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Renal manifestations and implications in polycystic ovary syndrome; an analytical review

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ABSTRACT

Insulin resistance in polycystic ovary syndrome (PCOS) contributes to renal dysfunction through multiple interconnected mechanisms. In PCOS, insulin resistance leads to compensatory hyperinsulinemia, which exacerbates metabolic disturbances including hyperandrogenism and systemic inflammation. These factors collectively promote renal injury. Meanwhile, insulin resistance in PCOS promotes hypertension and endothelial dysfunction, which impair renal microcirculation. Hyperinsulinemia increases sodium retention and activates the renin-angiotensin-aldosterone system (RAAS), further elevating blood pressure and causing glomerular hyperfiltration and damage. Insulin resistance also contributes to dyslipidemia and oxidative stress, accelerating atherosclerosis and renal vascular injury. Moreover, insulin resistance worsens hyperuricemia by reducing renal uric acid excretion, which is a direct nephrotoxic factor. Persistent hyperuricemia leads to inflammation and fibrosis within the kidneys, potentially progressing to chronic kidney disease (CKD). In addition, systemic low-grade inflammation and oxidative stress driven by insulin resistance and PCOS-related hyperandrogenism also induce renal tissue injury through inflammatory cytokines and apoptotic pathways, contributing to impairment in renal function.

Implication for health policy/practice/research/medical education:
Insulin resistance in polycystic ovary syndrome (PCOS) contributes to renal dysfunction by causing metabolic and hemodynamic changes including hypertension, hyperuricemia, oxidative stress, and inflammation, all of which damage kidney structure and function over time.

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Review

Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent and complex endocrine disorder affecting women of reproductive age globally (1). It is characterized by a constellation of symptoms including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (2). This disease is defined by the Rotterdam criteria, requiring the presence of at least two of the following; oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology, after excluding other etiologies (3). The pathophysiology of PCOS is multifactorial, involving a complex interplay

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of genetic predisposition, endocrine dysregulation, metabolic disturbances, and environmental factors (4). Central to its pathogenesis is the dysregulation of the hypothalamic-pituitary-ovarian axis, leading to increased luteinizing hormone (LH) secretion and ovarian hyperandrogenism (5). This hormonal imbalance disrupts normal follicular development, resulting in anovulation and the characteristic polycystic ovarian morphology (1,5). However, PCOS extends its influence far beyond reproductive health, presenting as a systemic condition with significant metabolic and cardiovascular implications (6). While its reproductive manifestations are widely studied, a growing body of evidence highlights the involvement of kidney abnormalities in PCOS, a connection that is increasingly recognized as clinically significant and warrants in-depth investigation (7). This review paper synthesizes current understanding of kidney involvement in PCOS, exploring its prevalence, pathophysiological mechanisms, diagnostic approaches, management strategies, and future research directions.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ), and Embase, using different keywords like polycystic ovary syndrome, PCOS, renal manifestations, chronic kidney disease, CKD, renal dysfunction, inflammation and oxidative stress.

Pathophysiology of PCOS and its systemic effects

PCOS is a complex disorder with heterogeneous presentation, influenced by genetic, environmental, and lifestyle factors (8). While the primary focus in PCOS has historically been on infertility, menstrual irregularities, and hirsutism, attention has shifted toward its metabolic and cardiovascular complications, including insulin resistance, type 2 diabetes mellitus, dyslipidemia, obesity, and non-alcoholic fatty liver disease (9). More recently, evidence has emerged suggesting that PCOS may also contribute to renal dysfunction and increased risk of chronic kidney disease (CKD) (7). Numerous studies found that, insulin resistance and hyperinsulinemia are existed in up to 70%–80% of women with PCOS, even in lean individuals (10); since, insulin resistance plays a pivotal role in both reproductive and metabolic disturbances; Similarly, hyperinsulinemia stimulates ovarian androgen production and reduces sex hormone-binding globulin, leading to increased free testosterone levels (11). Elevated androgen levels contribute to hirsutism, acne, and anovulation (12). Androgens may also influence adipose tissue distribution and exacerbate insulin resistance (13). Additionally, chronic low-grade inflammation by elevated levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), was seen in women with PCOS, which may contribute to endothelial dysfunction and organ damage (14). Moreover, approximately 40%–80% of women with PCOS are overweight or obese (15). Adipose tissue, particularly visceral fat, acts as an endocrine organ, secreting adipokines like leptin and adiponectin that modulate insulin sensitivity, inflammation, and vascular function (16). These interconnected pathways create a pro-inflammatory, pro-thrombotic, and pro-atherogenic state, predisposing women with PCOS to cardiovascular disease, metabolic syndrome, and potentially, renal injury (17).

