Stage-Specific Pathological Features Of Chronic Kidney Disease: An Article Review

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Abstract.

Chronic Kidney Disease (CKD) is a major global health challenge, with increasing prevalence, particularly in developing countries. CKD is characterized by a gradual and irreversible decline in kidney function, often progressing to End-Stage Renal Disease (ESRD). The pathophysiology of CKD involves structural and functional deterioration in various renal compartments, including the glomerulus, tubules, interstitial tissue, and blood vessels. Histopathological changes play a critical role in disease progression, with interstitial fibrosis, glomerulosclerosis, and tubular atrophy being the hallmark lesions observed across different CKD stages. This review highlights the anatomical pathology of CKD at various stages, focusing on histopathological changes, diagnostic techniques, and factors influencing disease progression. Renal biopsy remains the gold standard for assessing kidney damage, utilizing special stains such as Periodic Acid-Schiff (PAS) to identify fibrosis and sclerosis. However, noninvasive biomarkers like Neutrophil Gelatinase-Associated Lipocalin (NGAL) and Kidney Injury Molecule-1 (KIM-1) have emerged as promising tools for early detection. Studies indicate that histopathologic findings, including interstitial fibrosis and glomerulosclerosis, often correlate with CKD progression more accurately than estimated glomerular filtration rate (eGFR) alone. This review underscores the need for integrating histopathological, clinical, and molecular biomarkers to improve CKD diagnosis and management. A better understanding of kidney pathology can facilitate early detection, refine prognostic assessments, and enhance treatment strategies. Future research should focus on noninvasive diagnostic alternatives and novel therapeutic targets to slow CKD progression and mitigate its global health burden.

Keywords: *Chronic Kidney Disease, Histopathology, Interstitial Fibrosis, Glomerulosclerosis and Biomarkers.*

I. INTRODUCTION

Chronic Kidney Disease (CKD) is a significant global health issue, marked by a progressive and irreversible decline in kidney function that can ultimately lead to End-Stage Kidney Disease (ESKD). The global prevalence of CKD is estimated at 10–15% of the adult population, with the highest rates observed in regions burdened by diabetes mellitus and hypertension, which are key contributors to renal damage [1]–[3]. According to the 2017 Global Burden of Disease Study, CKD is the 12th leading cause of death worldwide, with mortality rates continuing to rise annually. In Indonesia, the prevalence of CKD reached 3.8% in 2018, particularly affecting the elderly, further emphasizing the urgent need to enhance prevention, awareness, and management strategies at the national level [4].CKD progresses through five distinct stages, as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which categorize the disease based on Glomerular Filtration Rate (GFR) and albuminuria levels, both of which reflect the extent of kidney damage [5]. Pathologically, CKD involves structural changes across multiple renal compartments, including glomerulosclerosis, tubular atrophy, and interstitial fibrosis, which become progressively severe as the disease advances [6]. In early stages, histological changes may be minimal, whereas advanced stages are characterized by extensive fibrosis, nephron loss, and renal atrophy [7].

Understanding these pathological changes is essential for early diagnosis, prognosis assessment, and the development of targeted therapeutic interventions.The increasing burden of CKD is further compounded by its association with comorbidities, particularly cardiovascular disease, which significantly elevates morbidity and mortality risks [8]. This interplay highlights the importance of a comprehensive approach to CKD management, encompassing not only renal protection but also cardiovascular risk mitigation. As CKD continues to pose a growing global health challenge, clinicians must remain vigilant in identifying stage-specific pathological features to ensure timely intervention. This review aims to provide a detailed analysis of CKD's anatomical pathology across its stages, offering valuable insights into disease progression, risk

factors, and management strategies. Future research should prioritize elucidating the mechanisms underlying these pathological changes and exploring innovative therapies to slow CKD progression and improve patient outcomes.

