TGF-beta signaling could contribute to the complex interplay between dysregulation, abnormal metabolism, and immunological defects in PCOS [46]. This path is essential to retain the T regulatory cells' activity, which plays a critical role in preventing autoimmune diseases and maintaining balanced immunities[47]. In this condition, longstanding low-grade inflammation has affected TGF-β signaling [48,49]. Additionally, the TGF-β pathway has been linked to fibrotic changes in PCOS women's ovaries indicating its involvement as part of disease-associated ovarian pathology[50]. The examination of TGF-β signaling concerning PCOS shows brilliant treatment alternatives. The immunologic and inflammatory aspects of improving the welfare of PCOS could theoretically relieve drugs that act on this cascade[51]. To design personalized care, a deep knowledge of the TGF-β pathway for PCOS is required. The role of TGF beta in PCOS can allow opportunities for customized treatments.

Conclusion

PCOS is a disorder that is caused by altered immune response, hormonal, and metabolic changes. Excessive androgen and persistent low-grade inflammation have a very close relationship which makes this condition difficult to manage. Using chemical and immune cell regulation, the reaction to polycystic ovary syndrome determines metabolic equilibrium. Some of the factors that lead to dysregulation in PCOS are Tregs, regulatory receptors like PD-1 and CTLA-4 B cells NK cells as well as macrophages. The dysregulation of the immune system can contribute to the pathogenesis of PCOS and, this is characterized by the persistence of inflammation and dysfunction.

Competing Interests

The authors declare that there is no conflict of interest.

Acknowledgments.

The authors would like to University of Baghdad and Mustansiriyah University to provide the necessary facilities to conduct the research..

References

[1] Luan, Y., Zhang, L., Peng, Y., Li, Y., Liu, R. and Yin, C. (2022) Immune regulation in polycystic ovary syndrome. Clinica Chimica Acta, 531, pp. 265–272.

[2] Hu, M., Zhang, Y., Lu, Y., Han, J., Guo, T., Cui, P., et al. (2023) Regulatory mechanisms of HMGB1 and its receptors in polycystic ovary syndrome-driven gravid uterine inflammation. The FEBS Journal, 290(7), pp. 1874–1906.

[3] Ibraheem, Q.A., Al Obaidy, L.H.A., Nasir, G.A. and Al Obaidi, M.T. (2020) Fat mass and obesity association gene polymorphism in PCOS Iraqi women. Baghdad Science Journal, 17(3 Suppl.), p. 1103.

[4] Johnson, B.S. and Laloraya, M. (2022) Polycystic ovary syndrome and immune deregulation: what do hormones want to say? Exploration of Immunology, 2(3), pp. 393–413.

[5] Sikiru, A.B., Adeniran, M.A., Akinola, K., Behera, H., Kalaignazhal, G. and Egena, S.S.A. (2023) Unraveling the complexity of the molecular pathways associated with polycystic ovary syndrome (PCOS) and identifying molecular targets for therapeutic development: A review of literature. Middle East Fertility Society Journal, 28(1), p. 16.

[6] Elpidio, L.N.S., de Alencar, J.B., Tsuneto, P.Y., Alves, H.V., Toretta, M.T., Taura, S.K.I., et al. (2018) Killer-cell immunoglobulin-like receptors associated with polycystic ovary syndrome. Journal of Reproductive Immunology, 130, pp. 1–6.

[7] Alsaadi, Y.L. and Mohamad, B.J. (2019) Prevalence of hyperandrogenism in Iraqi women with polycystic ovary syndrome. Iraqi Journal of Science, pp. 2600–2608.

[8] Wu, J., Wang, K., Wang, X., Pang, Y. and Jiang, C. (2021) The role of the gut microbiome and its metabolites in metabolic diseases. Protein & Cell, 12(5), pp. 360–373.

[9] Calcaterra, V., Rossi, V., Massini, G., Casini, F., Zuccotti, G. and Fabiano, V. (2023) Probiotics and polycystic ovary syndrome: A perspective for management in adolescents with obesity. Nutrients, 15(14), p. 3144.

[10] Stepto, N.K., Moreno-Asso, A., McIlvenna, L.C., Walters, K.A. and Rodgers, R.J. (2019) Molecular mechanisms of insulin resistance in polycystic ovary syndrome: unraveling the conundrum in skeletal muscle? The Journal of Clinical Endocrinology & Metabolism, 104(11), pp. 5372–5381.

[11] Hu, C., Pang, B., Ma, Z. and Yi, H. (2020) Immunophenotypic profiles in polycystic ovary syndrome. Mediators of Inflammation.

[12] Wang, J., Yin, T. and Liu, S. (2023) Dysregulation of immune response in PCOS organ system. Frontiers in Immunology, 14, p. 1169232.

