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The Role of ADAM17 in PCOS Pathogenesis: A review Paper

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Abstract

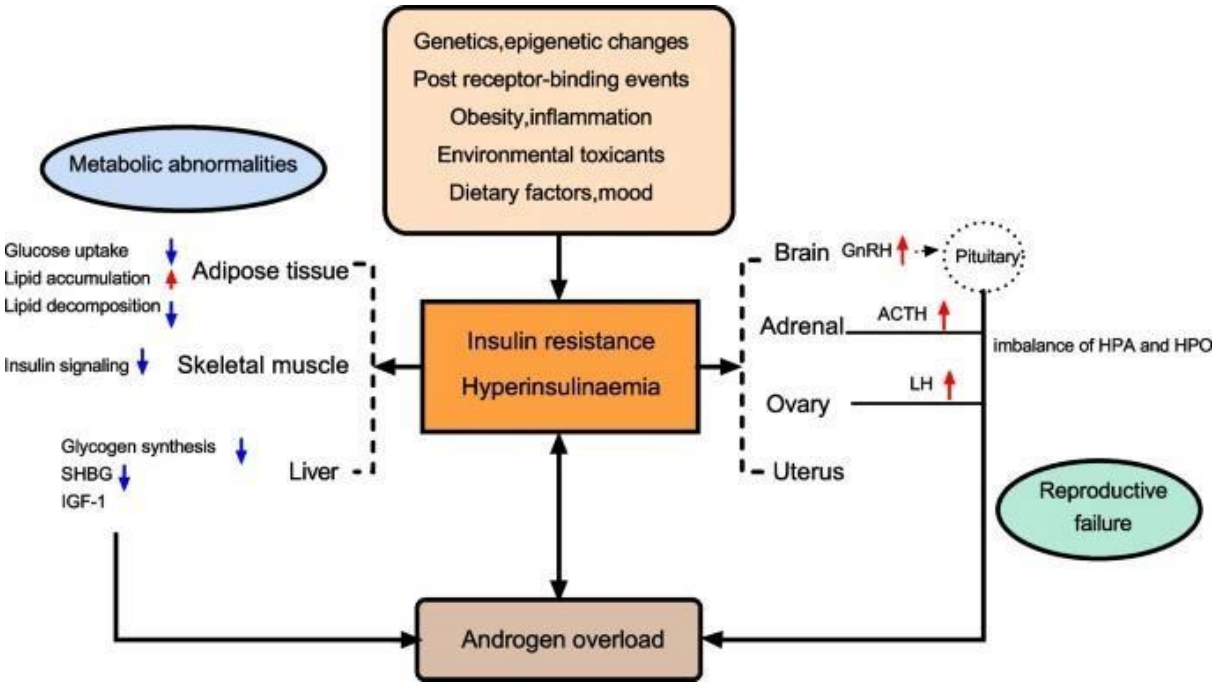
This review primarily focuses on the Role of metalloproteinase (ADAM 17). Gynecological disease contributes to approximately 4.5% of the worldwide disease burden. Gynecological problems in women of reproductive age are linked to both In terms of diagnosis and treatment. Because there are no defined biomarkers, identifying gynecological disorders, particularly malignancies, has been difficult in most cases, and histopathological exams remained the gold benchmark. M.M.P.s, ADAMs, and ADAMTSs, as well as their endogenous inhibitors (TIMPs), influence the protease-dependent bioavailability of local niche components. ADAM 17 has been implicated in various pathological processes, including inflammatory response, cardiovascular disease, and, recently, ovarian dysfunction. Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age and is characterized by chronic anovulation, insulin resistance, and increased prevalence of cardiovascular risk factors. So far, the PCOS has not assessed the circulating levels of MMPs and their tissue inhibitors (TIMPs). This review will concentrate on the Role of (ADAM17) in regulating gynecological disorder (PCOS) and their consequent modulation for therapeutic intervention.

Keywords: PCOS, ADAM17, Pathogenesis

1. Introduction

PCOS is now regarded as one of the most prevalent endocrine conditions in women of reproductive age (Deswal et al., 2020), having a worldwide incidence ranging from 6 to 21%, depending on the criteria for diagnosis (Neven et al., 2018). PCOS is a diverse disease consisting of hyperandrogenism, dysfunctional ovulation, and polycystic ovary morphology (Escobar-Morreale, 2018), as well as metabolic disorders that include insulin resistance (IR) and obesity, dyslipidemia, impaired glucose tolerance, overt type 2 diabetes mellitus, and

elevated systolic blood pressure, which is more common in obese young women with PCOS than in weight-matched controls (Giménez-Palomo et al., 2022). PCOS women had a significantly greater incidence of type 2 diabetes mellitus and hypertension when compared to age-matched controls (Kakoly et al., 2019), albeit not all studies support these findings. The underlying aetiology of PCOS, however, is unknown.



MATRIX METALLOPROTEINASES (MMPS) are zinc-binding proteolytic enzymes involved in extracellular matrix remodeling (Mondal et al., 2020). MMP activity is elevated in several diseases, including atherosclerosis and cardiovascular disease. MMP activity is regulated at several levels. ADAM17 can cleave membrane-bound proteins, including cytokines, growth factors, receptors, and adhesion molecules (Gheblawi et al., 2020). ADAM17 participates in various biological activities, including Inflammation, immunity, cell proliferation, and cell migration.

Recent studies have suggested that genetics, epigenetic changes, environmental factors, oxidative stress, chronic low-grade Inflammation, mitochondrial dysfunction, and metabolic disorders are involved in PCOS, thus damaging normal ovarian function. IR and compensatory hyperinsulinemia (HI) are considered major drivers of PCOS pathophysiology and are involved in the development of hyperandrogenaemia and reproductive dysfunction by various mechanisms (Zhao et al., 2023).

