REVIEW ARTICLE

Challenges and Solutions for Dialysis in Sickle Cell Nephropathy

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ABSTRACT

Sickle cell disease (SCD) is a hereditary condition characterized by abnormal hemoglobin S (HbS) and intermittent vaso-occlusive crises. Patients with SCD often develop sickle cell nephropathy (SCN), a significant cause of end-stage kidney disease (ESKD) that requires dialysis as a preferred mode of renal replacement therapy. These patients experience higher mortality rates than those with ESKD from other causes due to the unique challenges dialysis physicians face in managing SCN cases. This review discusses these challenges and proposes potential solutions.

Keywords: Sickle cell disease, sickle cell nephropathy, sickle cell crisis, end-stage kidney disease, dialysis, hemodialysis, peritoneal dialysis

Sickle cell nephropathy (SCN) is a crucial contributor to chronic kidney disease (CKD), which, despite its silent progression, significantly impacts survival. Toward the later stages of life, most individuals with sickle cell disease (SCD) require kidney replacement therapy. Although native kidney function is often preserved, kidney disease may go unrecognized, or the need for replacement therapy might be delayed.

SCD is a genetic disorder characterized by the presence of abnormal hemoglobin S (HbS) and recurrent vaso-occlusive crises (VOC). In SCD, the renal medulla is particularly vulnerable to damage when renal blood flow decreases, especially during dehydration, hypovolemia, and chronic anemia. Such events result in specific renal structural changes associated with SCD. CKD occurs in 5% to 18% of the general SCD population, increasing to nearly 30% in patients over 40 years of age[1]. SCN contributes substantially to premature mortality, accounting for 16% to 18% of deaths[2,3].

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Studies indicate a higher 1-year mortality rate following dialysis initiation in SCD patients, though early nephrology care can help reduce this mortality[2]. Rates of CKD and progression to end-stage kidney disease (ESKD) have risen significantly over the past decade, particularly among African American patients. Although CKD is prevalent in SCD and associated with high mortality[3], dialysis treatment for CKD in these patients remains under-examined. Here, we present the dialysis management challenges specific to this patient population.

CHALLENGES IN DIALYSIS FOR SICKLE CELL NEPHROPATHY

The authors, with experience in managing SCN, face various dialysis-related challenges in ESKD cases. These challenges are outlined in Table 1, emphasizing the need to raise awareness among nephrologists and dialysis physicians regarding the elevated mortality risk in SCN-ESKD patients compared to non-SCD patients on dialysis[4].

- **Hemodynamic instability:** Individuals with SCN-ESKD on dialysis have a heightened risk of hypotension due to relatively low blood pressure and anemia, possibly linked to salt-losing tubulopathy[5]. This condition limits blood flow during dialysis, often resulting in inadequate treatment. Extending dialysis duration can improve adequacy[6,7]. Hemoglobin levels must be optimized but should not exceed 10 g/dL to minimize the risk of sickle cell

crises[8]. Conditions like sickle cell cardiomyopathy and anemia-related heart failure also contribute to hemodynamic instability[9]. Sustained low efficiency dialysis (SLED) and peritoneal dialysis may serve as an optimal alternative for such cases[8].

- **Vascular access:** SCN-ESKD patients often exhibit poor compliance with arteriovenous fistula (AVF) creation and have high rates of primary AVF failure. Studies show better survival outcomes in patients using AVF or grafts for dialysis[10]. However, AVF can exacerbate hemodynamic instability, particularly in patients with pulmonary hypertension[11]. AVF use also increases the risks of stenosis, thrombosis, and infection[11]. In cases of access failure, peritoneal dialysis is a viable alternative with less hemodynamic instability[8].
- **Anemia:** Managing anemia in SCN-ESKD presents significant challenges due to resistance to erythropoietin (EPO) therapy, with unachievable targets even at high doses. High EPO doses are linked to elevated mortality and hospitalization risks in SCD[4] and may increase the frequency of VOC[8,12]. Most patients require repeated blood transfusions to reach target hemoglobin levels, posing additional risks of infection and iron overload[13].
- **Sickle cell crisis:** SCN is associated with an elevated risk of VOC[8]. Table 2 outlines the various

