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Review Article

Kidney Biopsy Findings in Patients with Sickle Cell Nephropathy: Updated Review

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Abstract

Sickle cell anemia (SCA) remains a prevalent hereditary disorder in various regions, including Saudi Arabia. Among its numerous systemic complications, sickle cell nephropathy (SCN) represents a major contributor to both morbidity and mortality. While the clinical manifestations of SCN have been well-documented, detailed histopathological descriptions are limited and dispersed across isolated case reports and small series. Notably, certain histologic alterations, although subtle, may carry important diagnostic, prognostic, and therapeutic implications. This review aims to provide a comprehensive review of the histopathological features associated with SCN, correlating them with underlying pathophysiological mechanisms and clinical presentation to enhance diagnostic accuracy and guide clinical management.

Keywords: Sickle cell anemia (SCA), sickle cell nephropathy (SCN), Hemoglobinopathy, Glomerular diseases, Tubulointerstitial diseases, Renal complications.

INTRODUCTION

Sickle cell anemia (SCA) is a monogenic autosomal recessive hemoglobinopathy caused by the production of hemoglobin S. It was first identified as a molecular disease in 1949 by Linus Pauling and colleagues, who observed abnormal electrophoretic mobility of hemoglobin S (Bunn, 1997). Since then, advances in understanding the disease's pathophysiology have significantly improved screening, diagnosis, and management. Despite these advances, SCA remains a global health burden, particularly in endemic regions (Colombatti *et al*., 2023; Mburu & Odame, 2019). In Saudi Arabia, epidemiological studies estimate a prevalence of 45,000 per 1,000,000 adults and 2,400 per 1,000,000 children and adolescents, with higher rates in the eastern, southern, and western regions(Al-Qurashi *et al*., 2008; Alhamdan *et al*., 2007; Memish & Saeedi, 2011). This regional variation is primarily attributed to the high national rate of consanguinity, which persists despite the robust efforts of premarital counselling (Alhamdan *et al*., 2007; El-Mouzan *et al*., 2007).

Sickle cell disease (SCD) can affect virtually any organ, often resulting in significant morbidity. Renal involvement, referred to as sickle cell nephropathy (SCN), is a well-recognized complication. In 1990, Michael Allon provided a detailed description of the renal manifestations associated with the disease, identifying a spectrum of abnormalities ranging from impaired urinary concentrating ability (hyposthenuria) to more severe pathologies such as renal papillary necrosis (Allon, 1990).

Although the renal complications of sickle cell anemia (SCA) have been well-documented in the literature, the detailed histopathological characterization of sickle cell nephropathy (SCN) remains limited, with only a few published reports addressing these findings. Despite the high prevalence of sickle cell anemia (SCA) in Saudi Arabia, the histopathological features of sickle cell nephropathy (SCN) have not been systematically studied or reported in the Saudi literature. The few available studies have primarily focused on clinical rather than histological aspects of the disease (Aleem, 2008, 2010; Alhwiesh, 2014). This article aims to provide a comprehensive overview of the renal manifestations of SCA, with a particular focus on the histopathological spectrum of SCN. Given that some of these histologic changes may be subtle and easily overlooked, it is essential for practicing pathologists—whether general or subspecialized in renal pathology—

to be familiar with these features to ensure accurate diagnosis and appropriate clinical correlation.

Pathogenesis of Sickle Cell Nephropathy

The development of sickle cell nephropathy (SCN) is associated with multiple regulatory disturbances along the nephron, resulting in progressive renal injury. The pathogenesis is primarily driven by three interrelated mechanisms (Ataga *et al*., 2022):

- Hypoxic injury due to medullary ischemia; Glomerular hyperfiltration, particularly in early disease stages, and chronic hemolysis and recurrent endothelial injury.

These pathogenic processes are not mutually exclusive; rather, they interact in complex ways. Some mechanisms may potentiate one another, while others may appear contradictory. Ultimately, the cumulative effect of these overlapping pathways results in progressive structural and functional renal damage characteristic of SCN.

Due to several unique microenvironmental factors, the renal medulla is particularly susceptible to vaso-occlusive events in individuals with sickle cell disease. Recurrent microvascular thrombosis in this region results in localized ischemic injury, which stimulates the release of prostaglandins. These vasodilatory mediators contribute to afferent arteriolar dilation, which subsequently induces glomerular hyperfiltration(Becker, 2011; Hariri *et al*., 2018). Systemic hemodynamic adaptations to chronic anemia, such as increased cardiac output and elevated renal blood flow, further exacerbate this hyperfiltration state (Haymann *et al*., 2021). Additionally, chronic intravascular hemolysis activates the heme oxygenase–carbon monoxide (HO–CO) pathway, leading to both systemic and intrarenal hyperperfusion (Nath & Hebbel, 2015).

Conversely, local hypoxia promotes the release of endothelin-1 (ET-1), a potent endothelium-derived vasoconstrictor that also stimulates the generation of reactive oxygen species (ROS). ROS production is further amplified by the release of cell-free hemoglobin during hemolysis, contributing to oxidative stress. The combined effects of vasoconstriction and oxidative injury result in sustained endothelial damage and progressive ischemia (Gurbanov *et al*., 1996; Heimlich *et al*., 2016). Furthermore, elevated levels of soluble vascular endothelial growth factor receptor 1 (sVEGFR1), commonly observed in the context of hemolysis, impair nitric oxide (NO) bioavailability, thereby exacerbating endothelial dysfunction and perpetuating the cycle of vascular injury (Youssry *et al*., 2015).