2. Clinical and Molecular Overview of PCOS

PCOS is complicated by factors such as irregular menstrual periods, hyperandrogenism, and hormonal abnormalities (Kostopoulou et al., 2020). PCOS is characterised by irregular menstrual periods, which may manifest as oligomenorrhea or even a complete absence of menstruation. These disruptions cause emotional and physical pain and play a crucial part in infertility, which is commonly linked with polycystic ovary syndrome (Witchel et al., 2019). Infertility is distressing and common because of the difficulties it causes in trying to conceive normally when ovulation and menstruation are irregular (Simionescu et al., 2021).

2.1 Clinical Characteristics of PCOS

2.1.1 Physiological Consequences:

Regarding infertility, concerns are substantial for women who have received a diagnosis of Polycystic Ovary Syndrome. PCOS is characterized by irregularities in menstrual cycles, which significantly contribute to infertility in those afflicted with the disorder (Zehravi et al., 2021). The absence of regular menstrual cycles and ovulation poses significant challenges for those seeking to conceive spontaneously. Ovulation, an essential phase of the menstrual cycle, is distinguished by the discharge of a mature egg from the ovaries, which can undergo fertilization. Anovulation, a condition distinguished by the absence of ovulation, is a common consequence of polycystic ovary syndrome (PCOS), which arises from hormonal disruptions and irregularities in the menstrual cycle. The absence of ovulation significantly diminishes the likelihood of conception, hence rendering infertility a widespread concern among women diagnosed with Polycystic Ovary Syndrome (PCOS) (Rohm et al., 2022).

2.1.2 Hormonal Imbalances in PCOS:

Polycystic Ovary Syndrome (PCOS) perturbs the intricate hormonal equilibrium inside the female physiology. One of the primary hormonal imbalances noticed in Polycystic Ovary Syndrome (PCOS) is the heightened levels of androgens, which are a group of hormones often associated with males. Elevated levels of androgens are frequently observed in persons diagnosed with polycystic ovary syndrome (PCOS). Elevated androgen levels are a contributing element to the manifestation of various distinctive symptoms linked to the condition, including menstrual cycle irregularities (Freeman et al., 2001) Androgens possess the capacity to impede the ovulation process through their interference with the development and subsequent discharge of eggs from the ovaries. Disruption of this kind is a major contributor to the irregular menstrual periods often seen in women with polycystic ovary syndrome. In addition, an excess of androgens has been linked to the development of hirsutism, characterised by an abnormal increase in hair growth across various body sites, including the face and chest (Ipsa et al., 2019).

2.1.3 Metabolic Disturbances in PCOS:

Insulin is pivotal in regulating blood glucose levels and facilitating glucose absorption into cells to support cellular energy metabolism (Sabir et al., 2019). Insulin resistance has the potential to alter the delicate balance in polycystic ovary syndrome (PCOS), resulting in metabolic abnormalities. Weight gain is a prominent outcome that impacts a considerable

number of women diagnosed with polycystic ovary syndrome (PCOS). The co-occurrence of hormonal abnormalities and insulin resistance can lead to an elevated susceptibility to obesity (Sanchez-Garrido & Tena-Sempere, 2020) .

2.1.4 Psychological Consequences:

Emotional Distress due to the lack of regularity and the inability to predict menstrual cycles can result in mental anguish and heightened anxiety in those diagnosed with Polycystic Ovary Syndrome (PCOS). The presence of ambiguity about fertility and the apprehension over potential long-term health implications serve to intensify these emotional difficulties (Light et al., 2021).

2.1.5 Hyperandrogenism in PCOS

Elevated concentrations of androgens distinguish PCOS (also referred to as male hormones) in the female body and are distinguished by hyperandrogenism. An excessive amount of acne and androgenic alopecia are among the numerous clinical manifestations that can be attributed to the underlying hormonal imbalance (Sanchez-Garrido & Tena-Sempere, 2020).

2.2 Molecular Mechanisms in PCOS

The precise biological pathways underlying polycystic ovary syndrome (PCOS) remain unclear. However, numerous major variables contribute to PCOS's onset and progression:

2.2.1 Insulin Resistance: PCOS is characterised by insulin resistance. It happens when the body's cells cannot respond efficiently to insulin, increasing blood sugar levels. Due to insulin resistance, the ovaries may be stimulated to create an abundance of androgens (male hormones). This hormonal disarray is a root cause of PCOS symptoms like irregular menstrual periods and hirsutism (Zeng et al., 2020).

2.2.2 Inflammation: PCOS patients frequently exhibit signs of chronic, low-grade Inflammation. C-reactive protein and other inflammatory indicators are higher in those who are afflicted. Insulin resistance and metabolic abnormalities may be exacerbated by inflammation (Rostamtabar et al., 2021).

2.2.3 Hormonal Dysregulation: PCOS alters how your body's hormones normally work. High amounts of testosterone and other androgens might cause a woman to have missed periods and unpredictable ovulation. Many of PCOS's clinical manifestations can be traced back to the underlying hormonal imbalance (Islam et al., 2019).

2.2.4 Genetic and Environmental Factors: The onset of PCOS is influenced by hereditary and environmental factors. Risk factors for polycystic ovary syndrome (PCOS) include a family history of the disorder and specific genetic variants. Environmental variables, such as diet and lifestyle, also have a role in the aetiology of PCOS (Kshetrimayum et al., 2019).

