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THE EVOLUTION OF HYPERKALEMIA MANAGEMENT IN HEMODIALYSIS PATIENTS: A NARRATIVE REVIEW

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ABSTRACT

Background: Hyperkalemia is a frequent and life-threatening complication among patients with chronic kidney disease (CKD) undergoing hemodialysis (HD). **Methodology:** This narrative review synthesizes evidence from epidemiological studies, historical management strategies, advances in dialysis-based approaches, pharmacological innovations, and emerging technological interventions. **Results:** Hyperkalemia affects more than 70% of maintenance HD patients annually, with recurrent episodes in the majority. Traditional management strategies—dietary restriction, potassium-binding resins, and dialysate adjustments—proved effective but limited by safety and tolerability concerns. **Conclusion:** The management of hyperkalemia in HD patients has progressed from empirical, generalized approaches to more patient-centered, evidence-based strategies. Integration of precision dialysis, novel pharmacotherapies, technological monitoring, and multidisciplinary care holds promise for reducing morbidity and mortality. However, accessibility and cost remain challenges, especially in resource-limited settings.

KEYWORDS: Hyperkalemia, Hemodialysis, Chronic Kidney Disease, Potassium Binders, Dialysis Prescription, Personalized Medicine, Patient Outcomes.

1. INTRODUCTION

Hyperkalemia remains a pervasive and clinically significant complication in patients with chronic kidney disease (CKD) undergoing hemodialysis (HD), reflecting complex interactions between pathophysiology, comorbid conditions, and contemporary management strategies.[1] Understanding its epidemiology, underlying mechanisms, clinical risks, and the rationale for continued evolution in its management is critical for optimizing patient outcomes. Hyperkalemia, defined as a serum potassium (K^+) concentration typically above 5.0 mEq/L, is extremely common in the hemodialysis population. Large-scale registry and cohort studies consistently report that the annual prevalence of any predialysis hyperkalemia (K^+ >5.0 mEq/L) exceeds 70–74% in maintenance HD patients, while moderate-to-severe hyperkalemia (K^+ >5.5 mEq/L) occurs in roughly 43%, and severe cases (>6.0 mEq/L) in up to 17% annually. Episodes of hyperkalemia are not only highly prevalent, but also frequently recurrent, with over 60% of patients experiencing two or more episodes within a year. Risk factors for elevated potassium in this cohort include younger age, female sex, Hispanic ethnicity, use of renin-angiotensin-aldosterone system (RAAS) inhibitors, and aspects of dialysis prescription, such as lower dialysate potassium concentrations.[2]

1.1. Pathophysiology of Potassium Imbalance in Chronic Kidney Disease

In healthy individuals, potassium balance is tightly regulated by renal excretion and, to a lesser extent, by the gastrointestinal tract and cellular uptake mechanisms. The kidneys excrete the majority (80–90%) of daily potassium intake, with the remainder lost via feces. maintenance of normal potassium homeostasis involves precise hormonal and tubular control—including aldosterone-mediated potassium secretion in the distal nephron and cellular uptake dependent on insulin and catecholamines.[3] In CKD and particularly end-stage kidney disease (ESKD) requiring hemodialysis, renal potassium elimination drastically diminishes. Additional factors influencing hyperkalemia in HD include: Intermittent potassium removal inherent to the thrice-weekly dialysis schedule, allowing for post-dialysis "rebound" and intradialytic swings in serum levels. Adaptive increases in gastrointestinal potassium excretion, where the colon compensates for reduced urinary clearance.[4] This pathway, however, is highly variable and influenced by gastrointestinal function, constipation, and the integrity of colonic potassium-secreting mechanisms. Altered total body potassium distribution, with research showing that, paradoxically, total body potassium may be normal or even reduced—indicating that hyperkalemia often reflects transcellular shifts and poor extracellular/intracellular distribution, rather than true potassium overload. (Figure 1) High interdialytic and dietary potassium loads, especially during "long" interdialytic intervals, further amplifying risk.