Common Clinical Presentation of Sickle Cell Nephropathy

Reviewing the patient's clinical history before evaluating any biopsy specimen is a critical component of renal pathology assessment. In the context of medical kidney diseases, histopathological alterations are often subtle and may lack the overt morphological changes observed in other organ systems; nonetheless, they can have significant clinical implications. Correlation with clinical data and ancillary laboratory findings is essential in directing the pathologist's attention to specific diagnostic possibilities. For instance, the presence of proteinuria necessitates careful examination for underlying glomerular pathology. It is important to note, however, that certain clinical manifestations may not always correspond to discernible histological abnormalities within the renal tissue.

Hyposthenuria, characterized by an impaired ability to concentrate urine, is recognized as one of the earliest and most consistent renal manifestations of sickle cell nephropathy. This defect in urinary concentrating capacity typically emerges in early infancy and persists throughout adulthood. Clinically, hyposthenuria often presents as nocturnal enuresis and predisposes affected individuals to an increased risk of dehydration due to the inability to conserve water effectively (Francis & Worthen, 1968; Naik & Derebail, 2017; Sharpe & Thein, 2014).

An elevated albumin excretion rate (AER) is observed in approximately two-thirds of patients with sickle cell disease(Guasch *et al*., 2006). The underlying mechanism of glomerular hyperfiltration plays a key role in the early onset of microalbuminuria, particularly in the pediatric population, with progression to macroalbuminuria frequently occurring in adulthood. Although nephrotic-range proteinuria is uncommon in this context, its presence should prompt consideration of alternative or coexisting glomerular pathologies (Naik & Derebail, 2017). When nephrotic syndrome does occur as a manifestation of sickle cell glomerulopathy, it is typically associated with poorer renal outcomes (Bakir *et al*., 1987; Powars *et al*., 1991).

Hematuria, typically characterized by the presence of non-dysmorphic red blood cells, is a common clinical manifestation in individuals with sickle cell disease and may be either microscopic or macroscopic(Kaze *et al*., 2013). Multiple etiologies contribute to this finding, including papillary necrosis, rupture of fragile renal vessels, hemoglobinuria-induced tubular injury, and, less commonly, early presentation of renal medullary carcinoma (Aleem, 2008; Baron *et al*., 1994; Becker, 2011). Overt hematuria may serve as a clinical indicator of these underlying renal pathologies.

Chronic kidney disease (CKD) is a significant complication in patients with sickle cell disease, with a reported prevalence of 11.6% (Hariri *et al*., 2018). In large cohort studies, CKD has been identified as the second leading cause of mortality in this population (Powars *et al*., 2005). Individuals with sickle cell anemia are also at increased risk for acute kidney injury (AKI), commonly triggered by hypovolemia, sepsis, nephrotoxic medications(Baddam *et al*., 2017), and, less frequently, vaso-occlusive crises (Audard *et al.*, 2010). The occurrence of AKI in these patients is associated with a heightened risk of CKD progression and increased mortality (Yeruva *et al*., 2016).

Histopathology of Sickle Cell Nephropathy

The histopathological features of sickle cell nephropathy (SCN) encompass more than just the presence of sickled erythrocytes within the renal vasculature. For a more structured and comprehensive evaluation, these findings can be broadly classified into glomerular and non-glomerular compartments.

Glomerular Findings:

- **Glomerular Hypertrophy**

Glomerular hypertrophy, also known as glomerulomegaly, represents a structural and functional adaptive response to increased metabolic demand or loss of nephrons. Although population variability has precluded the establishment of a definitive quantitative threshold (Hughson *et al*., 2011), glomeruli with a diameter exceeding 220 micrometres or occupying approximately half the field of view under a standard 40x objective lens are generally considered hypertrophied (Colvin *et al.*, 2023).

Early studies have proposed a pathogenic association between glomerulomegaly and progressive glomerular injury, particularly glomerulosclerosis. This adaptive response, while initially compensatory, may ultimately contribute to structural damage(Fogo & Ichikawa, 1991). In patients with sickle cell disease, glomerular enlargement—often accompanied by engorgement with sickled erythrocytes—has been consistently observed, particularly in the juxtamedullary glomeruli (Elfenbein *et al*., 1974). As previously noted, hyperfiltration is an early and common glomerular insult in sickle cell nephropathy, closely linked to the development of glomerulomegaly. This adaptation involves an increase in glomerular surface area, volume, and the ultrafiltration coefficient (Kf)(Haymann *et al*., 2021; Hirschberg, 2010).

- **Mesangial Hyperplasia**

The mesangium is a histological component of the glomerulus, composed of mesangial cells and extracellular matrix, which provides structural support to the glomerular capillary loops. In a standard 2-µm-thick section, up to two mesangial cell nuclei per mesangial area is considered within normal limits(Colvin *et al*., 2023; Silva, 2017). Experimental models of sickle cell disease have demonstrated both mesangial hyperplasia and hypertrophy(Manci *et al*., 2006). Consistent with these findings, Zahr *et al*., reported mesangial hypercellularity and/or mesangial matrix expansion in 75% of kidney biopsies in one of the largest histopathological studies of sickle cell nephropathy (Zahr *et al*., 2019). Similar to glomerular hypertrophy, mesangial expansion is a frequently observed and reproducible histologic feature in this patient population (Falk *et al*., 1992).