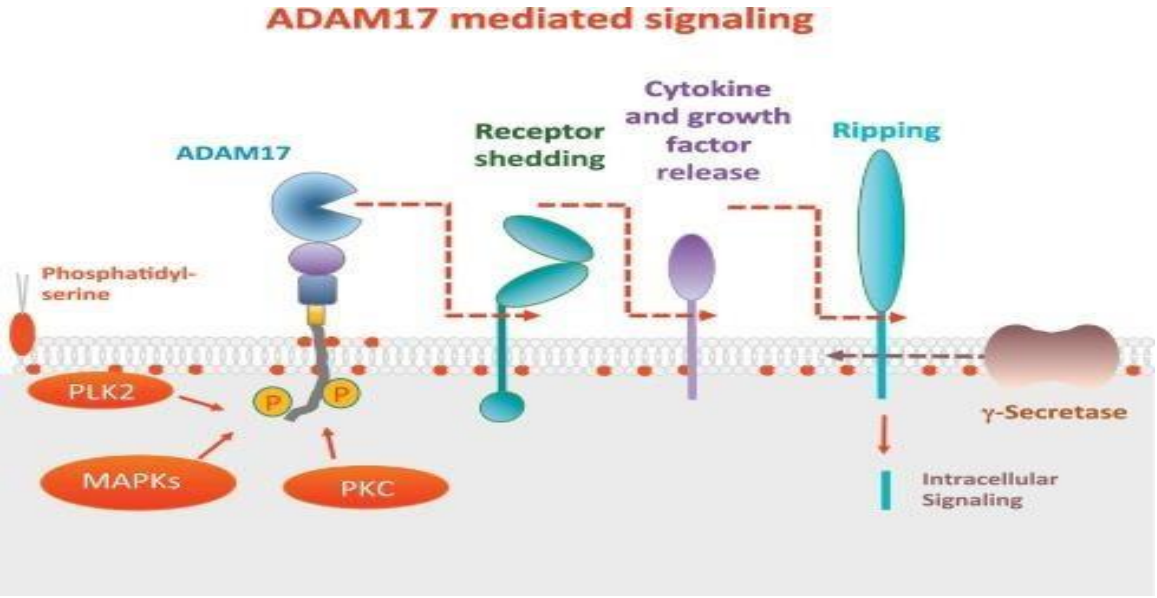
3.0 A disintegrant and metalloproteinase ADAM17

A disintegrant and metalloproteinase 17(ADAM 17) is a protein with several bodily functions. It participates in complex signalling pathways within cells and plays a role in proteolysis. Understanding the Role that ADAM17 plays in diverse cellular processes requires an

understanding of its structure and function (Düsterhöft, Lokau, et al., 2019). The initial discovery of ADAM17's Role in the shedding process of the proinflammatory cytokine TNF-α was documented in a study. A widely acknowledged association exists between TNF-α and obesity, Inflammation, and diabetes.

3.1 Structure of ADAM17:

The ADAM17 enzyme has a complex structure with multiple domains that all contribute to the enzyme's overall functionality. The pro-domain acts as a regulator, preventing ADAM17 from activating. The function of this mechanism is to inhibit premature proteolysis and sustain the enzyme's latency. The activation of ADAM17 entails the enzymatic cleavage or elimination of the pro-domain, enabling the metalloproteinase domain to attain catalytic activity. The enzymatic action of ADAM17 is primarily mediated by its metalloproteinase domain. This particular domain is accountable for the enzymatic cleavage of a diverse range of proteins attached to cellular membranes (Düsterhöft, Babendreyer, et al., 2019).



The proteolytic activities play a crucial role in cellular communication by liberating bioactive chemicals from the surface of cells, thereby beginning distinct signalling pathways. The disintegrant domain has distinctive sticky characteristics, crucial for cell adhesion and migration (Mahata & Corti, 2019). This domain mediates the interaction between ADAM17 and other proteins and the extracellular matrix, modulating cellular activity and motility. The membrane-proximal domain is a noteworthy constituent of ADAM17. The activity of the protein is intricately linked with its other domains, hence facilitating the process of membrane-bound protein shedding.

3.2 Enzymatic Function of ADAM17:

The enzymatic activity of ADAM17 plays a fundamental role in its significance throughout multiple physiological systems. The primary Role of ADAM17 is to facilitate the process of shedding membrane-bound proteins present in various cell types, such as hematopoietic cells. Shedding is crucial in various fundamental facets of cellular function and control (Xue et al., 2022).

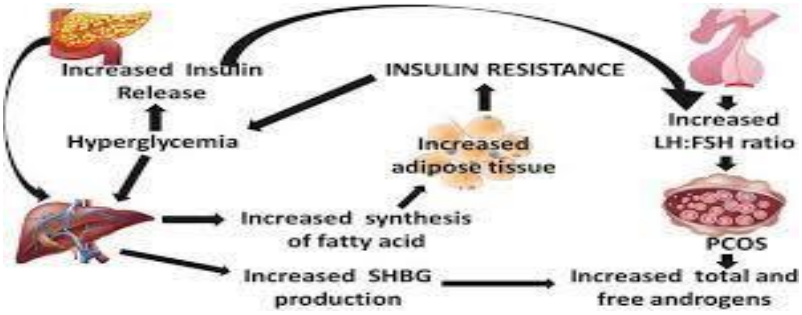
3.3 ADAM17-mediated shedding serves multiple functions:

The liberation of proteins attached to membranes, such as growth factors and cytokines, results in these biologically active molecules being discharged into the extracellular environment. Consequently, this process triggers distinct signalling cascades that govern essential cellular reactions. The sticky qualities of the disintegrant domain facilitate the ability of ADAM17 to influence cell adhesion (Grieve et al., 2017). ADAM17 is involved in cellular contacts, specifically with other proteins and the extracellular matrix, influencing cell-cell and cell-matrix connections. The abovementioned mechanisms encompass immunological responses, tissue regeneration, inflammatory reactions, and cellular migration.

4.0 ADAM17 Pathogenesis in PCOS

Recent studies have provided insights into a possible association between ADAM17 and Polycystic Ovary syndrome (PCOS), indicating that this metalloproteinase may play a significant role in developing this multifaceted illness (Kunvariya et al., 2023). The insights mentioned above possess significant therapeutic consequences, as an enhanced comprehension of the involvement of ADAM17 in polycystic ovary syndrome (PCOS) presents novel opportunities for diagnosing and treating this condition (Imanaka et al., 2020).

