The Intersection of Hepcidin and Polycystic Ovary Syndrome: A Review of Current Understanding

ABSTRACT

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting up to 13% of reproductive-age women. It is characterized by a constellation of symptoms including menstrual irregularities, hyperandrogenism, and polycystic ovaries, often intertwined with metabolic disturbances such as insulin resistance and dyslipidemia. Hepcidin is a liver-produced peptide hormone that regulates iron homeostasis, with a significant role in the pathophysiology of PCOS. Hepcidin controls iron absorption and storage by binding to ferroportin, leading to its degradation and reducing iron export from enterocytes and macrophages. In PCOS patients, hepcidin dysregulation is linked to underlying hormonal and metabolic abnormalities, including insulin resistance and hyperandrogenism. Studies consistently demonstrate decreased hepcidin levels in PCOS patients, resulting in altered iron metabolism parameters, such as increased serum iron and ferritin concentrations, leading to iron overload. This iron overload can exacerbate complications like anemia. The relationship between hepcidin, anemia, and PCOS is influenced by several mechanisms. Hyperandrogenism in PCOS inhibits hepcidin synthesis, reducing iron sequestration and increasing serum iron levels, contributing to erythropoiesis and potentially mitigating anemia, while also posing a risk of iron overload. Hyperinsulinemia associated with insulin resistance further decreases hepcidin levels, enhancing dietary iron absorption and increasing serum iron levels. Despite the chronic low-grade inflammation typical in PCOS, which usually increases hepcidin levels, the inflammation may not be sufficient to override the suppressive effects of hyperandrogenism and hyperinsulinemia on hepcidin expression. Oligomenorrhea or amenorrhea in PCOS leads to reduced menstrual blood loss, contributing to iron retention and further influencing hepcidin regulation. Genetic and epigenetic factors also significantly impact hepcidin expression and iron metabolism in PCOS.

KEYWORDS

Polycystic ovary syndrome (PCOS), Hepcidin, Iron metabolism, Hormonal dysregulation, Insulin resistance, Hyperandrogenism, Iron overload.

INTRODUCTION

Polycystic ovary syndrome (PCOS) stands as one of the most prevalent endocrine disorders affecting up to 13% of reproductive-age women [1]. PCOS is an enigmatic condition characterized by a constellation of symptoms including menstrual irregularities, hyperandrogenism, and polycystic ovaries, PCOS presents a complex clinical picture often intertwined with metabolic disturbances such as insulin resistance and dyslipidemia [2][3].

With the increasing number of PCOS cases worldwide, there is a need to understand the multifaceted pathophysiology of PCOS. Recent research has focused on explaining the role of various hormones and signaling pathways in their etiology and progression [4][5]. One such hormone that gathered attention in the context of PCOS is hepcidin. Hepcidin is a peptide hormone primarily known for its role in iron homeostasis and it acts as the major regulator of systemic iron balance by controlling iron absorption from the intestine and the recycling of iron from senescent red blood cells and macrophages [6][7][8]. Recent studies have indicated a strong connection between PCOS and hepcidin [9]. Researchers have made observations such as the disturbances in serum iron levels, ferritin concentrations, and transferrin saturation in PCOS patients influence hepcidin variations [9][10,32,33,34]. With these available shreds of knowledge about the role of hepcidin in iron regulation, investigating its relationship with PCOS pathogenesis holds significant promise, as it can improve potential clinical implications of Hepcidin dysregulation in PCOS, considering its impact on metabolic health, reproductive outcomes, and overall disease management. This review attempts to provide a brief outline of the unexplored domains and connect the scattered links between PCOS and hepcidin by analyzing the published studies from the last decade.