II. METHODS

The methodology employed in this review of stage-specific pathological features of chronic kidney disease (CKD) involved a comprehensive analysis of existing literature, focusing on various pathological mechanisms, diagnostic techniques, and treatment approaches associated with CKD. Initially, a systematic search was conducted across multiple academic databases, including PubMed, Scopus, and Web of Science, to identify relevant articles published in peer-reviewed journals. The search terms included chronic kidney disease, renal fibrosis, pathological features, diagnosis, and treatment, among others. This approach ensured a broad yet focused collection of literature that encompasses the multifaceted nature of CKD. Subsequently, the selected articles were categorized based on their relevance to specific stages of CKD and the corresponding pathological features. For instance, studies such as [9] and [6] provided insights into the role of renal fibrosis and tubular atrophy in the progression of CKD, highlighting the importance of these features in the diagnosis and management of the disease. Furthermore, articles like [10] and [11] were instrumental in elucidating the metabolic and hypoxic conditions that exacerbate kidney damage, thereby contributing to the understanding of CKD's pathophysiology.

In addition to qualitative analysis, quantitative data were extracted from relevant studies to support claims regarding the prevalence and impact of specific pathological features. For example, the prevalence of renal fibrosis as a common pathological process leading to end-stage renal disease was corroborated by multiple studies, including those by [12] and [13]. This quantitative approach not only reinforced the qualitative findings but also allowed for a more robust discussion regarding the implications of these pathological features on patient outcomes. Moreover, the review incorporated a critical evaluation of various diagnostic techniques utilized in identifying CKD and its stages. Techniques such as imaging modalities and biomarker assessments were discussed, drawing from studies like those by [14] and [15], which emphasized the evolving landscape of diagnostic approaches in nephrology. The integration of these diagnostic methods into clinical practice is crucial for timely intervention and management of CKD.Finally, the review synthesized findings from the literature to propose potential therapeutic strategies aimed at mitigating the progression of CKD. This included discussions on emerging treatments targeting specific pathological mechanisms, such as the role of mitochondrial dysfunction and oxidative stress in renal injury, as highlighted by studies like those of [15], [16]. The comprehensive nature of this methodology not only provides a detailed overview of the pathological features associated with CKD but also sets the stage for future research directions aimed at improving patient care and outcomes in this prevalent disease.

III. RESULT AND DISCUSSION

Research Review

Chronic Kidney Disease (CKD) is a condition of impaired kidney function that lasts for ≥3 months, characterized by a decrease in glomerular filtration rate (GFR) and/or the presence of kidney damage, including albuminuria, electrolyte abnormalities, or renal histopathological abnormalities. CKD is becoming one of the global health problems with an increasing prevalence due to aging population and increasing risk factors such as diabetes and hypertension [17]. Based on KDIGO (Kidney Disease: Improving Global Outcomes) 2024, CKD is classified into five stages based on GFR (Table 1). In making a diagnosis, the main parameters used are GFR and albuminuria. GFR is the key parameter to assess renal filtration function. Albuminuria is determined by albumin-creatinine ratio (ACR), Normal (A1) (ACR <30 mg/g), Microalbuminuria (A2) (ACR 30-300 mg/g), and Macroalbuminuria (A3) (ACR >300 mg/g) [5].

Table 1. CKD stage based on GFR

Stage	GFR value
Stage 1	≥90 mL/min/1.73m²
Stage 2	60-89 mL/min/1.73m²

Stage 3a	45-59 mL/min/1.73m²
Stage 3b	15-29 mL/min/1.73m²
Stage 4	<15 mL/min/1.73m² or requires renal replacement therapy

Source: Secondary Data Result, 2024

Anatomically, CKD results in progressive changes in kidney structure and function. Damage can occur in various renal compartments, including the glomerulus, tubules, blood vessels and interstitial tissue. Macroscopically, kidneys with CKD show a reduction in size, uneven surface, and fibrosis in the kidney capsule. Microscopically, in advanced stages, the kidneys often appear small and atrophic. The main changes include interstitial fibrosis; where there is an increase in extracellular matrix in the interstitium, glomerular sclerosis; where there is thickening of the glomerular basement membrane and obliteration of capillaries, and tubular atrophy; where there is loss of tubules with a dilated lumen and flat epithelium [18].

