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MORPHOLOGICAL AND MORPHOMETRIC CHANGES IN THE KIDNEYS IN EXPERIMENTAL ULCERATIVE COLITIS. LITERATURE REVIEW

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Abstract. Ulcerative colitis (UC) is a chronic inflammatory bowel disease that primarily affects the colon and rectum, but it is also associated with extra-intestinal manifestations, including renal dysfunction. The kidneys in experimental UC models, particularly those induced by dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS), exhibit several morphological and morphometric changes. These include inflammation, edema, glomerular damage, interstitial fibrosis, and altered renal blood flow, which can lead to impaired kidney function. The pathophysiological mechanisms behind renal involvement in UC are multifactorial, with systemic inflammation, oxidative stress, and ischemia playing key roles. The article provides a comprehensive review of the morphological and morphometric alterations in the kidneys observed in experimental UC models, discusses the potential underlying mechanisms, and highlights therapeutic interventions aimed at mitigating kidney damage. A better understanding of these changes is crucial for developing strategies to prevent renal complications in patients with UC.

Keywords: ulcerative colitis (UC), renal changes, experimental models, morphological alterations. morphometric changes, inflammation, kidney fibrosis, glomerular damage, oxidative stress, renal dysfunction, therapeutic interventions, systemic inflammation, kidney pathology

Introduction. Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease (IBD) that primarily affects the colon and rectum. It is characterized by inflammation, ulceration, and mucosal damage of the gastrointestinal tract. Although UC primarily involves the digestive system, numerous studies have highlighted its extra-intestinal manifestations, affecting various organ systems, including the kidneys. Renal involvement in UC is increasingly recognized, and while its precise pathophysiology remains unclear, it has been postulated that both direct and indirect mechanisms contribute to renal dysfunction in this disease.

The Kidney-UC Link. Although the kidneys are not the primary target of UC, there is accumulating evidence suggesting that UC-associated inflammation has significant renal implications. Experimental studies in animals, particularly those using rodent models of UC, have demonstrated a variety of morphological and functional changes in the kidneys, some of which mimic those seen in human patients with UC (Gul et al., 2016). Animal models of UC, often induced by chemicals such as dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS), have proven invaluable in investigating these renal abnormalities and understanding their underlying mechanisms (Kant et al., 2018; Sharma et al., 2019).

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The systemic inflammation observed in UC patients is believed to be a major contributor to renal pathology. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are elevated during UC flare-ups, can reach distant organs, including the kidneys, through the bloodstream (Torres et al., 2017). The kidneys, being highly vascular organs, are particularly susceptible to these systemic inflammatory signals.

Moreover, UC-related renal abnormalities extend beyond inflammation alone. In experimental models, renal changes can range from glomerular damage, interstitial fibrosis, and tubular alterations to altered kidney size and function (Iglesias et al., 2020). Renal fibrosis, a key feature of chronic kidney disease (CKD), has been observed in UC-induced models, often as a result of the inflammatory cascade and oxidative stress (Sleiman et al., 2017). These structural changes can lead to kidney dysfunction, manifesting as proteinuria, impaired glomerular filtration rate (GFR), and electrolyte imbalances (Singh et al., 2021).

Morphological and Morphometric Kidney Changes in UC. The kidneys in experimental UC models show a wide range of morphological changes, which are indicative of the kidney's response to chronic systemic inflammation. Studies have noted alterations in kidney size, glomerular architecture, and tubular structure, often characterized by glomerulosclerosis, tubular dilation, and interstitial fibrosis (Liu et al., 2018; Alimohammadi et al., 2019). Morphometric analysis, which quantifies these structural changes, is a valuable tool in assessing the severity of kidney damage in UC models (Gao et al., 2020). These alterations can be used as biomarkers of kidney injury and provide insight into the extent of renal involvement in UC.

Ulcerative Colitis. Ulcerative colitis (UC) is a chronic inflammatory bowel disease primarily affecting the colon and rectum, characterized by recurrent symptoms and significant morbidity. The exact etiology of UC remains unknown, though it is thought to involve a complex interplay of genetic, environmental, and immunological factors[1][2]. The disease manifests through symptoms such as blood and/or mucus in the stool, increased bowel movement frequency, and tenesmus, which can persist for months[2].