4.1 Insulin Resistance and Metabolic Disturbances:



Insulin resistance is a notable feature associated with PCOS (Zeng et al., 2020), (He & Li, 2020), which refers to a condition where the cellular reaction of the body to insulin is compromised (Hajam et al., 2022). When resistance is present, blood glucose levels rise, and secondary hyperinsulinemia develops (Taghipour et al., 2019), distinguished by the pancreas producing excessive insulin. ADAM17 has been recognised as a possible constituent within the intricate network governing insulin regulation. Previous research suggests that ADAM17 may have a major impact on the control of insulin resistance (Schumacher & Rose-John, 2022). Given that insulin resistance is a crucial element in the metabolic abnormalities that are frequently reported in patients with Polycystic Ovary Syndrome (PCOS), the significance of this subject cannot be overstated. Metabolic abnormalities encompass a multitude of disorders. Understanding the complex relationship between the insulin and ADAM17 pathways is crucial for elucidating its function in the pathophysiology of polycystic ovarian syndrome. More research may clarify potential treatment targets for managing insulin resistance and PCOS-related metabolic problems (Moldovan et al., 2021).

4.2 Hormonal Imbalances and PCOS:

The examination of the impact of ADAM17 on the secretion and modulation of these hormones is of great importance in comprehending its Role in the condition (Sisto et al., 2021).**Testosterone**: Increased levels of testosterone are a characteristic feature of polycystic ovary syndrome (PCOS) and play a role in the manifestation of several clinical symptoms, such as excessive hair growth (hirsutism) and the development of acne. The ovaries are recognised as a significant contributor to elevated testosterone levels in Polycystic Ovary Syndrome (PCOS); nevertheless, the precise mechanisms responsible for this excessive production are still being investigated. The putative Role of ADAM17 in the control of testosterone has recently gained significant attention in academic circles (Schumacher & Rose-John, 2019). Investigations examining the involvement of ADAM17 in the regulation of precursor molecule conversion to testosterone have the potential to offer valuable insights into the manifestation of hyperandrogenism observed in polycystic ovary syndrome (PCOS). Does ADAM17 impact the proteolytic cleavage of proteins attached to the cell membrane, thereby influencing testosterone synthesis in ovarian theca cells or other pertinent tissues? Further work is required to determine the connection between ADAM17 and the hormonal abnormalities that are characteristic of polycystic ovary syndrome (PCOS).

4.2.1 Luteinising Hormone (LH): Luteinising hormone (LH) is a crucial factor in the pathogenesis of polycystic ovary syndrome (PCOS) since it exerts a stimulatory effect on androgen synthesis originating from the theca cells within the ovaries (Lai et al., 2020). Polycystic ovary syndrome (PCOS) patients frequently exhibit heightened levels of luteinising hormone (LH) (Lai et al., 2020). The investigation of the potential impact of ADAM17 on the production of LH or its receptor signalling networks is a subject of interest within the field of polycystic ovary syndrome (PCOS) aetiology.

4.3 Disrupted ovarian androgen production: ADAM17 converts pro-androgens to their activated forms, testosterone and DHT These androgens can then attach to androgen receptors in ovarian cells, increasing androgen synthesis and secretion . One of the characteristics of PCOS is excessive production of androgen. ADAM17 cleaves the receptor for epidermal growth factor (EGFR), which is required for follicular development and maturation. ADAM17 cleavage of EGFR results in reduced EGFR signalling and poor follicular growth. Another symptom of PCOS is poor follicular development (Rodriguez Paris & Bertoldo, 2019).

4.4 Inflammation: ADAM17 plays multiple roles in the pathophysiology of PCOS inflammation. First, it can release proinflammatory cytokines from the surface of macrophages and other immune cells, such as IL-6 and TNF-. These can cause the body to enter a chronic inflammatory state, which can contribute to the development of insulin resistance, hyperandrogenism, and other PCOS-related symptoms[(Jung et al., 2019). ADAM17 can shed growth factors off the surface of ovarian thecal cells, such as TGF- and EGF. This can accelerate thecal cell proliferation and androgen synthesis, contributing to the emergence of hyperandrogenism in PCOS. ADAM17 can remove the androgen receptor from the surface of ovarian thecal cells. This can make cells more vulnerable to the actions of androgens, exacerbating hyperandrogenism. ADAM17 is important in the aetiology of PCOS inflammation. The release of proinflammatory cytokines and growth factors (Ciebiera et al., 2018).

4.5 Hyperandrogenism: When ABP is shed from theca cells, the amount of ABP accessible to bind to androgens decreases, resulting in higher blood levels of free androgens.ADAM17 may contribute to hyperandrogenism in PCOS through elevated resistance to insulin and Inflammation. Insulin resistance can result in higher circulation insulin levels, boosting androgen synthesis from theca cells. Inflammation can also boost theca cell synthesis of androgens (Huffman et al., 2021).