Focus on insulin resistance

Insulin resistance is a central feature of PCOS and a key driver of renal dysfunction (18). Hyperinsulinemia increases sodium reabsorption in the proximal tubules, contributing to volume expansion and hypertension (19). It also stimulates the release of endothelin-1 and activates RAAS (renin-angiotensin-aldosterone system), promoting vasoconstriction and glomerular hypertension (20). Besides, insulin-signaling pathways in podocytes and mesangial cells are crucial for maintaining glomerular integrity (21). Dysregulation of these pathways due to insulin resistance may lead to podocyte injury, mesangial expansion, and extracellular matrix accumulation, which are the hallmarks of diabetic nephropathy (22).

Focus on hyperandrogenism

Androgens, particularly dihydrotestosterone (DHT) and testosterone, may exert direct and indirect effects on the kidneys (23). Animal studies have shown that androgen excess accelerates the progression of diabetic nephropathy and induces glomerulosclerosis (24). In previous studies, elevated free testosterone levels correlate with increased urinary albumin-to-creatinine ratio and reduced renal function (25). Androgens may promote renal injury through enhancing oxidative stress and reducing antioxidant defenses, across with upregulating pro-inflammatory cytokines (e.g., TNF-α, IL-6) (26,27). Here, there is also stimulating the expression of transforming growth factor-beta, as a key mediator of fibrosis (28). In addition, an accelerated endothelial dysfunction following reduced NO synthesis was detected (29). Besides, androgen receptors are expressed in renal tubular cells, suggesting a direct role in tubular function and sodium handling (30).

Obesity and adipokines imbalance

Obesity is a major contributor to both PCOS and kidney disease (31). Adipose tissue, especially visceral fat, secretes a range of bioactive molecules named as adipokines, that influence renal function (32). Recent studies found that, leptin is elevated in obesity and PCOS (33); since, leptin promotes inflammation, oxidative stress, and mesangial cell proliferation (34). It may also contribute to glomerular

hypertrophy and sclerosis (35). Conversely, adiponectin typically reduced in PCOS (36); while, adiponectin has anti-inflammatory, insulin-sensitizing, and renoprotective properties (37). Similarly, low levels of adiponectin are associated with increased risk of microalbuminuria and CKD (38). Recent studies demonstrated that, resistin and visfatin as the pro-inflammatory adipokines are elevated in PCOS and may promote endothelial dysfunction and glomerular injury (39,40).

Focus on RAAS activation

Hypertension is more prevalent in women with PCOS, particularly those with obesity and insulin resistance (41). Elevated blood pressure is a major risk factor for CKD progression (42). More recent studies detected that, RAAS is often over-activated in PCOS due to insulin resistance and sympathetic over-activity (43). Angiotensin II, the primary effector of RAAS, induces vasoconstriction, sodium retention, and aldosterone release (44). It also promotes inflammation, fibrosis, and oxidative stress in the kidneys (45). Likewise, androgens may upregulate angiotensinogen and angiotensin II receptors, amplifying RAAS activity and contributing to renal damage (46).

A short look at the oxidative stress

Women with PCOS exhibit elevated levels of oxidative stress markers like malondialdehyde and 8-isoprostane and reduced antioxidant capacity such as glutathione, superoxide dismutase (47). Reactive oxygen species can damage glomerular and tubular cells, impair mitochondrial function, and activate pro-fibrotic pathways (48). Chronic inflammation, marked by elevated CRP, IL-6, and TNF-α, further exacerbates renal injury (49). Inflammatory cytokines promote leukocyte infiltration, endothelial activation, and matrix deposition in the glomeruli (50).