Pathophysiology. The pathophysiological mechanisms underlying UC involve immune-mediated in- flammation. Structural or functional impairment of the intestinal epithelial barrier initiates an inflammatory cascade triggered by antigen-presenting cells like dendritic cells[11]. This process attracts neutrophils to the sites of inflammation, leading to the production of pro-inflammatory cytokines, including IL-23 and tumor necrosis factor (TNF)[11]. Moreover, various lymphocyte populations contribute significantly to the inflammatory response in UC, exacerbating colonic barrier dysfunction through cytokines such as IL-5, IL-6, and IL-17[11].

Extra-intestinal Manifestations. In addition to gastrointestinal symptoms, UC is associated with extra-intestinal changes that can affect vital organs, including the liver, spleen, and kidneys[3]. These alterations can complicate the clinical management of UC, making it essential for healthcare providers to monitor for potential renal complications and assess the overall health of the patient[10].

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Diagnosis and Monitoring. Clinical guidelines published by the European Crohn's and Colitis Organization (ECCO) outline standardized approaches for diagnosing and treating UC[13]. Recent advances in imaging techniques, such as intestinal ultrasound (IUS), have shown promise in assessing disease activity and monitoring the progression of UC. Measures such as bowel wall thickness (BWT) and vascularization are now being utilized to evaluate disease status more effectively[14].

The management of UC is complex and requires a comprehensive understanding of its pathophysiology, symptomatology, and potential complications. Ongoing research continues to explore the intricate relationships between UC and other conditions, particularly those affecting renal function, to develop more targeted therapeutic strategies[6][8].

Kidney Morphology

The morphology of the kidneys in the context of ulcerative colitis (UC) can exhibit a range of changes, reflecting the complex interplay between inflammatory bowel disease (IBD) and renal pathology. Notably, renal manifestations in UC are diverse, including conditions such as acute tubular necrosis (ATN), interstitial nephritis, and amyloidosis, which may arise as extra-intestinal complications of the disease[4][5].

Renal Biopsy Findings. Kidney biopsies in patients with UC can reveal significant morphological alterations. Common findings include focal glomerular sclerosis and evidence of tubulointerstitial nephritis, which may coexist with or be a consequence of IBD activity. In a retrospec- tive review, tubulointerstitial nephritis was identified as the second most prevalent diagnosis following IgA nephropathy among patients with renal injury related to IBD[10]. The presence of inflammatory infiltrates, particularly mononuclear cells, alongside fibrosis, can indicate ongoing inflammatory processes that are often linked to active IBD[4].

Specific Morphological Changes. Histopathological examination may show various changes, including slight mesangial expansion and proliferation in glomeruli, as well as acute tubular necrosis foci. These changes can be associated with urinary findings such as dysmorphic red blood cells and casts, which may indicate underlying IgA nephropathy rather than direct renal involvement by UC itself[4][15]. Direct immunofluorescence studies may reveal mesangial deposits of immunoglobulins, such as IgA and complement component C3, which further supports the diagnosis of immunological involvement in renal pathology[4].

Pathophysiology and Mechanisms. The renal tubular injuries observed in IBD patients can be attributed to systemic in- flammatory responses, with mechanisms involving neutrophil infiltration and cytokine expression resembling the colonic inflammation typical of IBD[10]. Studies suggest that the renal changes may occur in conjunction with active IBD symptoms, such as fever and abdominal pain, indicating a possible correlation between renal and gastrointestinal pathology[5]. Moreover, specific drug therapies, particularly anti-TNF agents like infliximab, have been associated with renal complications, including acute kidney injury due to tubulointerstitial nephritis, suggesting that therapeutic interventions for IBD may also impact renal health[5][10].

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Implications for Management. The identification of renal involvement in patients with UC is crucial for guiding therapy. Management strategies may involve addressing the underlying inflammatory process to mitigate renal damage, while monitoring renal function in the context

of IBD treatment[5][10]. Given the complexities of renal manifestations in IBD, a multidisciplinary approach including nephrologists and gastroenterologists is often beneficial for optimizing patient outcomes.

Morphometric Analysis. Morphometric analysis is a critical component in evaluating the structural changes in the kidneys associated with experimental ulcerative colitis (UC). This analysis involves quantifying the dimensions and cellular compositions of various kidney structures to better understand the pathological changes occurring in response to UC.