4.6 OBESITY: Women with PCOS have higher levels of ADAM17 expression in their fatty tissue. This increase in ADAM17 expression is linked to higher leptin and adiponectin shedding. Leptin is a satiety hormone that regulates appetite and food consumption. Adiponectin is an insulin-stimulating adipokine that aids in glucose metabolism (Floyd et al., 2022). Increased leptin and adiponectin shedding in PCOS may contribute to the metabolic abnormalities associated with the illness, such as insulin resistance and obesity. ADAM17, which is involved in the shedding of the androgen-binding globulin (ABG) protein, may also have a role in the elevated androgen levels seen in PCOS. ABG is a protein in the blood that transports androgens. When ABG levels are reduced, more androgens are released into the bloodstream. Obese people have higher levels of ADAM17 expression in their fatty tissue. This increase in ADAM17 expression is linked to higher leptin and adiponectin shedding. Obesity-related increased shedding of leptin and adiponectin may contribute to metabolic abnormalities such as insulin resistance and type 2 diabetes. ADAM17 could contribute to the increased Inflammation associated with obesity (Murata et al., 2022)**.**

4.7 Cardiovascular: ADAM17 is highly expressed in theca cells of PCOS women, and it has been associated with a higher risk of cardiovascular disease (CVD) (Kawai et al., 2021). One potential mechanism by which ADAM17 overexpression leads to CVD in PCOS is its function in TNF- shedding. TNF- is a proinflammatory cytokine linked to vascular Inflammation, atherogenesis, and thrombosis (Ciumărnean et al., 2022). ADAM17 overexpression increases TNF-shedding from theca cells, possibly contributing to CVD development. Another way that ADAM17 overexpression may contribute to CVD in PCOS is through its participation in IL-6 shedding. IL-6 is a proinflammatory cytokine that has been linked to insulin resistance, which is a key risk factor for CVD. ADAM17 amplification causes theca cells to secrete more IL-6, which can contribute to developing insulin resistance and CVDI.ADAM17 has been demonstrated to increase the stimulation of the renin-angiotensin-aldosterone system (RAAS), a further significant mediator of CVD, and its Role in the shedding of proinflammatory cytokines. The RAAS is a hormonal system that aids in blood pressure regulation (Poulsen & Fenton, 2019). Overexpression of ADAM17 can result in RAAS overactivation, which can trigger the development of hypertension, a major risk factor for CVD. Overall, ADAM17 overexpression contributes significantly to the development of CVD in PCOS. ADAM17 overexpression can cause vascular Inflammation, atherogenesis, thrombosis, hypertension, and other cardiovascular problems by boosting the shedding of proinflammatory cytokines and activating the RAAS (Adamcova et al., 2021).

5.0 Hypothesis and Discussion

The development of hypotheses is a crucial component of the scientific investigation process, providing a systematic framework for further research and investigation (Barilla et al., 2020).

5.1 Hypothesis 1: The Role of ADAM17 in Insulin Resistance in PCOS

Insulin Resistance in PCOS:

Polycystic ovarian syndrome (PCOS) is characterised by insulin resistance as a primary symptom. Insulin signalling is disrupted in patients who have polycystic ovary syndrome (PCOS), a medical disorder. This difficulty with insulin is the defining characteristic of PCOS. Research published in peer-reviewed scientific journals has found a correlation between insulin resistance and PCOS. Insulin dysfunction is a major contributor to the metabolic difficulties that are common in persons with polycystic ovary syndrome (PCOS), such as obesity and excessive blood sugar levels (Xie et al., 2022).

Hypothesis Formulation:

Patients who have been diagnosed with PCOS are thought to have insulin resistance since ADAM17 plays a direct role in the development of this condition. According to this hypothesis, insulin production by the pancreas can be controlled, at least in part, by the enzyme ADAM17. It would appear that ADAM17 can play a role in PCOS-related metabolic difficulties through the influence that it has on insulin resistance. PCOS characterises these metabolic problems.

Discussion:

ADAM17's Role in cleaving proteins off cell surfaces, where they participate in crucial signalling and regulatory processes, connects it to insulin resistance. Moftah and Eswayah (2023) note that knowing how ADAM17's actions alter how insulin operates is necessary to utilise this as a potential treatment fully. Studying the interactions between ADAM17 and the insulin signalling mechanism will provide light on the protein's Role in developing insulin resistance in polycystic ovary syndrome (PCOS). The Role of ADAM17 in pancreatic insulin secretion should also be investigated. Schumacher et al. (2023) note that PCOS patients frequently have elevated insulin levels to compensate for insulin resistance. It's worth emphasising that ADAM17 may have a role in shaping this procedure. The metabolic dysregulation seen in polycystic ovarian syndrome (PCOS) has been linked to the enzyme adenosine deaminase 17 (ADAM17). Therefore, research into this area could lead to novel approaches to treating the condition.

5.2 Hypothesis 2: ADAM17's Impact on Hormone Regulation in PCOS

Hormonal Imbalances in PCOS:

Significant characteristics of polycystic ovarian syndrome (PCOS) are hormonal imbalances, specifically elevated testosterone and LH levels (Kumar et al., 2021). Polycystic ovarian syndrome (PCOS) manifests itself clinically as hirsutism, acne, and menstrual cycle irregularities; hormonal imbalances drive these symptoms. Understanding these hormone anomalies requires investigating the molecular circuits that control them.

Hypothesis Formulation:

Polycystic ovary syndrome (PCOS) is thought to be influenced by the enzyme adenosine deaminase 17 (ADAM17), according to another idea. According to this theory, ADAM17 is a

factor in the excessive synthesis of male hormones that is a hallmark of polycystic ovarian syndrome (PCOS).

6.0 Future Directions and Research Needs

According to Théret et al.'s report from 2021, future scientific initiatives should emphasise integrating in vitro and in vivo research within a framework that draws from multiple disciplines.

Elucidating the Mechanisms of ADAM17-Mediated Insulin Resistance:

In vitro Studies:

To further understand the link between ADAM17 and insulin resistance in polycystic ovarian syndrome, it is recommended that future studies emphasise in vitro methods. This research design must permit a complete grasp of the precise molecular processes through which ADAM17 produces insulin resistance in polycystic ovarian syndrome. For this reason, it is necessary to investigate the links between ADAM17 and the various parts of the insulin signalling system (Tang et al., 2020). It is crucial to study how ADAM17 affects insulin receptor function because of its implications for chemical signals and glucose uptake. Cell culture models could be used in in vitro studies examining the association between ADAM17 and insulin receptors, perhaps illuminating the likely substrates involved in the aetiology of insulin resistance. Manipulating ADAM17 levels and evaluating its impact on insulin-related pathways requires molecular biology techniques, including gene amplification and silencing.