- **Focal Segmental Glomerulosclerosis (FSGS)**

Focal segmental glomerulosclerosis (FSGS), defined by sclerosis affecting <50% of glomeruli (focal) and <50% of the glomerular tuft (segmental), represents a pattern of glomerular injury rather than a distinct disease entity. FSGS lesions can arise in association with various pathological processes(Silva, 2017). In sickle cell nephropathy, FSGS is the third most commonly observed glomerular lesion, following glomerular and mesangial hypertrophy, and is almost invariably associated with proteinuria, predominantly affecting younger patient (Maigne *et al*., 2010; Zahr *et al.*, 2019). Notably, prior studies have demonstrated that FSGS lesions often occur in the context of glomerular hypertrophy, suggesting that hyperfiltration-induced injury plays a role in their pathogenesis (Falk *et al*., 1992).

According to the Columbia classification, all major FSGS variants—including not otherwise specified (NOS), perihilar, cellular, tip, and collapsing—have been reported in sickle cell disease. These findings suggest that no single variant predominates in the context of sickle cell nephropathy.

- **Membranoproliferative Glomerulonephritis (MPGN)**

Membranoproliferative glomerulonephritis (MPGN) is a distinct pattern of glomerular injury characterized by thickening of the glomerular basement membrane, often due to duplication or "tram-tracking," accompanied by mesangial and endocapillary hypercellularity. Historically considered an immune complex–mediated process, the classification of MPGN has evolved significantly, now encompassing immune-mediated, complement-mediated, and pauci-immune subtypes(Sethi & Fervenza, 2012).

In the context of sickle cell disease, MPGN is reported less frequently than other glomerular lesions such as glomerular hypertrophy or FSGS. The underlying pathogenesis remains poorly understood, but reported cases—affecting both pediatric and adult patients—have typically demonstrated a non–immune complex–mediated pattern, even in the presence of chronic infections such as hepatitis C(Zahr *et al*., 2019). One proposed mechanism involves chronic, low-grade

microthrombotic events, which may lead to repeated vascular injury and reparative remodelling, ultimately contributing to the MPGN pattern(Sethi & Fervenza, 2012).

- **Thrombotic Microangiopathy (TMA)**

Thrombotic microangiopathy (TMA) has garnered increasing attention as a clinically significant renal lesion in recent years, particularly with the growing interest in the role of the complement system in its pathogenesis. Emerging evidence has elucidated the involvement of the alternative complement pathway, with numerous studies and theoretical frameworks seeking to clarify its activation and contribution to endothelial injury(Gallan & Chang, 2020).

TMA is fundamentally characterized by repetitive endothelial damage, which may be triggered by a variety of etiologies, including thrombotic thrombocytopenic purpura (TTP), typical and atypical hemolytic–uremic syndrome (HUS and aHUS), drug-induced TMA, and sickle cell disease, among other (Goldberg *et al*., 2010). Local tissue ischemia is believed to initiate injury via various mediators, while intravascular hemolysis and the resulting release of free heme act as a secondary insult, promoting further activation of the alternative complement pathway and amplifying endothelial injury (Frimat *et al*., 2013).

Thrombotic microangiopathy (TMA) has been reported more frequently in adults than in the pediatric population (Maigne *et al*., 2010; Zahr *et al.*, 2019). Histopathological features vary depending on the phase of the disease. In the acute phase, characteristic findings include mesangiolysis and thrombi within glomerular capillaries, whereas the chronic phase is marked by duplication and thickening of the glomerular basement membrane, resembling a membranoproliferative glomerulonephritis (MPGN) pattern (Colvin *et al*., 2023).

These histological features are not specific to sickle cell disease and may be observed in TMA resulting from a range of etiologies, as previously described. Importantly, thrombotic complications in patients with sickle cell disease are of particular concern, especially in the post-transplant setting, where they may significantly contribute to graft morbidity and overall patient outcomes (Kim *et al*., 2011).

Non-Glomerular Findings:

- **Hemosiderosis**

Hemosiderosis refers to the excess deposition of iron within cells, typically appearing as coarse, brown, cytoplasmic granules under light microscopy. Although traditionally not associated with significant clinical consequences, recent observations suggest that it may contribute to acute kidney injury (AKI) during sickle cell crises. This rare but important complication should not be overlooked (Calazans *et al*., 2012).

Hemosiderin deposition is almost universally observed in renal tissue from patients with sickle cell disease. While the deposits are most commonly localized to tubular epithelial cells, interstitial and mesangial involvement has also been reported (Falk *et al*., 1992; Zahr *et al*., 2019).

Although hemosiderin can often be recognized on routine hematoxylin and eosin (H&E) staining, special stains such as Prussian blue help confirm iron deposition and distinguish it from other brown pigments, including lipofuscin and melanin(Colvin *et al*., 2023).