[13] Hiam, D., Simar, D., Laker, R., Altıntaş, A., Gibson-Helm, M., Fletcher, E., et al. (2019) Epigenetic reprogramming of immune cells in women with PCOS impacts genes controlling reproductive function. The Journal of Clinical Endocrinology & Metabolism, 104(12), pp. 6155–6170.

[14] Khatun, M., Lundin, K., Naillat, F., Loog, L., Saarela, U., Tuuri, T., et al. (2023) Induced pluripotent stem cells as a possible approach for exploring the pathophysiology of polycystic ovary syndrome (PCOS). Stem Cell Reviews and Reports, pp. 1–21.

[15] Kicińska, A.M., Maksym, R.B., Zabielska-Kaczorowska, M.A., Stachowska, A. and Babińska, A. (2023) Immunological and metabolic causes of infertility in polycystic ovary syndrome. Biomedicines, 11(6), p. 1567.

[16] Rosenfield, R.L. and Ehrmann, D.A. (2016) The pathogenesis of polycystic ovary syndrome (PCOS): the hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocrine Reviews, 37(5), pp. 467–520.

[17] Raja, M.H.R., Javed, M.A. and Rehman, R. (2024) Pathophysiology of polycystic ovary syndrome. in: Polycystic Ovary Syndrome. Elsevier, pp. 23–32.

[18] Harada, M. (2022) Pathophysiology of polycystic ovary syndrome revisited: current understanding and perspectives regarding future research. Reproductive Medicine and Biology, 21(1), p. e12487.

[19] Al-Qaisi, S.M.A. and Al-Shammaa, N.M.J. (2017) Effect of Anti-Mullerian Hormone (AMH) on hyperthyroidism with and without polycystic ovarian syndrome (PCOS) in female patients. Iraqi Journal of Science, pp. 1808–1814.

[20] Banerjee, S., Cooney, L.G. and Stanic, A.K. (2023) Immune dysfunction in polycystic ovary syndrome. Immunohorizons, 7(5), pp. 323–332.

[21] Al-Naqqash, S., Jawad, M.M., Al-Asady, Z.T.S. and Abdulrazaq, S.A. (2021) Evaluation of EOS gene expression and IL-6 serum levels in Iraqi patients with psoriasis. Al-Rafidain Journal of Medical Sciences, 1, pp. 89–93.

[22] Al-Kubaisi, M.I. and Al-Abassi, H.M. (2019) Determination of IL-18, C3 and insulin in Iraqi females with polycystic ovary syndrome (PCOS). Biochemical & Cellular Archives, 19(2).

[23] Moulana, M. (2023) Androgen-induced cardiovascular risk in polycystic ovary syndrome: The role of T lymphocytes. Life, 13(4), p. 1010.

[24] Ascani, A., Torstensson, S., Risal, S., Lu, H., Eriksson, G., Li, C., et al. (2023) The role of B cells in immune cell activation in polycystic ovary syndrome. eLife, 12, p. e86454.

[25] Abraham Gnanadass, S., Divakar Prabhu, Y. and Valsala Gopalakrishnan, A. (2021) Association of metabolic and inflammatory markers with polycystic ovarian syndrome (PCOS): An update. Archives of Gynecology and Obstetrics, 303, pp. 631–643.

[26] Xu, Y., Zhou, Z.-Y., Pan, J.-X. and Huang, H.-F. (2022) Associations between asthma and polycystic ovary syndrome: Current perspectives. Frontiers in Endocrinology, 13, p. 936948.