Table 1. Challenges of SCN-ESKD on Dialysis and Possible Solutions

Challenges in SCN-ESKD	Underlying mechanism	Possible solutions
Hemodynamic instability	Relative hypotension due to salt-losing tubulopathies, anemia	• Low blood flow rate with longer duration of dialysis to improve dialysis adequacy • Optimize hemoglobin • SLED • Peritoneal dialysis can be adopted for patients with significant residual kidney function
Poor vascular access	Atherosclerosis due to endothelial dysfunction, chronic inflammation, and platelet activation	• Hydroxyurea to increase HbF and nitric oxide • Antiplatelet can be considered if there is significant cardiovascular risk • Consider peritoneal dialysis is vascular access is a challenge
Anemia	• Reduced EPO • Reduce red cell lifespan • Uremic toxins	• High-dose EPO • Exchange blood transfusion
Increase risk of sickle cell crisis	Refer to Table 2	• Refer to Table 2
Poor transplantation outcome	• High sensitization • Comorbidities (e.g., pulmonary hypertension, cardiomyopathy) • Increased thrombotic risk	• Careful patient selection and addressing comorbidities • Transfuse only when necessary, using leukocyte filter

SLED = Sustained low efficiency dialysis; HbF = Fetal hemoglobin; EPO = Erythropoietin.

Table 2. Factors that can Precipitate Sickle Cell Crisis in SCN-ESKD on Dialysis and Possible Solutions[14-21]

Factors precipitating sickle cell crisis	Challenges in sickle cell nephropathy	Possible solutions
Cold weather	Dialysate temperature	• Keep dialysate temperature above 36.5°C • Do not use cool dialysate in intradialytic hypotension
Physical and psychological stress	Exertion, Depression	• Keep stress-free environment • Start antidepressants if needed

Table 2. Factors that can Precipitate Sickle Cell Crisis in SCN-ESKD on Dialysis and Possible Solutions[14-21]

Factors precipitating sickle cell crisis	Challenges in sickle cell nephropathy	Possible solutions
Infections • Atypical bacteria (Chlamydia/ Mycoplasma) • Viruses (RSV/Parvovirus B19) • Encapsulated bacteria	High risk of infections in CKD (dialysis catheters, blood-borne infections, decreased immunity, etc.)	• Strict aseptic precautions • Timely vaccination against Pneumococcus and influenza
Dehydration	Higher risk of dehydration (restricted fluid intake/heat stress/high target ultrafiltration)	• Bioimpedance analysis for dry weight • Avoid heat stress • Weight charting
Low oxygen tension	Respiratory failure (diffusion failure in pulmonary edema and pneumonia or hypoventilation in uremic encephalopathy)	• Strict thrice weekly hemodialysis • Maintain dry weight • Avoid chest infections by applying precautions like face mask, etc.
Acidosis	Metabolic acidosis	• Regular monitoring of bicarbonate levels • Early dialysis initiation • Maintain [HCO_3^-] >23 mEq/L
Pregnancy	Most patients counseled to avoid pregnancy	• Regular counseling • Contraceptive use
Alcohol and Smoking	Most patients counseled to avoid substance abuse	• Regular counseling • Quit smoking and alcohol
Shock	Hypovolemic and cardiogenic shock	• Regular follow-up • Regular cardiology referral • Avoid intradialytic hypotension
Folic acid deficiency	Common in strict vegetarians Dietary restrictions	• Avoid strict dietary restrictions • Regular monitoring of serum folate levels

RSV = Respiratory seasonal virus; CKD = Chronic kidney disease; HCO_3^- = Bicarbonate.

factors contributing to this increased risk, alongside suggested solutions[14-21].

- **Transplantation:** Transplant rates among SCN-ESKD patients are lower, despite the significant survival benefits[4,22]. One-year post-transplant survival is lower in SCN-ESKD compared to non-SCN populations but remains significantly better than in those on dialysis[23]. Increased post-transplant risks, including thrombosis and infection, affect both graft and patient survival[24]. Perioperative blood transfusions to maintain hemoglobin above 10 g/dL and HbS below 30% are recommended to improve post-transplant outcomes[24].

CONCLUSION

In conclusion, dialysis physicians must be aware of the specific challenges in managing SCD-ESKD patients and recognize the factors that can precipitate sickle cell crises in these cases. An in-depth understanding of these conditions and appropriate management strategies are essential for early diagnosis, prompt treatment, and improved mortality and health outcomes in this ESKD population.

REFERENCES

1. Al-Mueilo SH. Renal replacement therapy in end-stage sickle cell nephropathy: presentation of two cases and literature review. Saudi J Kidney Dis Transpl. 2005;16(1):72-7.
2. McClellan AC, Luthi JC, Lynch JR, Soucie JM, Kulkarni R, Guasch A, et al. High one year mortality in adults with sickle cell disease and end-stage renal disease. Br J Haematol. 2012;159(3):360-7.
3. Olaniran KO, Eneanya ND, Zhao SH, Ofsthun NJ, Maddux FW, Thadhani RI, et al. Mortality and

hospitalizations among sickle cell disease patients with end-stage kidney disease initiating dialysis. Am J Nephrol. 2020;51(12):995-1003.