- **Interstitial Fibrosis and Tubular Atrophy**

Interstitial fibrosis and tubular atrophy are consistently reported histopathological features in cases of sickle cell nephropathy (SCN), and are considered hallmark findings across the existing literature. Despite their frequent occurrence, the degree of tubulointerstitial injury—whether mild, moderate, or severe—has been quantitatively assessed in only a limited number of studies. Of these, the majority of cases demonstrated mild interstitial and tubular damage, with only a single report documenting severe tubulointerstitial involvement (Falk *et al*., 1992). The microanatomical distribution of atrophic tubules has been most commonly localized to the renal medulla. This distribution is thought to reflect the unique pathophysiologic environment of the inner medulla, which is characterized by low oxygen tension, elevated osmolality, and acidic pH conditions that collectively promote intravascular sickling of erythrocytes. The resultant microvascular obstruction leads to repeated episodes of ischemic injury and contributes to chronic tubulointerstitial damage. In addition to medullary involvement, atrophic tubules are frequently observed in cortical regions adjacent to glomeruli exhibiting segmental sclerosis, suggesting a potential secondary insult due to localized glomerular injury and downstream effects on surrounding tubular structures (Becker, 2011; Colvin *et al*., 2023; Falk *et al.*, 1992; Hariri *et al*., 2018; Zahr *et al*., 2019). Tubulointerstitial fibrosis has been historically recognized as a common final pathway of renal injury, irrespective of the underlying etiology, and is strongly associated with progressive decline in renal function and the development of chronic kidney disease (CKD)(Remuzzi & Bertani, 1998).

- **Renal Cortical Necrosis**

Another significant histopathological finding, though seldom reported in the literature (Pham *et al*., 2000), is renal cortical necrosis, which has been previously observed in patients with sickle cell disease. In a cohort study of 36 individuals with SCD, this severe complication was identified in two cases, with one biopsy specimen demonstrating up to 50% cortical

necrosis (Zahr *et al*., 2019). This complication is known to result from various etiologies, including thrombotic microangiopathy (TMA), vascular disorders, and systemic hypotensive states such as shock. Notably, some of these underlying causes—particularly TMA—are already prevalent among patients with sickle cell disease (see discussion on TMA)(Colvin *et al*., 2023).

- **Papillary Necrosis**

The renal papilla represents the tapered apex of the renal pyramid, located within the inner medullary zone of the kidney, where it projects into a minor calyx. It serves as the terminal conduit for urine flow, conveying renal filtrate from the collecting ducts into the minor calyces of the renal pelvis. Owing to its unique anatomical location and functional role, the renal papilla is particularly susceptible to ischemic injury. This vulnerability is partly attributable to its relatively limited and dual blood supply, which is derived from the vasa recta and small arterial branches that traverse the adventitia of the adjacent minor calyces (Alleyne, 1975).

Papillary necrosis results from ischemia of the renal papilla, caused by vascular obstruction, inflammation, or toxic injury. Sloughing of the ischaemic papilla can lead to severe hemorrhage and obstruction and may be complicated by infection (Henderickx *et al*., 2017). Given that renal papillary necrosis is primarily defined by clinical presentation and radiologic findings, histopathological evaluation is typically of limited diagnostic utility. It is generally reserved for ambiguous cases or when papillary necrosis is incidentally identified in specimens from nephrectomies.

- **Medullary Peritubular Capillary (PTC) Thrombosis and PTC Abnormalities**

This subtle yet diagnostically valuable histopathological feature may represent the sole morphological abnormality identified in the kidneys of individuals with sickle cell hemoglobinopathies. Notably, this finding has been more frequently reported in individuals with sickle cell trait than in those with sickle cell disease, highlighting its potential significance even in milder genotypic variants (Khalighi *et al*., 2014).

Patients with sickle cell trait often do not exhibit the full clinical spectrum of sickle cell disease, such as vaso-occlusive crises. However, they remain at risk for subclinical ischemic injury due to microvascular thrombosis. In some cases, these individuals may undergo kidney biopsy for unrelated indications and be found to have incidental medullary peritubular capillary (PTC) thrombosis. Subsequent evaluation may then reveal an underlying sickle cell hemoglobinopathy that had not been previously diagnosed.

To date, only a single study by Bissonnette *et al*., has characterized the ultrastructural alterations observed in peritubular capillaries (PTCs) in a case of sickle cell trait. In their report, medullary PTCs exhibited basement membrane multilayering, a feature reminiscent of changes typically associated with chronic antibody-mediated rejection (Bissonnette *et al*., 2016).

- **Renal Medullary Carcinoma**

Renal medullary carcinoma (RMC) is a rare, highly aggressive neoplasm of the kidney, associated with a dismal prognosis and markedly reduced overall survival. It predominantly affects young individuals, shows a male predominance, and occurs commonly in patients of African descent. A strong and consistent association with sickle cell trait has been well established in the literature (Alvarez *et al*., 2015; Davis *et al*., 1995; Iacovelli *et al*., 2015).

Recent studies have implicated the loss of the SMARCB1 tumor suppressor gene as a key molecular driver in the pathogenesis of renal medullary carcinoma. The proposed underlying mechanism involves medullary hypoxia, a characteristic feature in sickle cell patients, which may promote genomic instability through increased susceptibility to chromosomal translocations and deletions. These alterations can ultimately result in SMARCB1 inactivation (Holland *et al*., 2020; Msaouel *et al*., 2018).

Clinically, renal medullary carcinoma (RMC) most commonly presents with hematuria and flank pain, which are the most frequently reported initial symptoms (Iacovelli *et al*., 2015).