In Vivo Investigations:

In vivo, studies are just as important as in vitro experiments to validate the findings and close the translational gap. Animal models, particularly PCOS-related rodent models, can be useful for determining how important ADAM17 is in the onset of insulin resistance. These models can recapitulate the metabolic disturbances seen in PCOS patients, laying the groundwork for studying the effect of ADAM17 on insulin resistance in a more physiological context (Xu et al., 2019). The effect of ADAM17 on insulin secretion must be considered in in vivo studies.

Exploring ADAM17's Influence on Hormone Regulation:

In vitro Experiments:

Investigating the effect that ADAM17 has should be the primary emphasis of the design of the in vitro study. These cell models can be used to regulate testosterone levels. The suggested studies have as their objective the investigation of the potential substrates that are cleaved by ADAM17, with a particular emphasis on the function that these substrates play in regulating the generation of androgens. The use of gene editing technologies to manipulate ADAM17 levels has the potential to shed light on the causal connections between the observed phenomena.

Animal Models:

Animal models aid in validating results obtained from in vitro laboratory experiments and offer valuable insights into the wider implications. To illustrate, transgenic rodents with ADAM17

expression modified through genetic engineering are indispensable for investigating the causal connections between ADAM17 and hormonal imbalances (Dou et al., 2017). Acquiring this knowledge is of the utmost importance to formulate precise therapies and interventions for those impacted by this condition. Fundamentally, animal models aid in translating scientific breakthroughs into possible clinical applications that could benefit patients with PCOS.

7.0 Conclusion

In a nutshell, ADAM17, an intricately functional metalloproteinase, has surfaced as a potential contributor to the pathogenesis of polycystic ovary syndrome. Further research on this subject should prioritise identifying the fundamental processes by which ADAM17 affects these patients' insulin resistance and hormone control. The accumulation of this knowledge can make fresh chances for detecting and managing this highly prevalent and complicated disorder, and it could do so if it were to support such opportunities.

References

Adamcova, M., Kawano, I., & Simko, F. (2021). The impact of micrornas in renin–angiotensin-system-induced cardiac remodelling. In *International Journal of Molecular Sciences* (Vol. 22, Issue 9). https://doi.org/10.3390/ijms22094762

Ciebiera, M., Włodarczyk, M., Zgliczyńska, M., Łukaszuk, K., Męczekalski, B., Kobierzycki, C., Łoziński, T., & Jakiel, G. (2018). The role of tumor necrosis factor α in the biology of uterine fibroids and the related symptoms. In *International Journal of Molecular Sciences* (Vol. 19, Issue 12). https://doi.org/10.3390/ijms19123869

Ciumărnean, L., Milaciu, M. V., Negrean, V., Orășan, O. H., Vesa, S. C., Sălăgean, O., Iluţ, S., & Vlaicu, S. I. (2022). Cardiovascular risk factors and physical activity for the prevention of cardiovascular diseases in the elderly. In *International Journal of Environmental Research and Public Health* (Vol. 19, Issue 1). https://doi.org/10.3390/ijerph19010207

Deswal, R., Narwal, V., Dang, A., & Pundir, C. S. (2020). The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. In *Journal of Human Reproductive Sciences* (Vol. 13, Issue 4). https://doi.org/10.4103/jhrs.JHRS_95_18

Dou, H., Feher, A., Davila, A. C., Romero, M. J., Patel, V. S., Kamath, V. M., Gooz, M. B., Rudic, R. D., Lucas, R., Fulton, D. J., Weintraub, N. L., & Bagi, Z. (2017). Role of Adipose Tissue Endothelial ADAM17 in Age-Related Coronary Microvascular Dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *37*(6). https://doi.org/10.1161/ATVBAHA.117.309430

Düsterhöft, S., Babendreyer, A., Giese, A. A., Flasshove, C., & Ludwig, A. (2019). Status update on iRhom and ADAM17: It's still complicated. In *Biochimica et Biophysica Acta - Molecular Cell Research* (Vol. 1866, Issue 10). https://doi.org/10.1016/j.bbamcr.2019.06.017

Düsterhöft, S., Lokau, J., & Garbers, C. (2019). The metalloprotease ADAM17 in inflammation and cancer. In *Pathology Research and Practice* (Vol. 215, Issue 6). https://doi.org/10.1016/j.prp.2019.04.002

Escobar-Morreale, H. F. (2018). Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. In *Nature Reviews Endocrinology* (Vol. 14, Issue 5). https://doi.org/10.1038/nrendo.2018.24

Floyd, R., Gryson, R., Mockler, D., Gibney, J., Duggan, S. N., & Behan, L. A. (2022). The Effect of Time-Restricted Eating on Insulin Levels and Insulin Sensitivity in Patients with Polycystic Ovarian Syndrome: A Systematic Review. In *International Journal of Endocrinology* (Vol. 2022). https://doi.org/10.1155/2022/2830545

Freeman, E. W., Kroll, R., Rapkin, A., Pearlstein, T., Brown, C., Parsey, K., Zhang, P., Patel, H., & Foegh, M. (2001). Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. *Journal of Women's Health and Gender-Based Medicine*, *10*(6). https://doi.org/10.1089/15246090152543148

Gheblawi, M., Wang, K., Viveiros, A., Nguyen, Q., Zhong, J. C., Turner, A. J., Raizada, M. K., Grant, M. B., & Oudit, G. Y. (2020). Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System: Celebrating the 20th Anniversary of the Discovery of ACE2. In *Circulation Research* (Vol. 126, Issue 10). https://doi.org/10.1161/CIRCRESAHA.120.317015