[27] Guo, H., Luo, J. and Lin, H. (2023) Exploration of the pathogenesis of polycystic ovary syndrome based on gut microbiota: A review. Medicine, 102(50), p. e36075.
[28] He, S., Mao, X., Lei, H., Dong, B., Guo, D., Zheng, B., et al. (2020) Peripheral blood inflammatory-immune cells as a predictor of infertility in women with polycystic ovary syndrome. Journal of Inflammation Research, pp. 441–450.
[29] Ye, Z., Zhao, J. and Li, R. (2022) Effects of immune cells and cytokines on the endometrial immune microenvironment in polycystic ovary syndrome. Gynecology and Obstetrics Clinical Medicine.
[30] Aru, N., Yang, C., Chen, Y. and Liu, J. (2023) Causal association of immune cells and polycystic ovarian syndrome: A Mendelian randomization study. Frontiers in Endocrinology, 14.
[31] Ho, C.-H., Chang, C.-M., Li, H.-Y., Shen, H.-Y., Lieu, F.-K. and Wang, P.S.-G. (2020) Dysregulated immunological and metabolic functions discovered by a polygenic integrative analysis for PCOS. Reproductive BioMedicine Online, 40(1), pp. 160–167.
[32] Parker, J. (2023) Pathophysiological effects of contemporary lifestyle on evolutionary-conserved survival mechanisms in polycystic ovary syndrome. Life, 13(4), p. 1056.
[33] Ismael, A.K. and Al-Abassi, H.M. (2023) PD-1 and NFATc1 as promising immunotherapy for SLE patients. Journal of Population Therapeutics and Clinical Pharmacology, 30(5), pp. 260–266.
[34] Shabbir, S., Khurram, E., Moorthi, V.S., Eissa, Y.T.H., Kamal, M.A. and Butler, A.E. (2023) The interplay between androgens and the immune response in polycystic ovary syndrome. Journal of Translational Medicine, 21(1), p. 1.
[35] Albaghdadi, A.J.H. and Kan, F.W.K. (2021) Therapeutic potentials of low-dose tacrolimus for aberrant endometrial features in polycystic ovary syndrome. International Journal of Molecular Sciences, 22(6), p. 2872.
[36] Chugh, R.M., Park, H., El Andaloussi, A., Elsharoud, A., Esfandyari, S., Ulin, M., et al. (2021) Mesenchymal stem cell therapy ameliorates metabolic dysfunction and restores fertility in a PCOS mouse model through interleukin-10. Stem Cell Research & Therapy, 12, p. 1.
[37] Su, Z., Su, W., Li, C., Ding, P. and Wang, Y. (2023) Identification and immune features of cuproptosis-related molecular clusters in polycystic ovary syndrome. Scientific Reports, 13(1), p. 980.
[38] Al-Saadi, H.H.A., Al-Abassi, H.M. and Jawad, M.M. (2021) Role of inhibitory check point (CTLA-4) in Iraqi women with breast cancer. Indian Journal of Forensic Medicine & Toxicology, 15(3), pp. 2337–2347.
[39] Scheinecker, C., Göschl, L. and Bonelli, M. (2020) Treg cells in health and autoimmune diseases: New insights from single cell analysis. Journal of Autoimmunity, 110, p. 102376.
[40] Abdullah, M.R. and Alabassi, H.M. (2024) The potential influence of immune modulatory molecules (TGF-βIII and CTLA-4) in pathogenicity of PCOS. Karbala International Journal of Modern Science, 10(3), p. 2.
[41] Ibrahim, M.I.I. and Al-Saffar, J.M. (2018) Serum level evaluation of interleukin-18 in obese women with polycystic ovary syndrome. Iraqi Journal of Science, pp. 1989–1994.
[42] Li, M., Liang, W., Luo, Y., Wang, J., Liu, X., Li, S., et al. (2024) Transforming growth factor-β1 mediates the SMAD4/BMF pathway to regulate ovarian granulosa cell apoptosis in small tail Han sheep. Theriogenology, 214, pp. 360–369.
[43] Alabassi, H.M. (2019) TGF-BRIII gene expression and TGF-B1 serum level in Iraqi children with asthma. Journal of Pharmaceutical Sciences and Research, 11(6), pp. 2292–2294.
[44] Rasheed, R.A. and Al-Abassi, H.M. (2021) TGF-BETA3 (gene expression) as a new biological marker for diagnosing gastric and colorectal cancer. Biochemical & Cellular Archives, 21(1).
[45] Abdullah, D.A.A., Alabassi, H.M., Al-Sharqi, S.A.H. and Wahab, M.S. (2022) Possible etiological role of CD16 and TGF-β1 in the pathogenesis of osteoarthritis in Iraqi patients. Biochemical & Cellular Archives, 22(1).
[46] Zhu, M., Xu, M., Zhang, J. and Zheng, C. (2023) The role of Hippo pathway in ovarian development. Frontiers in Physiology, 14, p. 1198873.
[47] Zhao, X., Wang, M., Wen, Z., Lu, Z., Cui, L., Fu, C., et al. (2021) GLP-1 receptor agonists: Beyond their pancreatic effects. Frontiers in Endocrinology, 12, p. 1040.
[48] Mahdi, Q.A., A.R.S.A. and M.F.M. (2017) Measurement of ferritin and transforming growth factor-β1 levels in Iraqi women with polycystic ovary syndrome. Ibn AL-Haitham Journal for Pure and Applied Sciences, 29(2), pp. 171–184.
[49] Pei, C.-Z., Jin, L. and Baek, K.-H. (2021) Pathogenetic analysis of polycystic ovary syndrome from the perspective of omics. Biomedicine & Pharmacotherapy, 142, p. 112031.
[50] Li, Y., Guo, J., Deng, S., Gao, Z., Liu, Y. and Gu, Q. (2020) Fibrin facilitates mesenchymal stem cells to ameliorate rats with polycystic ovary syndrome. Applied Sciences, 10(10), p. 3598.
[51] Chen, Q., Zheng, B., Du, S. and Lin, Y. (2021) Explore the potential molecular mechanism of polycystic ovarian syndrome by protein–protein interaction network analysis. Taiwanese Journal of Obstetrics and Gynecology, 60(5), pp. 807–815.