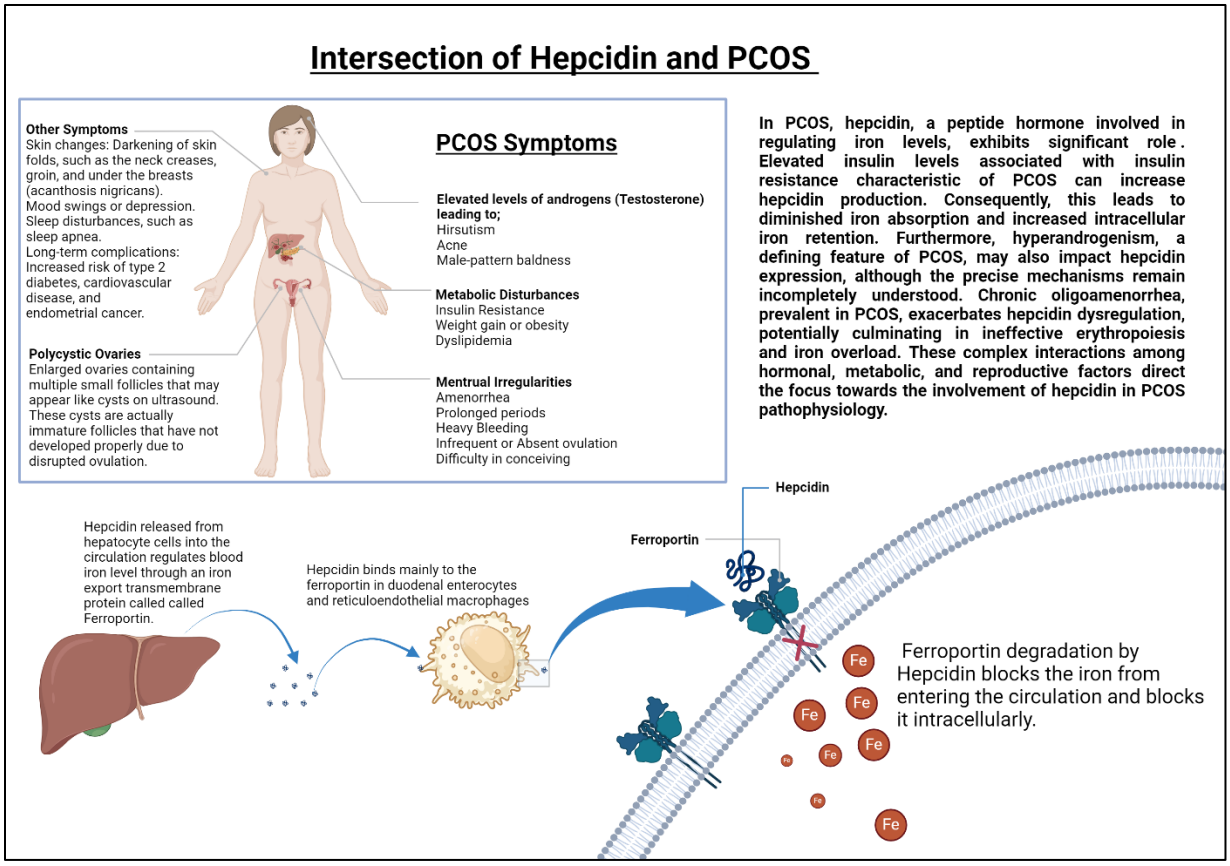

Figure 1; The regulatory axis of hepcidin is influenced by a variety of factors. This visual abstract summarizes the common findings from all the reviewed studies that investigated the link between PCOS and hepcidin. (Created with BioRender.com)

1. Hepcidin

Hepcidin, a liver-produced peptide hormone, maintains iron balance by regulating the absorption and storage of iron. Normal serum iron levels range from 65-175 mcg/dL in males and 50-170 mcg/dL in females [11][12]. Hepcidin is a key regulator of iron metabolism and is upregulated in response to inflammatory cytokines such as interleukin-6 (IL-6), leading to significant effects on iron homeostasis. The upregulation of hepcidin results in decreased dietary iron absorption and increased iron storage within cells. Hepcidin binds to ferroportin, the iron export protein on enterocytes and macrophages, causing its internalization and degradation [13]. This reduces iron export from these cells into the bloodstream, leading to lower serum iron levels as iron becomes sequestered intracellularly. Consequently, this sequestration initially causes normocytic normochromic anemia, where red blood cells (RBCs) are normal in size and color, but fewer in number (See Figure 1). If inflammation persists, the anemia can progress to a microcytic hypochromic form, characterized by smaller, pale RBCs with reduced hemoglobin content. Diagnostic indicators typically show decreased serum iron despite increased ferritin levels due to iron being stored within the cell. Therefore, understanding the role of

hepcidin in iron metabolism helps in the effective diagnosis and management of anemia associated with chronic diseases such as PCOS [12][14][15].

1.1. Hepcidin in PCOS Pathophysiology

Hepcidin is known to play a significant role in the pathophysiology of polycystic ovary syndrome (PCOS). The dysregulation of hepcidin may be linked to the underlying hormonal and metabolic abnormalities characteristic of PCOS, such as insulin resistance and hyperandrogenism [16]. Moreover, the presence of chronic oligomenorrhea in PCOS further complicates iron metabolism by altering hepcidin levels, potentially exacerbating iron overload. Understanding the involvement of hepcidin in PCOS pathophysiology sheds light on the complex interplay between iron metabolism, hormonal dysregulation, and metabolic dysfunction in this syndrome. The precise mechanisms underlying hepcidin dysregulation in PCOS are still not clear, and its clinical implications for iron homeostasis and overall health in affected individuals need to be identified [17][9].