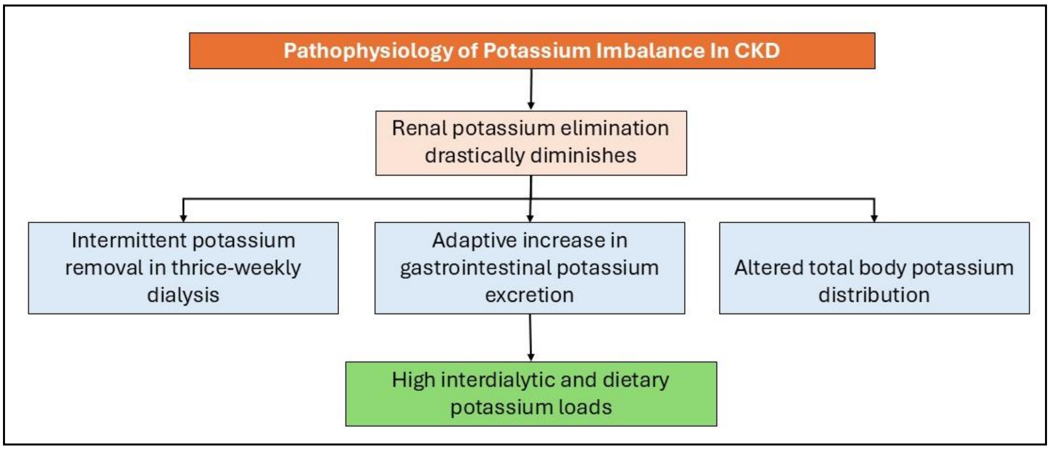

Figure 1: Pathophysiology of Potassium Imbalance in Chronic Kidney Disease.

1.2. Impact of Hyperkalemia on Morbidity, Mortality, and Healthcare Utilization

The clinical impact of hyperkalemia in HD patients is profound. Numerous large observational studies and meta-analyses reveal a robust and independent association between elevated serum potassium and all-cause as well as cardiovascular mortality. Hyperkalemia confers a higher risk of arrhythmias, sudden cardiac death, and major adverse cardiovascular events, making it one of the most modifiable risk factors in this population.[5] There is a "U-shaped" relationship between serum potassium and mortality, with both hyperkalemia (usually above 5.6–6.0 mEq/L) and hypokalemia portending increased risk. Electrolyte shifts connected to HD further compound arrhythmic risk, especially in susceptible patients.[6]

1.3. Rationale for Reviewing the Evolution of Management Strategies

Given the epidemiological burden, pathophysiological complexity, and high clinical stakes of hyperkalemia in hemodialysis patients, the imperative for effective and evolving management is clear. Traditional approaches, centered on dietary restriction, dialysate potassium concentration adjustment, and use of older potassium binding resins, have been challenged by recent insights into potassium physiology, new diagnostic and monitoring tools, and the advent of novel pharmacotherapies.[7] These medications not only enable better potassium control but may permit broader use of life-saving but potassium-raising drugs such as RAAS inhibitors. Dietary recommendations are also evolving, with contemporary data questioning the necessity and safety of severe potassium restriction in all patients, especially given the adverse effects on nutrition and quality of life.[8]

2. Historical Perspectives and Early Management Approaches

Patients is characterized by progressive advances that reflect both clinical necessity and expanding therapeutic options. The initial recognition of hyperkalemia in these patients relied on the observation of nonspecific clinical features—such as muscle weakness, cardiac conduction abnormalities, and electrocardiogram (ECG) changes coupled with the development of laboratory assays for serum potassium.[9]

2.1.Dialysis as the first effective therapeutic option

Dialysis revolutionized the management of hyperkalemia by offering the first truly effective therapeutic option for potassium removal. Prior to widespread use of dialysis, treatment strategies were largely limited to dietary restriction and pharmacologic measures, often with limited efficacy. While rapid redistribution of potassium from the extracellular to intracellular space using insulin or beta-2 agonists was occasionally employed for acute stabilization, definitive management required the physical clearance provided by dialysis.[10]

Alongside dialysis, historical dietary recommendations emphasized stringent restriction of potassium-rich foods and fluids. Patients were counseled to avoid common sources of potassium, including certain fruits, vegetables, and dairy products. Despite this, maintaining potassium balance through dietary modification alone proved challenging, with frequent non-adherence and persistent risk due to the ubiquity of potassium in the Western diet. As a result, potassium-binding resins, most notably sodium polystyrene sulfonate (SPS), were developed and introduced as adjunctive therapy. However, efficacy data for SPS were historically limited, and later research revealed several limitations and adverse effects.[11] More alarmingly, use of SPS has been associated with serious gastrointestinal adverse events, including intestinal necrosis and colonic perforation, particularly in patients with advanced renal failure.