Histopathologically, it exhibits a broad and heterogeneous spectrum of histomorphological patterns, reflecting its aggressive and poorly differentiated nature. The most common architectural features include sheet-like growth often accompanied by coagulative necrosis, and neoplastic cells may demonstrate rhabdoid features with prominent nucleoli. Additional patterns include a sieve-like or cribriform architecture, with tumour nests embedded in a desmoplastic stroma, and a reticular or yolk sac tumour (YST)-like pattern, characterized by irregular tumour aggregates within a loose myxoid background, mimicking testicular YST. Other variants include tubulopapillary and intracystic papillary patterns, the latter showing micropapillae lacking fibrovascular cores. An infiltrating glandular pattern may also be present, with irregular glands invading a myxoid stroma. A distinguishing feature in RMC is the frequent histologic presence of sickled erythrocytes, which provides a diagnostic clue, particularly in the context of sickle cell trait (Ohe *et al.*, 2018).

Kidney Transplant in Sickle Cell Patients

Historically, short-term renal allograft outcomes in patients with end-stage sickle cell nephropathy (SCN) have been comparable to those observed in individuals with end-stage renal disease

(ESRD) due to other etiologies. However, long-term graft survival in the SCN population has consistently been reported as relatively poorer (Ojo *et al*., 1999).

However, emerging evidence indicates that patients with sickle cell disease–associated kidney failure derive similar mortality benefits from kidney transplantation as those with other causes of kidney failure (Bae *et al*., 2021).

These emerging insights underscore the complexity of decision-making regarding renal transplantation in this population and reflect the ongoing debate surrounding its optimal clinical management.

From a histopathological perspective, graft failure in this patient population is most often attributed to intravascular thrombosis, a complication that, unfortunately, is frequently associated with early allograft loss (Cornell *et al*., 2024; Kim *et al*., 2011).

CONCLUSION

In conclusion, although renal biopsy is not routinely performed in patients with sickle cell anemia (SCA), it can yield highly informative findings that reflect the underlying pathophysiological alterations inherent to the disease. This review aimed to summarize the previously reported histopathological features of sickle cell nephropathy and to contextualize them within the broader framework of disease pathophysiology. Given the substantial population of individuals affected by SCA in Saudi Arabia, kidney biopsies or nephrectomy specimens are occasionally obtained for various clinical indications. It is imperative that pathologists, including those without subspecialty training in medical kidney pathology, remain vigilant in identifying subtle but diagnostically significant features such as glomerular hypertrophy, mesangial hypercellularity, and hemosiderin deposition. These changes may serve as early indicators of glomerular injury and should prompt appropriate evaluation and follow-up.

Furthermore, as highlighted in this review, patients with SCA are at increased risk for serious renal complications, including the development of, renal malignancies and post-transplant allograft failure. Despite the high prevalence of SCA in Saudi Arabia, there remains a notable absence of comprehensive pathological analyses of renal biopsy or nephrectomy specimens within this population.

As I near the completion of my fellowship training in medical and transplant kidney pathology, I am increasingly motivated to engage in multidisciplinary collaboration aimed at improving the recognition, diagnosis, and management of sickle cell nephropathy (SCN). Given the complex pathophysiology of SCN and its significant burden in Saudi Arabia with a high prevalence of sickle cell disease, such efforts are both timely and clinically imperative. I look forward to establishing collaborative partnerships with nephrologists and hematologists who share a similar commitment to addressing the knowledge gaps surrounding SCN, particularly within our local healthcare context. Through integrated clinical and pathological insights, we can enhance early detection, refine diagnostic criteria, and ultimately contribute to more effective and targeted therapeutic strategies for patients affected by this condition.

REFERENCES

- Aleem, A. (2008). Renal abnormalities in patients with sickle cell disease: a single center report from Saudi Arabia. *Saudi J Kidney Dis Transpl*, *19*(2), 194-199.
- Aleem, A. (2010). Proteinuria in adult Saudi patients with sickle cell disease is not associated with identifiable risk factors. *Saudi J Kidney Dis Transpl*, *21*(5), 903-908.
- Alhamdan, N. A., Almazrou, Y. Y., Alswaidi, F. M., & Choudhry, A. J. (2007). Premarital screening for thalassemia and sickle cell disease in Saudi Arabia. *Genet Med*, *9*(6), 372-377. https://doi.org/10.1097/gim.0b013e318065a9e8
- Alhwiesh, A. (2014). An update on sickle cell nephropathy. *Saudi J Kidney Dis Transpl*, *25*(2), 249-265. https://doi.org/10.4103/1319-2442.128495
- Alleyne, G. A. (1975). The kidney in sickle cell anemia. *Kidney Int*, *7*(6), 371-379. https://doi.org/10.1038/ki.1975.54
- Allon, M. (1990). Renal abnormalities in sickle cell disease. *Arch Intern Med*, *150*(3), 501-504.
- Al-Qurashi, M. M., El-Mouzan, M. I., Al-Herbish, A. S., Al-Salloum, A. A., & Al-Omar, A. A. (2008). The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. *Saudi Med J*, *29*(10), 1480-1483.
- Alvarez, O., Rodriguez, M. M., Jordan, L., & Sarnaik, S. (2015). Renal medullary carcinoma and sickle cell trait: A systematic review. *Pediatr Blood Cancer*, *62*(10), 1694-1699. https://doi.org/10.1002/pbc.25592
- Ataga, K. I., Saraf, S. L., & Derebail, V. K. (2022). The nephropathy of sickle cell trait and sickle cell disease. *Nat Rev Nephrol*, *18*(6), 361-377. https://doi.org/10.1038/s41581-022-00540-9
- Audard, V., Homs, S., Habibi, A., Galacteros, F., Bartolucci, P., Godeau, B.,…Mekontso Dessap, A. (2010). Acute kidney injury in sickle patients with painful crisis or acute chest syndrome and its relation to pulmonary hypertension. *Nephrol Dial Transplant*, *25*(8), 2524-2529. https://doi.org/10.1093/ndt/gfq083
- Baddam, S., Aban, I., Hilliard, L., Howard, T., Askenazi, D., & Lebensburger, J. D. (2017). Acute kidney injury during a pediatric sickle cell vaso-