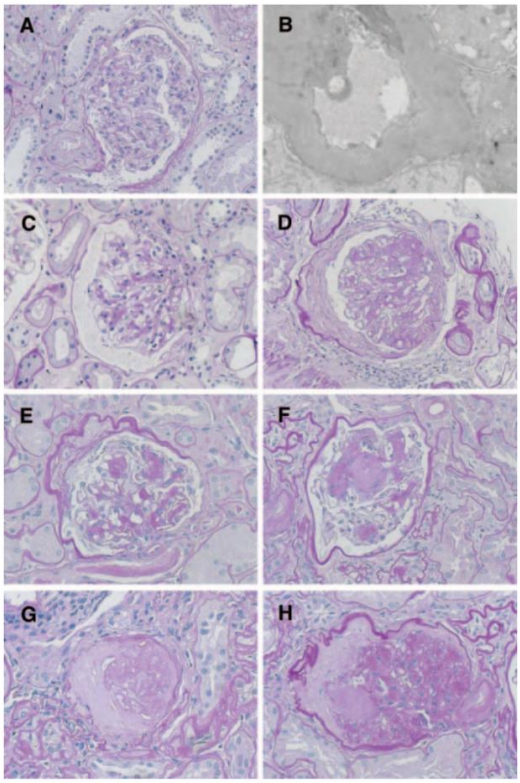

Fig 1. Morphologic lesions in diabetic nephropathy:
(A) Glomerulus with mild ischemic and Bowman's capsule separation, without obvious mesangial changes,
(B) EM showing GBM averaging 671 nm, class I classification,
(C, D) Class II: mild (IIa) and moderate (IIb) mesangial expansion,
(E, F) Class III: obvious Kimmelstiel-Wilson lesions
(F), whereas E fits better with class IIb,
(G, H) Class IV: glomerular vascular polar hyalinosis
(H) and global glomerulosclerosis ≥50%
(G). (Tervaert et al., 2010)

* EM : Electron
* GBM : Glomerular basement membrane

Various factors influence the course of chronic kidney disease (CKD) pathology. Major etiologies include diabetes mellitus, which causes diabetic nephropathy characterized by nodular glomerulosclerosis. Hypertension is also an important factor that induces nephrosclerosis due to chronic high blood pressure. In addition, glomerulonephritis, characterized by glomerular inflammation, may progress to progressive fibrosis. Comorbid factors also contribute to the worsening of CKD. Chronic infections increase the risk of renal inflammation, while vascular diseases exacerbate renal ischemia, thus accelerating renal tissue damage [5], [18].

Table 2. Research Review

Author, Year	Title	Study Design	Results
Lopez-Marin et al., 2014	Histopathology of Chronic Kidney Disease of Unknown Etiology in Salvadoran Agricultural Communities	Cross-sectional	• Stage 2: Mild lesions, with interstitial fibrosis in 13.3% and glomerulosclerosis in 26.7%. • Stage 3a: Moderate lesions, in which interstitial fibrosis increased to 63.7%, glomerulosclerosis reached 54.5%, and glomerulomegaly decreased to 36.4%. • Stage 3b: Severe lesions, characterized by 100% interstitial fibrosis, 85% glomerulosclerosis, 20% severe tubular atrophy, as well as predominant vascular changes. • Progression of CKD is associated with increased histopathologic damage to the kidney.
Trevisani et al., 2023	Renal Histology in CKD Stages: Match or Mismatch with Glomerular Filtration Rate?	Mini-review	• The eGFR value is not always directly related to the histopathological features of the kidney. • Although eGFR is often used as an important parameter in assessing renal function, they do not reflect the extent of histologic damage, such as interstitial fibrosis, tubular atrophy, and glomerular sclerosis.
Gunawardena et al., 2021	A Systematic Review of Renal Pathology in Chronic Kidney Disease of Uncertain Etiology	Systematic Review	• Histopathologic changes in interstitials and tubules, such as fibrosis and tubular atrophy, are associated with advanced stages of CKD. Interstitial fibrosis is found in more than 80% of patients and is a predictor for CKD stage 3 or more. • The pathogenesis of CKD involves acute inflammation, chronic toxin exposure, and the possible role of agricultural toxins.
Trevisani et al., 2020	Renal histology across the stages of chronic kidney disease	Cohort Study	• Analysis of renal histology in 200 patients who underwent radical nephrectomy showed a discrepancy between CKD stage and histologic damage. • Patients with CKD stage 1 sometimes showed more severe histologic damage, despite their normal eGFR. The chronicity score increased with CKD stage, with a score of 2-3 found in all cases of CKD stage 4-5. These results were similar when using MDRD, FAS, and MCQ scores. These findings emphasize the importance of histopathological examination to evaluate renal damage in CKD patients.
Wijetunge et al., 2015	Endemic chronic kidney disease of unknown etiology in Sri Lanka: Correlation of pathology with clinical stages 1	Cohort Study	• Chronic kidney disease of unknown etiology (CKDU) is endemic in rural farming communities in Sri Lanka. This study analyzed 251 kidney biopsies that showed significant histopathological damage. • In stage I, damage was dominated by mild to moderate interstitial fibrosis without interstitial inflammation. • In stage II, moderate interstitial fibrosis was found, both with and without inflammation. • Stage III shows moderate to severe interstitial fibrosis, interstitial inflammation, tubular atrophy and glomerulosclerosis. • Stage IV shows more significant severe fibrosis, inflammation, tubular atrophy and glomerulosclerosis.