Focus on hyperuricemia

Elevated serum uric acid levels, or hyperuricemia, are consistently observed in women with PCOS compared to healthy controls (51). A recent meta-analysis demonstrated a significantly higher serum uric acid in PCOS patients, with a mean difference of 0.70 mg/dL (52). The hyperuricemia is strongly associated with insulin resistance, obesity, and hyperandrogenism, which are characteristic features of PCOS (51). Elevated uric acid may serve as a marker of oxidative stress and endothelial dysfunction, contributing to renal impairment through pro-inflammatory pathways and accelerating kidney damage (53). Routine assessment of uric acid in PCOS patients is recommended as a simple tool for risk stratification for kidney disease (52).

Kidney involvement in PCOS

Growing clinical and epidemiological data suggest that women with PCOS may be at increased risk of renal dysfunction (54). Although overt kidney disease is not typically considered a hallmark of PCOS, subtle changes in renal structure and function have been consistently observed (54). One of the earliest detectable renal changes in PCOS is glomerular hyperfiltration as a condition characterized by an elevated glomerular filtration rate (GFR) (55). Preliminary investigations have shown that women with PCOS exhibit significantly higher GFR compared to age- and BMI (body mass index)-matched controls (55). As an example, a cross-sectional study by Katsikis et al reported that women with PCOS had higher GFR values, independent of BMI and insulin resistance (56). Likewise, glomerular hyperfiltration is commonly observed in early stages of diabetes and obesity-related kidney disease (57). In PCOS, glomerular hyperfiltration may result from insulin resistance and hyperinsulinemia, which increase renal plasma flow and glomerular capillary pressure (23). Furthermore, activation of the RAAS and sympathetic nervous system, both of which are heightened in PCOS, may contribute to intra-glomerular hypertension (58). Though hyperfiltration may initially represent a compensatory mechanism, it can lead to glomerular hypertrophy, podocyte stress, and eventual glomerulosclerosis over time as the key steps in the progression to CKD (59). Given that, micro-albuminuria is a well-established marker of early renal damage and endothelial dysfunction (60). Several studies have demonstrated a higher prevalence of micro-albuminuria in women with PCOS compared to healthy controls (55). Previous studies also found that women with PCOS had significantly higher urinary albumin-to-creatinine ratio (7). This association remained significant even after adjusting for BMI, insulin resistance, and blood pressure. In fact, micro-albuminuria in PCOS may reflect systemic endothelial dysfunction, driven by insulin resistance, oxidative stress, and chronic inflammation. Endothelial cells lining the glomerular capillaries are particularly vulnerable to these insults, leading to increased permeability and albumin leakage. Furthermore, hyperandrogenism may directly impair endothelial function (61). Testosterone has been shown to reduce nitric oxide (NO) bioavailability and promote vasoconstriction, contributing to microvascular damage (62,63).

Renal hemodynamic alterations

Beyond biochemical markers, PCOS is associated with discernible alterations in renal hemodynamics (52). Studies using renal Doppler ultrasonography have indicated changes in kidney blood flow in normotensive women with PCOS (64). It was detected that, the peak systolic velocity of the mean renal artery was found to be lower in the PCOS group, while the mean renal venous impedance was higher compared to controls (64). Although the mean renal resistive index was only slightly higher and

not statistically significant in some earlier studies, since more recent research consistently reports elevated renal resistive index (RRI) levels in PCOS patients (65). These higher renal resistive index levels correlate positively with systolic blood pressure and homeostasis model assessment of insulin resistance (HOMA-IR), suggesting increased renal arterial resistance indicative of early renal vascular and cardiovascular risk in PCOS (65). Such alterations may represent the long-term renal and cardiovascular complications stemming from the metabolic disturbances characteristic of PCOS (7).

Role of metabolic syndrome and comorbidities

Metabolic syndrome, a cluster of conditions including obesity, hypertension, insulin resistance, and dyslipidemia, is highly prevalent in women with PCOS and significantly exacerbates renal involvement (66,67). Obesity, as a common comorbidity, places additional strain on the kidneys through increased visceral adiposity, leading to renal hemodynamic alterations such as glomerular hyperfiltration and tubular hypertrophy (68). Adipose tissue secretes adipokines and pro-inflammatory cytokines, fostering endothelial dysfunction and further insulin resistance, promoting a pro-fibrotic state within the kidneys (69). Hypertension, another frequent companion of PCOS, causes sustained glomerular hypertension, leading to progressive glomerular damage (70). Type 2 diabetes mellitus, often developed in PCOS patients due to severe insulin resistance, is a well-established cause of diabetic nephropathy, inducing hyperglycemia-mediated renal injury (71,72). The combined impact of these comorbidities leads to amplified oxidative stress, microvascular injury, podocyte damage, and increased expression of pro-fibrotic factors like transforming growth factor-beta, collectively accelerating renal function decline in PCOS patients (7,73,74).