occlusive pain crisis. *Pediatr Nephrol*, *32*(8), 1451-1456. https://doi.org/10.1007/s00467-017-3623-6

- Bae, S., Johnson, M., Massie, A. B., Luo, X., Haywood, C., Jr., Lanzkron, S. M.,…Purnell, T. S. (2021). Mortality and Access to Kidney Transplantation in Patients with Sickle Cell Disease-Associated Kidney Failure. *Clin J Am Soc Nephrol*, *16*(3), 407-414. https://doi.org/10.2215/cjn.02720320
- Bakir, A. A., Hathiwala, S. C., Ainis, H., Hryhorczuk, D. O., Rhee, H. L., Levy, P. S., & Dunea, G. (1987). Prognosis of the nephrotic syndrome in sickle glomerulopathy. A retrospective study. *Am J Nephrol*, *7*(2), 110-115. https://doi.org/10.1159/000167444
- Baron, B. W., Mick, R., & Baron, J. M. (1994). Hematuria in sickle cell anemia--not always benign: evidence for excess frequency of sickle cell anemia in African Americans with renal cell carcinoma. *Acta Haematol*, *92*(3), 119-122. https://doi.org/10.1159/000204199
- Becker, A. M. (2011). Sickle cell nephropathy: challenging the conventional wisdom. *Pediatr Nephrol*, *26*(12), 2099-2109. https://doi.org/10.1007/s00467-010-1736-2
- Bissonnette, M. L., Henriksen, K. J., Delaney, K., Stankus, N., & Chang, A. (2016). Medullary Microvascular Thrombosis and Injury in Sickle Hemoglobin C Disease. *J Am Soc Nephrol*, *27*(5), 1300-1304. https://doi.org/10.1681/asn.2015040399
- Bunn, H. F. (1997). Pathogenesis and treatment of sickle cell disease. *N Engl J Med*, *337*(11), 762-769. https://doi.org/10.1056/nejm199709113371107
- Calazans, L. M., de Souza Santos, R. F., de Souza Gonçalves, M., Dos-Santos, W. L., & Rocha, P. N. (2012). Renal hemosiderosis complicating sickle cell anemia. *Kidney Int*, *81*(7), 709. https://doi.org/10.1038/ki.2011.470
- Colombatti, R., Hegemann, I., Medici, M., & Birkegård, C. (2023). Systematic Literature Review Shows Gaps in Data on Global Prevalence and Birth Prevalence of Sickle Cell Disease and Sickle Cell Trait: Call for Action to Scale Up and Harmonize Data Collection. *J Clin Med*, *12*(17). https://doi.org/10.3390/jcm12175538
- Colvin, R., Cornell, L., & Chang, A. (2023). *Kidney Diseases*. Elsevier.
- Cornell, L. D., Shankaranarayanan, D., Rodriguez, P. S., & Damgard, S. E. (2024). Sickle cell disease in the kidney transplant. *Kidney Int*, *105*(4), 892. https://doi.org/10.1016/j.kint.2023.09.022
- Davis, C. J., Jr., Mostofi, F. K., & Sesterhenn, I. A. (1995). Renal medullary carcinoma. The seventh sickle cell nephropathy. *Am J Surg Pathol*, *19*(1), 1-11. https://doi.org/10.1097/00000478-199501000-00001
- Elfenbein, I. B., Patchefsky, A., Schwartz, W., & Weinstein, A. G. (1974). Pathology of the glomerulus in sickle cell anemia with and without nephrotic syndrome. *Am J Pathol*, *77*(3), 357-374.
- El-Mouzan, M. I., Al-Salloum, A. A., Al-Herbish, A. S., Qurachi, M. M., & Al-Omar, A. A. (2007). Regional variations in the prevalence of consanguinity in Saudi Arabia. *Saudi Med J*, *28*(12), 1881-1884.
- Falk, R. J., Scheinman, J., Phillips, G., Orringer, E., Johnson, A., & Jennette, J. C. (1992). Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med*, *326*(14), 910-915. https://doi.org/10.1056/nejm199204023261402
- Fogo, A., & Ichikawa, I. (1991). Evidence for a pathogenic linkage between glomerular hypertrophy and sclerosis. *Am J Kidney Dis*, *17*(6), 666-669. https://doi.org/10.1016/s0272-6386(12)80347-7
- Francis, Y. F., & Worthen, H. G. (1968). Hyposthenuria in sickle cell disease. *J Natl Med Assoc*, *60*(4), 266-270.
- Frimat, M., Tabarin, F., Dimitrov, J. D., Poitou, C., Halbwachs-Mecarelli, L., Fremeaux-Bacchi, V., & Roumenina, L. T. (2013). Complement activation by heme as a secondary hit for atypical hemolytic uremic syndrome. *Blood*, *122*(2), 282-292. https://doi.org/10.1182/blood-2013-03-489245
- Gallan, A. J., & Chang, A. (2020). A New Paradigm for Renal Thrombotic Microangiopathy. *Semin Diagn Pathol*, *37*(3), 121-126. https://doi.org/10.1053/j.semdp.2020.01.002
- Goldberg, R. J., Nakagawa, T., Johnson, R. J., & Thurman, J. M. (2010). The role of endothelial cell injury in thrombotic microangiopathy. *Am J Kidney Dis*, *56*(6), 1168-1174. https://doi.org/10.1053/j.ajkd.2010.06.006
- Guasch, A., Navarrete, J., Nass, K., & Zayas, C. F. (2006). Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. *J Am Soc Nephrol*, *17*(8), 2228-2235. https://doi.org/10.1681/asn.2002010084
- Gurbanov, K., Rubinstein, I., Hoffman, A., Abassi, Z., Better, O. S., & Winaver, J. (1996). Differential regulation of renal regional blood flow by endothelin-1. *Am J Physiol*, *271*(6 Pt 2), F1166-1172. https://doi.org/10.1152/ajprenal.1996.271.6.F1166
- Hariri, E., Mansour, A., El Alam, A., Daaboul, Y., Korjian, S., & Aoun Bahous, S. (2018). Sickle cell nephropathy: an update on pathophysiology, diagnosis, and treatment. *Int Urol Nephrol*, *50*(6), 1075-1083. https://doi.org/10.1007/s11255-018-1803-3
- Haymann, J. P., Hammoudi, N., Livrozet, M., Santin, A., Mattioni, S., Letavernier, E.,…Lionnet, F. (2021). Hemodynamic and biological correlates of glomerular hyperfiltration in sickle cell patients before and under renin-angiotensin system blocker.