Source: Secondary Data Result, 2024

Anatomical pathology diagnosis techniques play an important role in assessing kidney damage. Renal biopsy is a standard method that uses special stains such as PAS (Periodic Acid-Schiff) to identify fibrosis and glomerular sclerosis. Imaging, such as ultrasonography, is used to assess kidney size and the presence of obstruction, while CT or MRI provides a detailed picture of the anatomical structure of the kidney. Biomarkers are also useful diagnostic tools in detecting kidney damage at an early stage. Biomarkers such as NGAL (Neutrophil Gelatinase-Associated Lipocalin) and KIM-1 (Kidney Injury Molecule-1) have proven effective in monitoring the progression of CKD [19], [20].

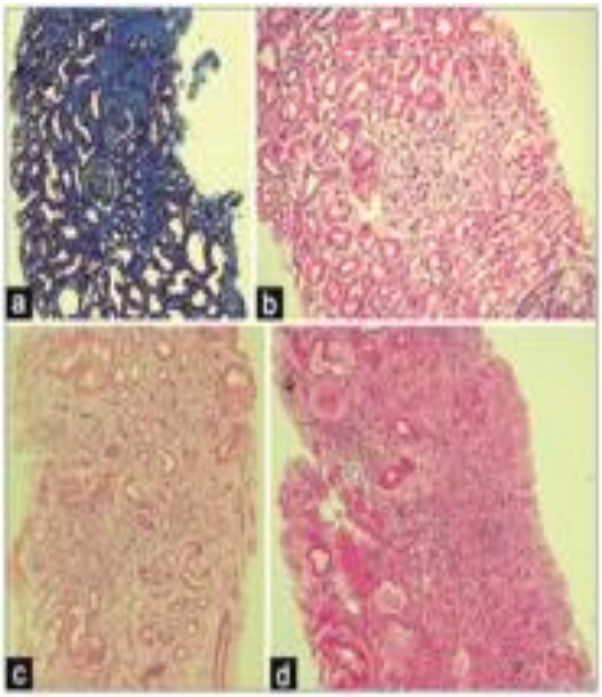

Fig 2. Pathological features of chronic kidney disease endemic to Sri Lanka:
(a) Stage I: Blue interstitial fibrosis (Masson trichrome, 10x10);
(b) Stage I: Interstitial fibrosis, tubule atrophy, minimal inflammation (H&E, 10x10);
(c) Stage III: Interstitial fibrosis, multifocal tubule atrophy, inflammatory infiltration (10x10);
(d) Stage IV: Extensive fibrosis, tubular atrophy, diffuse inflammatory infiltration, glomerular sclerosis (10x10).