Chibanda *et al.,* (2023) investigated the role of hepcidin in the iron overload seen in PCOS. The study found that patients with PCOS had lower levels of circulating hepcidin and higher ferritin-to-hepcidin ratios compared to those without the syndrome. Notably, patients with PCOS and chronic oligomenorrhea exhibited even lower hepcidin levels, potentially exacerbating iron overload [18]. Their findings uncovered the relationship between hormonal imbalances, insulin sensitivity, and iron metabolism in PCOS, suggesting potential implications for managing iron overload in these patients.

The study of Luque-Ramírez *et al.,* (2011) was into the involvement of hepcidin in the iron overload observed in patients with polycystic ovary syndrome (PCOS), characterized by hormonal imbalances and insulin resistance. Conducted as a case-control study followed by a randomized clinical trial, the research involved 34 PCOS patients and 30 control subjects. Findings revealed significantly decreased serum hepcidin levels and increased ferritin-to-hepcidin ratios in PCOS patients compared to controls. Notably, PCOS patients with chronic oligomenorrhea exhibited even lower hepcidin levels. The study highlighted the association between PCOS and reduced hepcidin concentrations, potentially leading to iron overload due to enhanced intestinal iron absorption. Furthermore, the imbalance between iron stores and hepcidin levels was attributed to insulin resistance and androgen excess, common features of PCOS. Interestingly, treatment with an antiandrogenic oral contraceptive normalized the ferritin-to-hepcidin ratio, suggesting a potential therapeutic approach [19]. Overall, the study provided valuable insights into the complex link between hormonal dysregulation, insulin resistance, and iron metabolism in PCOS, opening the way for further research in this area.

Similarly, in another case-control study involving 56 patients with PCOS and 41 healthy control subjects, the researchers measured plasma levels of hepcidin, IL-6, serum insulin, ferritin, and serum iron levels, alongside insulin resistance using HOMA. The results indicated significantly lower hepcidin levels and higher insulin levels in the PCOS group compared to the control group. Furthermore, an inverse relationship was observed between hepcidin levels and both HOMA-IR and IL-6 in both groups. The adjusted odds ratio highlighted a significant association between serum hepcidin and HOMA with PCOS.

Overall, the findings suggest that decreased hepcidin levels and increased insulin resistance may contribute to the risk of PCOS. Evidence from this study proves the relationship between iron metabolism and insulin resistance in the pathophysiology of PCOS [20].

The study of Al-Obaidi *et al.,* (2021) aimed to explore the concentrations of critical variables, including hepcidin, erythropoietin, testosterone, and various hematological parameters, in women diagnosed with polycystic ovary syndrome (PCOS) compared to healthy counterparts. Blood serum samples were collected from 55 PCOS-afflicted women and 25 healthy women, each group selected based on body mass index (BMI) criteria. The results unveiled noteworthy disparities between the two cohorts. Such as in PCOS patients, there was a marked elevation ($P \leq 0.01$) in testosterone and iron levels, concomitant with heightened hemoglobin levels, red blood cell counts, and packed cell volume (PCV), indicative of increased erythropoiesis. However, interestingly, there was a significant decrease ($P \leq 0.05$) in both hepcidin and ferritin concentrations among PCOS subjects, suggesting a potential dysregulation in iron metabolism. Notably, erythropoietin concentrations exhibited no significant alterations in women with PCOS compared to the control group. These findings also point to the interplay between hormonal dysregulation, iron metabolism, and hematological parameters in the pathophysiology of PCOS [21]. The observed discrepancies in hepcidin and ferritin levels may signify underlying disruptions in iron homeostasis in PCOS, warranting further investigation into the mechanisms involved.

The study by Zheng *et al.,* in 2023, presents significant findings regarding the underlying mechanisms of liver dysfunction in patients with polycystic ovary syndrome (PCOS). By employing a combination of clinical investigation and animal modeling, the researchers made a clarity on a previously unexplained aspect of PCOS pathology, focusing specifically on liver damage and iron overload. One of the key strengths of this study lies in both clinical observation in PCOS patients according to established criteria and the creation of a PCOS animal model using dihydrotestosterone (DHEA) sustained-release tablets. The identification of liver damage in a subset of PCOS patients and in the animal model, independent of nonalcoholic fatty liver disease (NAFLD), is a new finding that highlights the complexity of PCOS-related comorbidities. Moreover, the increased iron deposition observed in conjunction with liver damage underscores the importance of iron metabolism in PCOS-associated liver dysfunction. The downregulation of hepcidin and GPX4, a crucial effector protein for ferroptosis, in the liver further explains the role of iron dysregulation in PCOS-related liver pathology. By investigating the miR-761-hepcidin/GPX4 axis, the study provides mechanistic insights into how dysregulation of this pathway contributes to ferroptosis and iron deposition, ultimately impacting PCOS disease phenotype and liver function. Additionally, the demonstration of changes in PCOS disease phenotype and ferroptosis through manipulation of miR-761, hepcidin, and GPX4 levels further supports the significance of these molecular pathways in PCOS pathology. Additionally, elucidating the interplay between iron metabolism, ferroptosis, and other PCOS-related comorbidities could provide further insights into disease pathogenesis and therapeutic strategies [22].