Sci Rep, *11*(1), 11682. https://doi.org/10.1038/s41598-021-91161-y

- Heimlich, J. B., Speed, J. S., O'Connor, P. M., Pollock, J. S., Townes, T. M., Meiler, S. E.,…Pollock, D. M. (2016). Endothelin-1 contributes to the progression of renal injury in sickle cell disease via reactive oxygen species. *Br J Pharmacol*, *173*(2), 386-395. https://doi.org/10.1111/bph.13380
- Henderickx, M., Brits, T., De Baets, K., Seghers, M., Maes, P., Trouet, D.,…De Win, G. (2017). Renal papillary necrosis in patients with sickle cell disease: How to recognize this 'forgotten' diagnosis. *J Pediatr Urol*, *13*(3), 250-256. https://doi.org/10.1016/j.jpurol.2017.01.020
- Hirschberg, R. (2010). Glomerular hyperfiltration in sickle cell disease. In *Clin J Am Soc Nephrol* (Vol. 5, pp. 748-749). https://doi.org/10.2215/cjn.01340210
- Holland, P., Merrimen, J., Pringle, C., & Wood, L. A. (2020). Renal medullary carcinoma and its association with sickle cell trait: a case report and literature review. *Curr Oncol*, *27*(1), e53-e56. https://doi.org/10.3747/co.27.5043
- Hughson, M. D., Hoy, W. E., Douglas-Denton, R. N., Zimanyi, M. A., & Bertram, J. F. (2011). Towards a definition of glomerulomegaly: clinical-pathological and methodological considerations. *Nephrol Dial Transplant*, *26*(7), 2202-2208. https://doi.org/10.1093/ndt/gfq688
- Iacovelli, R., Modica, D., Palazzo, A., Trenta, P., Piesco, G., & Cortesi, E. (2015). Clinical outcome and prognostic factors in renal medullary carcinoma: A pooled analysis from 18 years of medical literature. *Can Urol Assoc J*, *9*(3-4), E172-177. https://doi.org/10.5489/cuaj.2373
- Kaze, F. F., Kengne, A. P., Atanga, L. C., Monny Lobe, M., Menanga, A. P., Halle, M. P.,…Ashuntantang, G. (2013). Kidney function, urinalysis abnormalities and correlates in equatorial Africans with sickle cell disease. *Clin Kidney J*, *6*(1), 15-20. https://doi.org/10.1093/ckj/sfs100
- Khalighi, M. A., Meehan, S. M., & Chang, A. (2014). Medullary peritubular capillary thrombi: a harbinger of sickle cell nephropathy. *Kidney Int*, *86*(4), 861. https://doi.org/10.1038/ki.2014.94
- Kim, L., Garfinkel, M. R., Chang, A., Kadambi, P. V., & Meehan, S. M. (2011). Intragraft vascular occlusive sickle crisis with early renal allograft loss in occult sickle cell trait. *Hum Pathol*, *42*(7), 1027-1033. https://doi.org/10.1016/j.humpath.2010.09.013
- Maigne, G., Ferlicot, S., Galacteros, F., Belenfant, X., Ulinski, T., Niaudet, P.,…Audard, V. (2010). Glomerular lesions in patients with sickle cell disease. *Medicine (Baltimore)*, *89*(1), 18-27. https://doi.org/10.1097/MD.0b013e3181ca59b6
- Manci, E. A., Hillery, C. A., Bodian, C. A., Zhang, Z. G., Lutty, G. A., & Coller, B. S. (2006). Pathology of Berkeley sickle cell mice: similarities and differences with human sickle cell disease. *Blood*, *107*(4), 1651-1658. https://doi.org/10.1182/blood-2005-07-2839
- Mburu, J., & Odame, I. (2019). Sickle cell disease: Reducing the global disease burden. *Int J Lab Hematol*, *41 Suppl 1*, 82-88. https://doi.org/10.1111/ijlh.13023
- Memish, Z. A., & Saeedi, M. Y. (2011). Six-year outcome of the national premarital screening and genetic counseling program for sickle cell disease and β-thalassemia in Saudi Arabia. *Ann Saudi Med*, *31*(3), 229-235. https://doi.org/10.4103/0256-4947.81527