2.2.Limitations and adverse effects of early methods

The limitations and adverse effects of these early management approaches spurred continued innovation. Dietary restriction often compromised nutritional status, leading to protein-energy malnutrition and poorer outcomes. SPS, while still in use, is now recognized for its variable efficacy and significant safety concerns. Dialysis, although highly effective, imposes substantial logistical and economic burdens and does not prevent "rebound" hyperkalemia in the interdialytic interval. The historical context of hyperkalemia management, marked by the foundational roles of dialysis, diet, and potassium binders, continues to inform both contemporary practice and the search for safer, more effective therapeutic options.[12]

3. Advances in Dialysis-Based Management

The optimization of potassium management in hemodialysis (HD) patients has undergone a profound evolution influenced by changing clinical paradigms, advances in dialysis technologies, a deeper understanding of potassium kinetics, and increased emphasis on individualized prescriptions. Historically, approaches to potassium control reflected limited technological options and an incomplete grasp of potassium redistribution physiology, resulting in protocols that often prioritized safety at the expense of patient comfort or long-term outcomes.[13]

3.1. Dialysate Potassium Concentration Optimization: Historical Perspective to Current Practice

One of the foundational decisions in HD practice is the selection of dialysate potassium concentration (dK). Historically, nephrologists favored lower dK, often 1.0–2.0 mmol/L, to maximize the potassium concentration gradient from plasma to dialysate, thereby ensuring a rapid drop in serum potassium during the session. This strategy derived from early fears regarding hyperkalemia-induced arrhythmias and sudden cardiac death, which were prevalent before the widespread use of regular dialysis. As knowledge advanced, it became clear that a swift plasma-to-dialysate gradient could precipitate dangerous arrhythmogenic shifts and sudden cardiac events due to rapid extracellular potassium reduction, particularly during the early phases of HD.[14] A key turning point arrived with the recognition that the “one-size-fits-all” approach was inadequate; optimal pre-dialysis potassium concentrations in HD are generally higher than in patients with preserved renal function, and interindividual variability in “safe” potassium gradients is substantial.[15] Further, studies demonstrated a U-shaped relationship between both predialysis potassium and dK with mortality: too little or too much potassium removal increases risk, suggesting the need for “physiological” dK concentrations centered around 2.0–3.0 mmol/L for most patients. The advent of potassium profiling—gradual reduction of dK during a session to follow anticipated intradialytic serum potassium decline—represents a further step towards physiologic dialysis. While current machines often require manual dialysate changes for profiling, new dialysis consoles are being developed with automated real-time potassium adjustment, which will allow for even tighter potassium control.

3.2.Advances in Dialysis Technologies and Potassium Clearance

Technological progress has been pivotal in enhancing potassium removal and tailoring therapy to individual risk profiles. Modern advances include refined dialyzer membranes with increased permeability, which allow for more effective diffusion and convective clearance of potassium, as well as improved monitoring of serum potassium in real time. Innovations such as online hemodiafiltration (HDF) combine diffusive and convective transport to increase small and middle-molecule clearance—including potassium—beyond the capabilities of conventional HD alone.[16]

The deployment of HDF and high-efficiency HD has demonstrated superior potassium mass removal, achieved through higher ultrafiltration rates and greater solute clearance. Moreover, technologies like short daily or nocturnal dialysis, extended treatment times, and machine-linked potassium sensing facilitate safer, more consistent, and more gradual potassium management, thereby reducing the risk of dangerous post-dialysis rebound and interdialytic fluctuations.

3.3.Individualized Dialysis Prescriptions and Potassium Kinetics

Appreciation of the inter- and intra-individual variability in potassium homeostasis has expanded the paradigm of dialysis prescription from protocol-driven to individualized care. Potassium fluxes during and after HD reflect a non-linear process: rapid removal from the extracellular compartment produces steep early declines in serum potassium during the session, while redistribution from intracellular stores and subsequently from hepatic and skeletal muscle compartments leads to a “rebound” phenomenon in the hours following dialysis completion. This effect is further amplified after the long interdialytic interval and in patients with greater muscle mass or increased dietary potassium load. Consequently, individualized regimens now incorporate not just average serum potassium, but day-of-week timing, recent dietary intake, comorbidities affecting shifting and risk of arrhythmia.[17]

Approaches such as incrementally increasing dialysis session frequency (from thrice-weekly to four or more), extending session length, or employing frequent short daily dialysis, have been shown through modeling and clinical study to enable use of higher, safer dK (e.g., 2.5–3.0 mmol/L) while maintaining normokalemia, thus mitigating rapid changes and reducing the risk of sudden cardiac events.