Discussion

In a cross-sectional study conducted histopathological findings showed that renal damage in CKDu is generally tubulointerstitial nephritis with interstitial fibrosis associated with the stage of CKD, which is more severe in individuals with extreme working conditions [21]. Interstitial fibrosis and tubular atrophy are found in most renal biopsies, with variations in severity based on gender, occupation and disease stage. Although most of the tubulointerstitial damage was attributed to secondary glomerulosclerosis, other studies suggest the involvement of environmental toxic factors such as heavy metals (arsenic and cadmium) as potential causes. This study also found compensatory glomerular hypertrophy contributing to further glomerulosclerosis and hypertension. A similar histopathologic study in Sri Lanka showed consistent results, reinforcing the hypothesis that tubulointerstitial damage is the major pathological event in CKDu. However, the exact mechanism remains unclear, with the main suspects including chemical nephrotoxicity and renal ischemia due to dehydration and exposure to high temperatures. This study is the first in the US to comprehensively study the histopathology of CKDu at various stages of the disease. However, limitations in the use of electron microscopy limit the detailed understanding of the lesions found, so further studies are needed to clarify the pathogenesis of CKDu [21].The mini-review study evaluated that renal histopathology, including interstitial fibrosis, tubular atrophy, and glomerular sclerosis, is an important indicator of chronic kidney damage that is often not detected through functional parameters such as eGFR and albuminuria.

Histology scoring systems such as Remuzzi score and Chronicity Score help stratify the degree of renal tissue damage to support clinical decision-making, including indications for transplantation. However, studies have shown that eGFR values do not always reflect the degree of histologic damage, necessitating a more comprehensive diagnostic approach. Although renal biopsy remains an important method to determine the etiology of CKD, this procedure carries the risk of complications, especially in elderly patients or those with low eGFR. Therefore, the use of noninvasive biomarkers such as KIM-1, MCP-1, and NGAL is a promising alternative to detect kidney damage at an early stage and predict the progressivity of CKD. Integration between histopathological analysis, renal function parameters, and molecular biomarkers can

improve the accuracy of diagnosis, guide more specific therapy, and help prevent the progression of chronic kidney disease [22].A systematic review study mentioned that histopathological changes in interstitials and tubules have an important role in assessing kidney damage, with interstitial fibrosis as the most dominant and earliest pathological change, which is seen in more than 80% of patients, even in those with acute symptoms [23]. The severity of interstitial fibrosis is often associated with advanced stages of chronic kidney disease (CKD) and decreased glomerular filtration rate (GFR). Interstitial inflammation is generally less noticeable, but increases as fibrosis progresses, and is an independent predictor of CKD stage 3 or higher. Tubular atrophy is found in more than 90% of cases, generally in a mild to moderate form, affecting less than 50% of the cortical area, and is closely associated with renal damage.

Tubulitis, although rarely reported, is found in the majority of acute cases, with some involving more than 60% of the biopsy area. Other tubular changes, such as intracellular lysosomal lesions, were observed in patients with Sri Lankan and Mesoamerican nephropathy, which were similar to lesions found in patients receiving calcineurin inhibitor treatment. The pathogenesis of these tubulointerstitial changes is debated, with some researchers attributing the damage to acute tubular inflammation, while others propose fibrosis resulting from chronic, low-grade toxin exposure, leading to a further cycle of ischemia, inflammation and fibrosis. In addition, some studies suggest that agricultural toxins may play a role in the disease through the calcineurin inhibition pathway. Histopathologic changes in glomeruli and blood vessels showed several key findings related to CKD. Glomerulosclerosis was found in varying degrees of severity, with more advanced stages of CKD showing increased glomerulosclerosis. Glomerular enlargement is more common in patients with early stages of CKD (e.g. stage 2 CKD). On electron microscopy, cytoplasmic inclusions of podocytes and decreased podocyte foot processes are observed in patients from advanced stages. Vascular changes, which are usually mild to moderate, are more common in advanced stages, such as intimal proliferation and arteriolar hyalinosis. Pathogenesis hypotheses include glomerular changes secondary to interstitial fibrosis, with glomerular ischemia as a result of changes in renal architecture, which progresses as the stage of CKD increases [23]. In a cohort study conducted that the chronicity score was calculated by evaluating four renal histology parameters: glomerulosclerosis, cortical interstitial fibrosis, tubular atrophy, and arteriosclerosis [24]. Each parameter was scored based on the degree of area involvement as follows: For glomerulosclerosis, a score of 0 was given if <10% of the glomerular area was involved, score 1 for 10-25%, score 2 for 25-50%, and score 3 for >50%.