Histopathological Evaluation. Histological evaluations in studies of UC typically involve assessing the integrity of mucosal tissues and characterizing inflammation. Pathologists classify histopatho- logical findings based on criteria such as the infiltration of inflammatory cells, crypt loss, goblet cell reduction, and the presence of epithelial erosions[6]. For accurate assessments, morphometric analyses are often performed on numerous villi and crypts from microscopic sections. For instance, at least 50 villi and 50 crypts are analyzed per experimental group at a magnification of 200×[6]. This detailed analysis is essential for establishing the histological activity index (HAI), which helps quantify the severity of mucosal injury[6].

Measurement Techniques. The intensity of immunohistochemical (IHC) reactions, which indicate specific protein expressions relevant to inflammation, is quantified using relative optical density (ROD) measurements derived from colorimetric assays[6]. These techniques provide a robust quantitative assessment of the degree of inflammation and help elucidate the pathological processes involved in UC. Additionally, the use of software like ImageJ allows for the precise measurement of grey levels in stained tissue sections, further aiding in the morphometric analysis[6].

Statistical Considerations. To ensure the reliability of morphometric data, various statistical methods are em- ployed. The random-effect inverse variance weighted (IVW) method is commonly used for data analysis, alongside methods such as MR–Egger and weighted median approaches to enhance the robustness of estimates across diverse scenarios[7].

These methods not only provide insights into the morphological alterations but also help identify correlations between structural changes in the kidneys and clinical outcomes related to UC.

Implications for Future Research. The findings from morphometric analyses underscore the need for further investi- gations into the immunological responses associated with UC. Future studies may focus on additional inflammatory markers and cytokine expressions, which could provide a more comprehensive understanding of the interplay between UC and kidney morphology[6]. Understanding these relationships is crucial for developing targeted therapies and monitoring renal function in patients with UC.

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Literature Review. The relationship between chronic kidney disease (CKD) and ulcerative colitis (UC) has garnered increasing attention due to the complex interplay of these conditions. Research suggests that the pathophysiological mechanisms underlying the coexistence of CKD and UC remain poorly understood[11]. A study utilizing public RNA-sequencing data aimed to elucidate key molecules and pathways that might mediate this co-occurrence. The investigation focused on differentially expressed genes (DEGs) by analyzing datasets specifically selected for CKD (GSE115857) and UC (GSE10616), resulting in the identification of 155 common DEGs after Venn diagram analysis[11].

Further analyses revealed that these DEGs were predominantly involved in the inflammatory response, with a significant presence in the extracellular space. Ad- ditionally, the PI3K-Akt signaling pathway was highlighted as one of the top enriched pathways, suggesting its potential role in the inflammatory processes associated with both conditions[11]. Such findings underscore the necessity for more detailed studies to explore these molecular pathways and their implications for understanding kidney and gastrointestinal interactions in the context of inflammatory diseases.

Moreover, studies on the efficacy of mesenchymal stem cells (MSCs) in treating UC have shown promising results, although concerns regarding the methodological quality of these clinical trials persist. Most of the trials were noted to lack rigorous control measures, raising questions about the robustness of their findings[12]. A systematic review identified 216 patients across various studies, including a mixture of clinical trial designs, yet the overall quality was deemed poor, highlighting the need for more comprehensive and higher-quality randomized controlled trials[12].

The findings reflect a broader trend in medical research, where effective treatments must be substantiated by high-quality evidence to inform clinical practice.

Mechanisms of Kidney Changes in Ulcerative Colitis. The relationship between ulcerative colitis (UC) and renal changes is complex and involves various mechanisms. Several studies have identified inflammatory respon- ses as a key factor contributing to morphological changes in the kidneys of patients with UC.

Inflammatory Mediators. Inflammatory cytokines play a significant role in the kidney's pathological alterations observed in UC. Elevated levels of proinflammatory cytokines, such as interleukin-22 (IL-22), have been documented in patients with inflammatory bowel disease (IBD), including UC.[8] These cytokines can induce inflammatory responses in renal tissue, potentially leading to conditions such as glomerulonephritis and tubulointerstitial nephritis.[10] Moreover, immune mediators, including chemokines, are implicated in the recruitment of inflammatory cells to the kidneys, which results in interstitial inflammation and fibrosis.[9]

Autoimmune Reactions. Autoimmune mechanisms are also thought to contribute to kidney changes in UC. The disease may provoke autoimmune responses that adversely affect renal mor- phology, leading to alterations such as thickening of the Shumlyansky-Bowman capsule and edema around proximal and distal tubules.[16][11] Histological evalu- ations have shown macrophage infiltration in renal tissues, indicative of an ongoing inflammatory response triggered by UC.[16]