3.4.Comparative Discussions: Conventional HD vs. Hemodiafiltration vs. New Modalities

Conventional HD, using low- or moderate-dK, remains the mainstay of potassium management, yet limitations exist in terms of rapid potassium shifts, post-dialysis rebound, and insufficient adaptability to variable potassium burdens between patients. In contrast, HDF—

particularly high-volume post-dilution online HDF—offers substantial advantages, combining diffusion and convection to increase total potassium removal and decrease serum potassium fluctuation across sessions, without increasing treatment-related hypotension or adverse events. Studies demonstrate that HDF and other newer platforms (e.g., expanded HD, wearable and portable dialysis devices) broaden the options for personalized potassium management, and ongoing trials support their integration for higher-risk strata.[18] Nocturnal HD, whether in-center or at home, and extended/frequent regimens have also gained favor for select patients, as these modalities provide near-continuous potassium clearance, thereby avoiding the long intervals and abrupt gradient shifts inherent to conventional protocols. Such practices have been associated with better potassium homeostasis, reduced cardiovascular events, and potentially improved survival, although they often require patient motivation and greater health system resources.[19] Lastly, emerging automatic (real-time) potassium sensing and dialysate adjustment, including closed-loop feedback systems, are poised to further individualize and optimize potassium kinetics during HD, although their routine use remains under investigation. As machine learning and digital health become further embedded in HD practice, future approaches will likely integrate detailed patient risk profiling, continuous potassium monitoring, diet and medication data, and algorithmic dialysis prescription adjustment to minimize arrhythmogenic risk and maximize patient safety.

4. Pharmacological Management: From Old to New

The pharmacological management of hyperkalemia in hemodialysis (HD) patients bridges long-standing approaches using traditional potassium-binding resins and modern innovations with newer agents like patiromer and sodium zirconium cyclosilicate (SZC). Over recent decades, comparative effectiveness, safety profiles, and tolerability data for these agents have significantly influenced their role as adjuncts to dialysis for optimizing potassium balance.

4.1. Traditional Potassium-Binding Resins: Scope and Limitations

Sodium polystyrene sulfonate (SPS) has long been the mainstay pharmacologic agent for chronic hyperkalemia, including in HD settings. SPS is a non-absorbed cation-exchange resin that acts in the gut by exchanging sodium for potassium, facilitating fecal potassium elimination. Used widely since the 1960s, SPS is inexpensive and can be administered either orally or rectally. However, efficacy data for SPS are limited and mixed. Randomized trial evidence shows serum potassium reductions after short-term SPS therapy tend to be modest—typically in the range of 0.7–0.8 mEq/L after a week. The safety and tolerability profile of SPS is less favorable.[20] Gastrointestinal adverse events, particularly constipation and diarrhea, are frequent, and rare but severe complications such as colonic necrosis and intestinal perforation have been documented, especially when combined with sorbitol or in patients with advanced CKD. Observational studies confirm increased risk of GI complications (adjusted hazard ratio for severe GI events with SPS use: 1.25; more pronounced with higher doses), with ulcers and perforations being most common. Chronic use also exposes patients to sodium overload (risk of hypertension, fluid retention, and exacerbation of heart failure) and, less often, to electrolyte derangements such as hypocalcemia and hypomagnesemia. Poor palatability and GI intolerance contribute to frequent discontinuation and poor adherence.[21]

4.2.Newer Potassium Binders: Patiromer and Sodium Zirconium Cyclosilicate

Recognizing the limitations of SPS, two novel non-absorbed potassium binders—patiromer and SZC—were approved for chronic hyperkalemia management over the last decade. Both feature improved tolerability, greater pharmacodynamic predictability, and fewer systemic adverse effects. Patiromer is an orally administered polymer that exchanges calcium for potassium in the colon, leading to dose-dependent fecal potassium loss. It is approved for the management of chronic hyperkalemia, including in patients with advanced CKD and those on renin-angiotensin-aldosterone system inhibitors (RAASi). Sodium zirconium cyclosilicate (SZC) is a selective inorganic cation exchanger that traps potassium in exchange for sodium and hydrogen throughout the gut. Both agents are effective for persistent hyperkalemia in HD patients and can be titrated for long-term maintenance.