For cortical interstitial fibrosis, a score of 0 is given if <10% of the cortical area is involved, score 1 for 10-25%, score 2 for 25-50%, and score 3 for >50%. Tubule atrophy was assessed in the same way, with a score of 0 for <10% tubule area involved, score 1 for 10-25%, score 2 for 25-50%, and score 3 for >50%. Arteriosclerosis was simply scored as 0 (no arteriosclerosis) or 1 (arteriosclerosis present). The total score of all parameters was used to determine the extent of renal damage: minimal (0-1), mild (2-4), moderate (5-7), or severe (≥ 8). The findings of the histology analysis showed that approximately 30-40% of patients with CKD stage 3 showed mild or no lesions (Chronicity Score 0-1), while 7-10% of patients with CKD stage 1 showed moderate to severe histology lesions (Chronicity Score ≥ 3), with differences in histology damage despite similar estimated glomerular filtration rate (eGFR) values [24].In a cohort study analyzed the histopathological features in patients with chronic kidney disease (CKD) which showed a significant correlation between histological parameters and the clinical stage of CKD [25]. In stage I, most patients showed mild interstitial fibrosis and no tubular atrophy or severe glomerular sclerosis. Meanwhile, in stages II and III, there was an increased prevalence of interstitial fibrosis and tubular atrophy, as well as more significant glomerulosclerosis. Stage IV shows more severe fibrosis and tubular atrophy, with more hypertension-related vascular changes occurring. Although most patients remain asymptomatic and are detected through screening, proteinuria (+1) is found in 82.5% of patients. Histologic parameters, such as interstitial fibrosis, interstitial inflammation, tubule atrophy, and glomerular sclerosis, showed a strong correlation with decreased glomerular filtration rate (GFR), with significant R2 correlation coefficients in each parameter ($P < 0.001$). These findings highlight the importance of histologic evaluation in the determination of chronic kidney disease progression and the relationship with renal function [25].

IV. CONCLUSION

In conclusion, Chronic Kidney Disease (CKD) represents a significant global health challenge characterized by a progressive decline in kidney function, leading to serious complications such as End-Stage Kidney Disease (ESKD). The prevalence of CKD is notably high in populations affected by diabetes mellitus and hypertension, with a substantial burden on healthcare systems worldwide. Histopathological studies have consistently demonstrated that tubulointerstitial nephritis, interstitial fibrosis, and tubular atrophy are key pathological features associated with CKD progression. These changes are often exacerbated by environmental factors, including exposure to heavy metals and agricultural toxins, which contribute to renal damage. The relationship between histopathological findings and clinical parameters, such as eGFR and albuminuria, underscores the necessity for a comprehensive diagnostic approach.

While eGFR is a critical measure of renal function, it does not always correlate with the extent of histological damage, highlighting the importance of renal biopsy and histological evaluation in assessing kidney health. Emerging non-invasive biomarkers, such as KIM-1, MCP-1, and NGAL, offer promising alternatives for early detection of kidney damage and monitoring disease progression. Furthermore, the integration of histopathological analysis with clinical data and molecular biomarkers can enhance diagnostic accuracy and inform targeted therapeutic strategies. As research continues to explore the underlying mechanisms of CKD and its associated pathologies, it is crucial for healthcare professionals to remain vigilant in recognizing the significance of histopathological changes. This understanding will facilitate timely interventions, improve patient outcomes, and ultimately contribute to more effective management of chronic kidney disease. Future studies should focus on elucidating the pathogenesis of CKD and developing innovative therapies aimed at slowing disease progression and enhancing renal protection.

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