4. Nielsen L, Canoui-Poitrine F, Jais JP, Dahmane D, Bartolucci P, Bentaarit B, et al. Morbidity and mortality of sickle cell disease patients starting intermittent haemodialysis: a comparative cohort study with non-sickle dialysis patients. Br J Haematol. 2016;174(1): 148-52.
5. Brito PL, Dos Santos AF, Chweih H, Favero ME, Gotardo EMF, Silva JAF, et al. Reduced blood pressure in sickle cell disease is associated with decreased angiotensin converting enzyme (ACE) activity and is not modulated by ACE inhibition. PloS One. 2022;17(2):e0263424.
6. Dai WD, Zhang DL, Cui WY, Liu WH. Effect of long intermittent hemodialysis on improving dialysis adequacy of maintenance hemodialysis patients. Chin Med J. 2013;126(24):4655-9.
7. Borzou SR, Gholyaf M, Zandiha M, Amini R, Goodarzi MT, Torkaman B. The effect of increasing blood flow rate on dialysis adequacy in hemodialysis patients. Saudi J Kidney Dis Transpl. 2009;20(4):639-42.
8. Boyle SM, Jacobs B, Sayani FA, Hoffman B. Management of the dialysis patient with sickle cell disease. Semin Dial. 2016;29(1):62-70.
9. Desai AA, Machado RF, Cohen RT. The cardiopulmonary complications of sickle cell disease. Hematol Oncol Clin North Am. 2022;36(6):1217-37.
10. Arhuidese IJ, Wanogho J, Faateh M, Aji EA, Rideout DA, Malas MB. Hemodialysis and peritoneal dialysis access related outcomes in the pediatric and adolescent population. J Pediatr Surg. 2020;55(7):1392-9.
11. Delville M, Manceau S, Ait Abdallah N, Stolba J, Awad S, Damy T, et al. Arterio-venous fistula for automated red blood cells exchange in patients with sickle cell disease: complications and outcomes. Am J Hematol. 2017;92(2):136-40.
12. Obeagu EI. Maximizing longevity: erythropoietin's impact on sickle cell anaemia survival rates. Ann Med Surg (Lond). 2024;86(3):1570-4.
13. Raghupathy R, Manwani D, Little JA. Iron overload in sickle cell disease. Adv Hematol. 2010;2010:272940.
14. Friedman EA, Rao TK, Sprung CL, Smith A, Manis T, Bellevue R, et al. Uremia in sickle-cell anemia treated by maintenance hemodialysis. N Engl J Med. 1974;291(9): 431-5.
15. Khan SA, Damanhouri G, Ali A, Khan SA, Khan A, Bakillah A, et al. Precipitating factors and targeted therapies in combating the perils of sickle cell disease – A special nutritional consideration. Nutr Metab (Lond). 2016;13:50.
16. Serjeant GR. Natural history and determinants of clinical severity of sickle cell disease. Curr Opin Hematol. 1995;2(2):103-8.
17. Kassim AA, Leonard A. Debating the future of sickle cell disease curative therapy: haploidentical hematopoietic stem cell transplantation vs. gene therapy. J Clin Med. 2022;11(16):4775.
18. Borhade MB, Patel P, Kondamudi NP. Sickle Cell Crisis. [Updated 2024 Feb 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526064/
19. Morley SL. Non-invasive ventilation in paediatric critical care. Paediatr Respir Rev. 2016;20:24-31.
20. Baum KF, Dunn DT, Maude GH, Serjeant GR. The painful crisis of homozygous sickle cell disease. A study of the risk factors. Arch Intern Med. 1987;147(7):1231-4.
21. Elendu C, Amaechi DC, Alakwe-Ojimba CE, Elendu TC, Elendu RC, Ayabazu CP, et al. Understanding sickle cell disease: causes, symptoms, and treatment options. Medicine (Baltimore). 2023;102(38):e35237
22. Bae S, Johnson M, Massie AB, Luo X, Haywood C Jr, Lanzkron SM, et al. Mortality and access to kidney transplantation in patients with sickle cell disease-associated kidney failure. Clin J Am Soc Nephrol. 2021;16(3):407-14.
23. Ojo AO, Govaerts TC, Schmouder RL, Leichtman AB, Leavey SF, Wolfe RA, et al. Renal transplantation in end-stage sickle cell nephropathy. Transplantation. 1999;67(2):291-5.
24. Duquesne A, Habibi A, Audard V, Dahan K. Kidney transplantation in patients with sickle cell disease: a French multicenter study. Abstract #C1757. Transplantation. 2014;98:569-70.

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