4.3.Comparative Effectiveness, Onset, Tolerability, and Safety

For acute hyperkalemia, a recent study found no significant difference between patiromer and SZC in magnitude of potassium reduction at 6 to 24 hours, suggesting both are viable options for relatively rapid correction in stable, non-emergent cases. SZC may exhibit a slightly faster onset, beginning to reduce potassium within one hour and reaching peak effect within 24–48 hours. Patiromer generally achieves maximal serum potassium reduction over two to seven days, with dosing flexibility for acute and maintenance therapy. Both agents are designed for outpatient and chronic use; neither is appropriate as monotherapy for life-threatening, rapidly evolving hyperkalemia, when urgent dialysis or temporizing stabilization is needed.[22] In terms of safety and tolerability, both agents are generally well tolerated. Patiromer is associated principally with mild gastrointestinal disturbances—constipation (7.6%), diarrhea (4.5%), and hypomagnesemia (7.1%), given its non-selective binding of other cations as a class effect. Hypomagnesemia may necessitate monitoring and supplementation in some patients. SZC's principal adverse events are related to mild edema (0.9%) and, less frequently, urinary tract infections (1.1%), attributed to sodium load; this requires cautious use in heart failure or salt-sensitive populations.[23]

4.4.Adjunct Role and Clinical Integration with Dialysis

Far from supplanting dialysis, pharmacologic binders serve as essential adjuncts to enhance potassium stability between sessions and enable continued use of life-prolonging RAASi in appropriate candidates. Multiple large randomized trials support this paradigm; in these, patiromer facilitated ongoing or re-initiated RAASi without hyperkalemia recurrence in CKD and ESKD populations, including those on maintenance dialysis.[24] Both patiromer and SZC support potassium stabilization during the long interdialytic interval and help limit dangerous “rebound hyperkalemia” post-dialysis, especially in patients with substantial risk factors for arrhythmia.[25]

5.Technological Innovations and Monitoring Approaches

Technological innovations and monitoring approaches for potassium management in hemodialysis patients are rapidly advancing, enabling more precise, real-time, and remote surveillance of potassium levels. These developments hold promise for early detection of dangerous hyperkalemia, enhanced risk stratification, and improved patient outcomes through personalized interventions and timely therapeutic adjustments.[26]

5.1.Role of Point-of-Care Testing and Continuous Monitoring

Point-of-care (POC) testing for potassium has emerged as a pivotal tool in dialysis units, enabling near-instantaneous measurement of serum potassium from small blood samples during or immediately before hemodialysis sessions. This capability is especially important considering the rapid potassium shifts during dialysis and the narrow therapeutic window for potassium concentrations.[27]

More recently, research and commercial development have focused on portable and minimally invasive POC devices requiring only a finger-prick or single drop of blood, thereby expanding accessibility to potassium monitoring beyond the dialysis center. Some devices integrate microfluidic and electrochemical technologies to balance accuracy, cost-effectiveness, and ease of use, fostering patient-centered models of care.[28] Continuous potassium monitoring, though technically challenging given potassium’s serum-bound nature, is under investigation with promising preliminary approaches. These employ continuous blood sensors or surrogate markers aiming to capture dynamic potassium fluctuations during interdialytic intervals before symptoms or acute events occur.

5.2. Remote Monitoring and Digital Health Applications

Remote potassium monitoring, integrated with telemedicine and digital health platforms, is gaining traction as a vital component for managing chronic dialysis patients outside clinical settings. This facilitates real-time surveillance, trend visualization, and early warnings for dangerous potassium excursions, potentially reducing emergency hospitalizations.[29] Digital health platforms increasingly use machine learning-driven analytics to interpret potassium data within the broader clinical context, accounting for medications, diet, comorbidities, and dialysis prescriptions.