Giménez-Palomo, A., Gomes-da-Costa, S., Dodd, S., Pachiarotti, I., Verdolini, N., Vieta, E., & Berk, M. (2022). Does metabolic syndrome or its component factors alter the course of bipolar disorder? A systematic review. In *Neuroscience and Biobehavioral Reviews* (Vol. 132). https://doi.org/10.1016/j.neubiorev.2021.11.026

Grieve, A. G., Xu, H., Künzel, U., Bambrough, P., Sieber, B., & Freeman, M. (2017). Phosphorylation of iRhom2 at the plasma membrane controls mammalian TACE-dependent inflammatory and growth factor signalling. *ELife*, *6*. https://doi.org/10.7554/eLife.23968

Hajam, Y. A., Rani, R., Ganie, S. Y., Sheikh, T. A., Javaid, D., Qadri, S. S., Pramodh, S., Alsulimani, A., Alkhanani, M. F., Harakeh, S., Hussain, A., Haque, S., & Reshi, M. S. (2022). Oxidative Stress in Human Pathology and Aging: Molecular Mechanisms and Perspectives. *Cells*, *11*(3). https://doi.org/10.3390/cells11030552

He, F. F., & Li, Y. M. (2020). Role of gut microbiota in the development of insulin resistance and the mechanism underlying polycystic ovary syndrome: A review. In *Journal of Ovarian Research* (Vol. 13, Issue 1). https://doi.org/10.1186/s13048-020-00670-3

Huffman, A. M., Rezq, S., Basnet, J., Cardozo, L. L. Y., & Romero, D. G. (2021). Sars-cov-2 viral entry proteins in hyperandrogenemic female mice: implications for women with pcos and covid-19. *International Journal of Molecular Sciences*, *22*(9). https://doi.org/10.3390/ijms22094472

Imanaka, S., Maruyama, S., Kimura, M., Nagayasu, M., & Kobayashi, H. (2020). Towards an understanding of the molecular mechanisms of endometriosis-associated symptoms (Review). In *World Academy of Sciences Journal* (Vol. 2, Issue 4). https://doi.org/10.3892/wasj.2020.53

Ipsa, E., Cruzat, V. F., Kagize, J. N., Yovich, J. L., & Keane, K. N. (2019). Growth Hormone and Insulin-Like Growth Factor Action in Reproductive Tissues. In *Frontiers in Endocrinology* (Vol. 10). https://doi.org/10.3389/fendo.2019.00777

Islam, R. M., Bell, R. J., Green, S., Page, M. J., & Davis, S. R. (2019). Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised

controlled trial data. *The Lancet Diabetes and Endocrinology*, *7*(10). https://doi.org/10.1016/S2213-8587(19)30189-5

Jung, Y. J., Tweedie, D., Scerba, M. T., & Greig, N. H. (2019). Neuroinflammation as a Factor of Neurodegenerative Disease: Thalidomide Analogs as Treatments. In *Frontiers in Cell and Developmental Biology* (Vol. 7). https://doi.org/10.3389/fcell.2019.00313

Kakoly, N. S., Earnest, A., Teede, H. J., Moran, L. J., & Joham, A. E. (2019). The impact of obesity on the incidence of type 2 diabetes among women with polycystic ovary syndrome. *Diabetes Care*, *42*(4). https://doi.org/10.2337/dc18-1738

Kawai, T., Elliott, K. J., Scalia, R., & Eguchi, S. (2021). Contribution of ADAM17 and related ADAMs in cardiovascular diseases. In *Cellular and Molecular Life Sciences* (Vol. 78, Issue 9). https://doi.org/10.1007/s00018-021-03779-w

Kostopoulou, E., Anagnostis, P., Bosdou, J. K., Spiliotis, B. E., & Goulis, D. G. (2020). Polycystic ovary Syndrome in Adolescents: Pitfalls in Diagnosis and Management. In *Current obesity reports* (Vol. 9, Issue 3). https://doi.org/10.1007/s13679-020-00388-9

Kshetrimayum, C., Sharma, A., Mishra, V. V., & Kumar, S. (2019). Polycystic ovarian syndrome: Environmental/ occupational, lifestyle factors; an overview. In *Journal of the Turkish German Gynecology Association* (Vol. 20, Issue 4). https://doi.org/10.4274/jtgga.galenos.2019.2018.0142

Kunvariya, A. D., Dave, S. A., Modi, Z. J., Patel, P. K., & Sagar, S. R. (2023). Exploration of multifaceted molecular mechanism of angiotensin-converting enzyme 2 (ACE2) in pathogenesis of various diseases. In *Heliyon* (Vol. 9, Issue 5). https://doi.org/10.1016/j.heliyon.2023.e15644

Lai, W., Li, X., Zhu, H., Zhu, X., Tan, H., Feng, P., Chen, L., & Luo, C. (2020). Plasma luteinizing hormone level affects the brain activity of patients with polycystic ovary syndrome. *Psychoneuroendocrinology*, *112*. https://doi.org/10.1016/j.psyneuen.2019.104535

Light, R. S., Chilcot, J., & McBride, E. (2021). Psychological Distress in Women Living with Polycystic Ovary Syndrome: The Role of Illness Perceptions. *Women's Health Issues*, *31*(2). https://doi.org/10.1016/j.whi.2020.11.003

Mahata, S. K., & Corti, A. (2019). Chromogranin a and its fragments in cardiovascular, immunometabolic, and cancer regulation. In *Annals of the New York Academy of Sciences* (Vol. 1455, Issue 1). https://doi.org/10.1111/nyas.14249

Moldovan, G. E., Miele, L., & Fazleabas, A. T. (2021). Notch signaling in reproduction. In *Trends in Endocrinology and Metabolism* (Vol. 32, Issue 12). https://doi.org/10.1016/j.tem.2021.08.002