A short look at the genetic and molecular factors

Genetic and molecular factors play a significant role in mediating the complex relationship between PCOS and kidney disease, indicating a shared underlying pathophysiology (5, 7). Genome-wide association studies have identified genetic susceptibility loci for PCOS that also overlap with genes influencing kidney function and CKD, suggesting a shared genetic architecture (7, 54). Mendelian randomization studies have provided causal evidence linking PCOS to CKD risk, supported by genetic variants associated with both conditions (75). Specific single nucleotide polymorphisms linked to PCOS correlate with serological indicators of CKD, such as elevated fibroblast growth factor 23, creatinine, and cystatin C (54). As an example, genetic clusters in PCOS individuals have been identified, with one cluster associated with obesity (FTO gene) and increased type 2 diabetes risk, while others relate to hormonal changes, inflammatory markers, or insulin resistance/liver enzymes (76). The polygenic risk for CKD has been shown to affect the penetrance of monogenic kidney diseases, suggesting that a complex interplay of genetic factors influences renal vulnerability (77). In addition, gene expression profiling offers further insights into the molecular overlap between PCOS and kidney disease (7). Studies reveal altered mRNA patterns in kidney tissues from individuals with renal diseases that resemble molecular changes observed in PCOS, including inflammatory gene up-regulation (78, 79). For instance, genes involved in androgen receptor signaling and metabolic functions, which are critical to PCOS pathophysiology, are also expressed in the kidney (80). The expression of certain inflammatory cytokines and signaling pathways, such as JAK/STAT3, are altered in renal tissues in PCOS models, contributing to inflammation and oxidative stress that damage the kidneys (81). These changes collectively underscore shared molecular pathways that contribute to disease progression in both conditions (81).

Structural kidney changes

Emerging imaging studies suggest that women with PCOS may exhibit structural alterations in the kidneys (7). Ultrasonographic evaluations have revealed increased kidney volume and cortical thickness in PCOS patients (82). Previous authors found that kidney volume was significantly greater in women with PCOS, correlated positively with insulin resistance and testosterone levels (25, 52). Increased kidney size may be secondary to glomerular and tubular hypertrophy induced by hyperinsulinemia and hyperglycemia (57). While not pathognomonic, such changes may represent early adaptive responses that, if sustained, could predispose to fibrosis and functional decline (83).

Association of PCOS with CKD

Although most women with PCOS are young and may not exhibit overt CKD, longitudinal data suggest an increased risk of developing CKD later in life (54,70). Recent population-based cohort studies revealed that women with PCOS, face an increased risk of developing CKD compared to control groups, even after adjusting for various comorbidities. This finding suggests a significant association between PCOS and CKD independent of other health conditions (7,54,84). Furthermore, a higher incidence of reduced estimated glomerular filtration rate among women with PCOS in retrospective studies was detected (52,55).

These studies also highlighted that PCOS women were more prone to developing chronic renal failure, particularly if they also developed type 2 diabetes mellitus or hypertension (54,85).

These compelling findings underscore the critical importance of consistent and long-term renal monitoring for women diagnosed with PCOS. This is especially crucial as they advance in age and accrue additional metabolic risk factors, which can further exacerbate the risk of kidney complications (7,54).

Conclusion

Polycystic ovary syndrome is increasingly recognized as a multisystem disorder with significant implications for long-term health, including renal function. Evidence from clinical, biochemical, and imaging studies indicates that women with PCOS are at higher risk of glomerular hyperfiltration, microalbuminuria, structural kidney changes, and ultimately, CKD. The underlying mechanisms involve a complex interplay of insulin resistance, hyperandrogenism, obesity, inflammation, and RAAS activation. Since, overt kidney disease may not be apparent in young women with PCOS; early signs of renal dysfunction suggest the need for proactive monitoring and intervention. Routine screening for microalbuminuria and eGFR, along with aggressive management of metabolic risk factors, may help prevent or delay the progression of renal damage.

Authors' contribution

Conceptualization: Zahra Hamidi Madani, Sina Salem Ahim, and Mehrdad SalekShahabi.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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