- Msaouel, P., Tannir, N. M., & Walker, C. L. (2018). A Model Linking Sickle Cell Hemoglobinopathies and SMARCB1 Loss in Renal Medullary Carcinoma. *Clin Cancer Res*, *24*(9), 2044-2049. https://doi.org/10.1158/1078-0432.ccr-17-3296
- Naik, R. P., & Derebail, V. K. (2017). The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait. *Expert Rev Hematol*, *10*(12), 1087-1094. https://doi.org/10.1080/17474086.2017.1395279
- Nath, K. A., & Hebbel, R. P. (2015). Sickle cell disease: renal manifestations and mechanisms. *Nat Rev Nephrol*, *11*(3), 161-171. https://doi.org/10.1038/nrneph.2015.8
- Ohe, C., Smith, S. C., Sirohi, D., Divatia, M., de Peralta-Venturina, M., Paner, G. P.,…Trpkov, K. (2018). Reappraisal of Morphologic Differences Between Renal Medullary Carcinoma, Collecting Duct Carcinoma, and Fumarate Hydratase-deficient Renal Cell Carcinoma. *Am J Surg Pathol*, *42*(3), 279-292. https://doi.org/10.1097/pas.0000000000001000
- Ojo, A. O., Govaerts, T. C., Schmouder, R. L., Leichtman, A. B., Leavey, S. F., Wolfe, R. A.,…Agodoa, L. Y. (1999). Renal transplantation in end-stage sickle cell nephropathy. *Transplantation*, *67*(2), 291-295. https://doi.org/10.1097/00007890-199901270-00018
- Pham, P. T., Pham, P. C., Wilkinson, A. H., & Lew, S. Q. (2000). Renal abnormalities in sickle cell disease. *Kidney Int*, *57*(1), 1-8. https://doi.org/10.1046/j.1523-1755.2000.00806.x
- Powars, D. R., Chan, L. S., Hiti, A., Ramicone, E., & Johnson, C. (2005). Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. *Medicine (Baltimore)*, *84*(6), 363-376. https://doi.org/10.1097/01.md.0000189089.45003.52
- Powars, D. R., Elliott-Mills, D. D., Chan, L., Niland, J., Hiti, A. L., Opas, L. M., & Johnson, C. (1991). Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. *Ann Intern Med*, *115*(8), 614-620. https://doi.org/10.7326/0003-4819-115-8-614

- Remuzzi, G., & Bertani, T. (1998). Pathophysiology of progressive nephropathies. *N Engl J Med*, *339*(20), 1448-1456. https://doi.org/10.1056/nejm199811123392007
- Sethi, S., & Fervenza, F. C. (2012). Membranoproliferative glomerulonephritis--a new look at an old entity. *N Engl J Med*, *366*(12), 1119-1131. https://doi.org/10.1056/NEJMra1108178
- Sharpe, C. C., & Thein, S. L. (2014). How I treat renal complications in sickle cell disease. *Blood*, *123*(24), 3720-3726. https://doi.org/10.1182/blood-2014-02-557439
- Silva, F. (2017). *Silva's Diagnostic Renal Pathology* (Second Edition ed.). Cambridge.
- Yeruva, S. L., Paul, Y., Oneal, P., & Nouraie, M. (2016). Renal Failure in Sickle Cell Disease: Prevalence, Predictors of Disease, Mortality and Effect on Length of Hospital Stay. *Hemoglobin*, *40*(5), 295-299. https://doi.org/10.1080/03630269.2016.1224766
- Youssry, I., Makar, S., Fawzy, R., Wilson, M., AbdAllah, G., Fathy, E., & Sawires, H. (2015). Novel marker for the detection of sickle cell nephropathy: soluble FMS-like tyrosine kinase-1 (sFLT-1). *Pediatr Nephrol*, *30*(12), 2163-2168. https://doi.org/10.1007/s00467-015-3172-9
- Zahr, R. S., Yee, M. E., Weaver, J., Twombley, K., Matar, R. B., Aviles, D.,…Greenbaum, L. A. (2019). Kidney biopsy findings in children with sickle cell disease: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol*, *34*(8), 1435-1445. https://doi.org/10.1007/s00467-019-04237-3