Mondal, S., Adhikari, N., Banerjee, S., Amin, S. A., & Jha, T. (2020). Matrix metalloproteinase-9 (MMP-9) and its inhibitors in cancer: A minireview. In *European Journal of Medicinal Chemistry* (Vol. 194). https://doi.org/10.1016/j.ejmech.2020.112260

Murata, H., Tanaka, S., & Okada, H. (2022). The Regulators of Human Endometrial Stromal Cell Decidualization. In *Biomolecules* (Vol. 12, Issue 9). https://doi.org/10.3390/biom12091275

Neven, A. C. H., Laven, J., Teede, H. J., & Boyle, J. A. (2018). A summary on polycystic ovary

syndrome: Diagnostic criteria, prevalence, clinical manifestations, and management according to the latest international guidelines. *Seminars in Reproductive Medicine*, *36*(1). https://doi.org/10.1055/s-0038-1668085

Poulsen, S. B., & Fenton, R. A. (2019). K+ and the renin–angiotensin–aldosterone system: new insights into their role in blood pressure control and hypertension treatment. In *Journal of Physiology* (Vol. 597, Issue 17). https://doi.org/10.1113/JP276844

Rodriguez Paris, V., & Bertoldo, M. J. (2019). The Mechanism of Androgen Actions in PCOS Etiology. In *Medical sciences (Basel, Switzerland)* (Vol. 7, Issue 9). https://doi.org/10.3390/medsci7090089

Rohm, T. V., Meier, D. T., Olefsky, J. M., & Donath, M. Y. (2022). Inflammation in obesity, diabetes, and related disorders. In *Immunity* (Vol. 55, Issue 1). https://doi.org/10.1016/j.immuni.2021.12.013

Rostamtabar, M., Esmaeilzadeh, S., Tourani, M., Rahmani, A., Baee, M., Shirafkan, F., Saleki, K., Mirzababayi, S. S., Ebrahimpour, S., & Nouri, H. R. (2021). Pathophysiological roles of chronic low-grade inflammation mediators in polycystic ovary syndrome. In *Journal of Cellular Physiology* (Vol. 236, Issue 2). https://doi.org/10.1002/jcp.29912

Sabir, S., Akash, M. S. H., Fiayyaz, F., Saleem, U., Mehmood, M. H., & Rehman, K. (2019). Role of cadmium and arsenic as endocrine disruptors in the metabolism of carbohydrates: Inserting the association into perspectives. In *Biomedicine and Pharmacotherapy* (Vol. 114). https://doi.org/10.1016/j.biopha.2019.108802

Sanchez-Garrido, M. A., & Tena-Sempere, M. (2020). Metabolic dysfunction in polycystic ovary syndrome: Pathogenic role of androgen excess and potential therapeutic strategies. In *Molecular Metabolism* (Vol. 35). https://doi.org/10.1016/j.molmet.2020.01.001

Schumacher, N., & Rose-John, S. (2019). Adam17 activity and il-6 trans-signaling in inflammation and cancer. In *Cancers* (Vol. 11, Issue 11). https://doi.org/10.3390/cancers11111736

Schumacher, N., & Rose-John, S. (2022). ADAM17 orchestrates Interleukin-6, TNFα and EGF-R signaling in inflammation and cancer. *Biochimica et Biophysica Acta - Molecular Cell Research*, *1869*(1). https://doi.org/10.1016/j.bbamcr.2021.119141

Simionescu, G., Doroftei, B., Maftei, R., Obreja, B.-E., Anton, E., Grab, D., Ilea, C., & Anton, C. (2021). The complex relationship between infertility and psychological distress (Review). *Experimental and Therapeutic Medicine*, *21*(4). https://doi.org/10.3892/etm.2021.9737

Sisto, M., Ribatti, D., & Lisi, S. (2021). Organ fibrosis and autoimmunity: The role of inflammation in TGFβ-dependent EMT. In *Biomolecules* (Vol. 11, Issue 2). https://doi.org/10.3390/biom11020310

Taghipour, Y. D., Hajialyani, M., Naseri, R., Hesari, M., Mohammadi, P., Stefanucci, A., Mollica, A., Farzaei, M. H., & Abdollahi, M. (2019). Nanoformulations of natural products for management of metabolic syndrome. In *International Journal of Nanomedicine* (Vol. 14). https://doi.org/10.2147/IJN.S213831

Witchel, S. F., Oberfield, S. E., & Peña, A. S. (2019). Polycystic Ovary Syndrome: Pathophysiology, Presentation, and Treatment with Emphasis on Adolescent Girls. In

Journal of the Endocrine Society (Vol. 3, Issue 8). https://doi.org/10.1210/js.2019-00078

Xue, F., Cheng, J., Liu, Y., Cheng, C., Zhang, M., Sui, W., Chen, W., Hao, P., Zhang, Y., & Zhang, C. (2022). Cardiomyocyte-specific knockout of ADAM17 ameliorates left ventricular remodeling and function in diabetic cardiomyopathy of mice. *Signal Transduction and Targeted Therapy*, *7*(1). https://doi.org/10.1038/s41392-022-01054-3

Zehravi, M., Maqbool, M., & Ara, I. (2021). Polycystic ovary syndrome and reproductive health of women: A curious association. In *International Journal of Adolescent Medicine and Health* (Vol. 33, Issue 6). https://doi.org/10.1515/ijamh-2021-0031

Zeng, X., Xie, Y. jie, Liu, Y. ting, Long, S. lian, & Mo, Z. cheng. (2020). Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. In *Clinica Chimica Acta* (Vol. 502). https://doi.org/10.1016/j.cca.2019.11.003

Zhao, H., Zhang, J., Cheng, X., Nie, X., & He, B. (2023). Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation, and treatment. In *Journal of Ovarian Research* (Vol. 16, Issue 1). https://doi.org/10.1186/s13048-022-01091-0