The study by Jihad & Sarhat (2023) provided valuable insights into the relationship between Anti-Mullerian hormone (AMH) and various other markers, including hepcidin,

ferritin, serum iron, and interleukin-6, among women with polycystic ovary syndrome (PCOS). The inclusion of 60 PCOS women and 30 healthy volunteers in the study cohort allows for a robust comparison between the two groups. The observed decrease in hepcidin levels among PCOS women compared to the control group suggests a potential dysregulation of iron metabolism in PCOS. Concurrently, the significantly elevated levels of AMH in PCOS women further underscore the hormonal disturbances characteristic of this syndrome. The findings regarding serum iron and ferritin levels provide additional insights into iron metabolism in PCOS. The higher average serum iron and ferritin levels in PCOS women compared to controls highlight the importance of assessing iron status in this population. Furthermore, the study's observation of higher hepcidin levels in overweight PCOS women compared to those with normal BMI suggests a possible association between adiposity and hepcidin regulation in PCOS. The negative correlation between serum hepcidin and iron, ferritin, and AMH levels among PCOS women is a consistent finding that appears in all investigations [16]. Understanding the underlying mechanisms driving these correlations could provide valuable insights into the pathophysiology of PCOS-related metabolic disturbances.

1.2. Hepcidin and Anaemia in PCOS

Anemia is a common hematological disorder characterized by a decrease in the number of red blood cells (RBCs) or the hemoglobin concentration, resulting in reduced oxygen-carrying capacity of the blood [23]. The relationship between hepcidin and anemia is particularly significant given hepcidin’s central role in iron metabolism. The relationship between hepcidin, anemia, and PCOS can be explained by several mechanisms. The most important one among them is -Hyperandrogenism. Androgens inhibit hepcidin synthesis, reducing iron sequestration and increasing serum iron levels, which can contribute to erythropoiesis and mitigate anemia. However, the excess iron could also pose a risk of iron overload [24][25]. Hyperinsulinemia associated with insulin resistance decreases hepcidin levels, enhancing dietary iron absorption and increasing serum iron levels. This mechanism aligns with the observed lower hepcidin levels in PCOS patients [26]. The inflammation typically increases hepcidin levels [12]. But in PCOS the chronic low-grade inflammation in PCOS might not be sufficient to override the suppressive effects of hyperandrogenism and hyperinsulinemia on hepcidin expression [27][28]. Another mechanism that is explained in studies is oligomenorrhea or amenorrhea, where reduced menstrual blood loss in PCOS leads to iron retention, leading to iron overload and influencing hepcidin regulation [29][30]. Along with these discussed mechanisms genetic and epigenetic factors also have a significant influence on hepcidin expression and iron metabolism in PCOS [31].

2. CONCLUSION

Hepcidin dysregulation, along with insulin resistance, hyperandrogenism, chronic oligomenorrhea, inflammation, and genetic and molecular mechanisms, contributes to the multidimensional pathophysiology of PCOS. Studies consistently highlight decreased hepcidin levels in PCOS patients, accompanied by alterations in iron metabolism parameters. PCOS is commonly associated with iron overload due to decreased hepcidin levels, which can exacerbate the risk of iron-related complications such as anemia. Understanding the relationship between hepcidin dysregulation and anemia in PCOS is crucial for developing effective diagnostic and therapeutic strategies, ultimately improving the management and quality of life for women with PCOS. Further research is required to elucidate the complex connections between hepcidin, hormonal dysregulation, metabolic dysfunction, and anemia in PCOS, thereby enhancing our understanding and management of this prevalent endocrine disorder.

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AUTHORS' CONTRIBUTIONS

"Athira P R" designed the study, and wrote the first draft of the manuscript. 'Athira P R', 'Dr. Swathi. D', 'Dr. Sukesh' and 'Dr. Ajita Pillai' managed the analyses of the study and managed the literature searches. 'Delna N.S' and 'Athira P R' created the visual abstract and conducted the final proofreading before submission. All authors read and approved the final manuscript.

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