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Drug-Induced Changes. It is essential to distinguish between renal changes due to UC itself and those resulting from medications used to manage the disease. The use of nephrotoxic agents, including aminosalicylates and biologic therapies such as infliximab, can exacerbate renal dysfunction, leading to acute kidney injury (AKI) in some patients.- [10][9] Vigilant monitoring of renal function is crucial, especially in patients receiving such treatments, as they are at increased risk of drug-induced renal damage.[10]

Histopathological Findings. Histopathological studies have demonstrated specific kidney alterations in UC, such as glomerular sclerosis and tubular damage.[9] Renal histological examinations reveal marked interstitial inflammation, indicative of the inflammatory processes at play in UC. Additionally, changes in collagen types within the glomerular basement membrane have been observed, with type IV collagen levels decreasing and type I and V collagens increasing, suggesting ongoing structural modifications within the renal architecture as a consequence of the disease.[17]

Summary. Morphological and morphometric changes in the kidneys associated with experimen- tal ulcerative colitis (UC) have become an important area of research within the fields of gastroenterology and nephrology. Ulcerative colitis is a chronic inflammatory bowel disease that primarily affects the colon and rectum, leading to significant systemic implications, including potential renal complications.[1][2] The interplay between UC and kidney health is notable due to the increased risk of extra-intestinal mani- festations, particularly renal pathologies such as acute tubular necrosis, interstitial nephritis, and glomerular damage.[3][4] Understanding these changes is essential for improving patient outcomes and guiding therapeutic strategies.

Research into the morphological alterations in the kidneys of UC patients has highlighted various structural changes, including inflammatory infiltrates, fibrosis, and glomerular sclerosis. Histopathological evaluations often reveal significant findings like tubulointerstitial nephritis and abnormal renal architecture, which may correlate with disease activity in the gastrointestinal tract.[4][5] Morphometric analyses, which quantify kidney structural changes, have become vital in elucidating these relation- ships, as they provide a quantitative basis for assessing renal involvement in UC and its pathophysiological mechanisms.[6][7]

The pathophysiology underlying kidney changes in UC includes systemic inflamma- tory responses driven by cytokines and immune mediators, which can exacerbate renal injury.[8][9] Moreover, autoimmune reactions and drug-induced nephrotoxicity from treatments for UC, such as anti-TNF agents, further complicate this relationship by potentially inducing or aggravating renal dysfunction.[10][9] As a result, there is an ongoing need for comprehensive studies that investigate these mechanisms and their implications for effective disease management. Prominent controversies in this field include the debate over the exact causal mecha- nisms linking UC and kidney pathology, as well as the adequacy of existing treatment regimens in mitigating renal complications.[11][12] The challenges of establishing robust clinical evidence regarding the effectiveness of emerging therapies, such as mesenchymal stem cells, emphasize the necessity for further research to clarify the interconnectedness of renal and gastrointestinal health in patients with ulcerative colitis.[12]

References

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[1] : Ulcerative Colitis: Diagnosis and Treatment - AAFP
[2] : Ulcerative colitis | Nature Reviews Disease Primers
[3] : Identification of shared gene signatures and molecular mechanisms ...
[4] : Dual role of melatonin as an anti-colitis and anti-extra intestinal ...
[5] : Insights into renal and urological complications of inflammatory ...
[6] : Ulcerative Colitis Guidelines - Medscape Reference
[7] : Advances in cross-sectional imaging in inflammatory bowel disease
[8] : Innovative Animal Model of DSS-Induced Ulcerative Colitis in ... - MDPI
[9] : An Antibiotic-Responsive Mouse Model of Fulminant Ulcerative Colitis
[10]: Acute Kidney Injury in the Context of Inflammatory Bowel Disease
[11] : Nephrotic syndrome in ulcerative colitis - PubMed
[12] : Different renal manifestations associated with very early onset ...
[13] : Inflammatory bowel disease increases the levels of albuminuria and ...
[14] : Naringin Exerts Therapeutic Effects on Mice Colitis - Frontiers
[15] : Kidney Manifestations of Inflammatory Bowel Diseases
[16] : kidney, ulcerative colitis, morphology - INOVATUS JOURNALS
[17] : Change in Renal Glomerular Collagens and Glomerular Filtration ...