5.3. Advances in Predictive Models and AI-Based Risk Stratification

Artificial intelligence (AI), particularly in combination with electrocardiogram (ECG) data, is transforming potassium risk stratification and prognostication. AI-enhanced ECG algorithms analyze subtle changes in cardiac electrical activity that correlate with potassium levels, going beyond static serum values to capture functional myocardial effects. These sophisticated AI models continuously learn from large clinical datasets that encompass ECG waveforms, laboratory values, and patient demographics, thereby improving predictive accuracy and safety alerts.[30]

5.4.Potential of Wearable Sensors for Real-Time Potassium Monitoring

The development of wearable sensor technology for continuous, non-invasive potassium monitoring represents an exciting frontier in dialysis care. Real-time alerts can notify patients and providers of impending dangerous hyperkalemia, facilitating prompt intervention before biochemical confirmation or symptomatic manifestations.[31] Although sweat potassium monitoring is indirect and has yet to replace blood measurements, correlational studies and clinical trials are ongoing to validate practicality and accuracy.

6. Emerging Horizons and Future Perspectives

The management of hyperkalemia in hemodialysis patients is on the cusp of transformation through emerging horizons in personalized medicine, clinical innovation, and integrative therapeutic strategies. Personalized medicine in CKD and dialysis is evolving to integrate genetic, epigenetic, and microbiome data to optimize potassium management and associated therapies. Polymorphisms affecting the WNK1 kinase influence potassium excretion and may modulate hyperkalemia risk with diuretic use or dialysis regimens.[32]

6.1. Ongoing Clinical Trials for Newer Binders and Adjunct Therapies

Multiple ongoing randomized controlled trials are evaluating the efficacy, safety, and comparative effectiveness of novel potassium binders often as adjuncts to dialysis and pharmacotherapy. Trials such as the KBindER study compare these binders head-to-head for acute hyperkalemia treatment in emergency and inpatient contexts, evaluating potassium reduction kinetics, gastrointestinal tolerability, and hospital length of stay. Others investigate long-term maintenance dosing regimens aiming to sustain normokalemia without compromising cardiovascular stability or nutritional status(Table 1).[33]

Table 1: Ongoing Clinical Trials for Newer Binders and Adjunct Therapies.

Study Design & Population	Intervention(s)	Status/Years	Key Outcome(s)/Focus	Ref
RCT, HFrEF on dual RAASi, K+ > 5.0 mmol/L	Patiromer + RAASi vs Placebo	Ongoing	Maintain RAASi, hyperkalemia recurrence, CV outcomes	[34]
RCT, HFrEF, MRA titration	Patiromer vs Control	Ongoing	MRA tolerability, HF outcomes	[35]
RCT, ER/hospitalized, K+ ≥5.5 mmol/L	Patiromer vs SZC vs SPS vs Laxative	Ongoing	Acute K+ lowering, GI side effects, LOS	[36]
Multicenter RCT, Hyperkalemia, Japanese population	Patiromer vs Placebo	Published 2025	Recurrence, sK reduction, adverse events	[37]
RCT, Dialysis/non-dialysis, Japanese population	Patiromer vs Placebo	Published 2024	Dose efficacy, long-term safety, normokalemia	[38]
RCT, ESKD, thrice-weekly HD patients	Patiromer	Published 2024	Frequency of hyperkalemia reduction	[39]
Multicenter RCT, Japanese, non-dialysis and dialysis	Patiromer vs Placebo	Published 2025	K+ maintenance, adverse events	[40]
Meta-analysis, CKD/Heart Failure	Patiromer	Meta-analysis	All-cause mortality, efficacy & adverse events	[41]

Pharmacogenetic data are increasingly integrated into these studies, facilitating identification of subgroups who may benefit most from specific agents or dosing strategies.[42]

6.2.Integration of Precision Dialysis with Pharmacological and Dietary Strategies

Future potassium management frameworks emphasize integrative precision medicine approaches combining customized dialysis prescriptions, pharmacological optimization, and tailored nutritional interventions Emerging digital health tools integrate real-time dietary data with serum potassium monitoring, supporting adaptive dietary adjustments and patient engagement.[43]

6.3.Challenges in Developing Countries and Resource-Limited Settings

Despite technological and pharmacological advances, managing hyperkalemia in developing countries faces substantial obstacles related to healthcare infrastructure, affordability, and patient education. Healthcare workforce shortages and limited laboratory capacity impede routine, timely potassium monitoring and individualized treatment adjustments.[44] These systemic factors contribute to delayed Partnerships between governmental, non-governmental, and academic institutions are pivotal to scale innovations sustainably. Additionally, tailoring dietary recommendations to locally available foods and incorporating traditional practices enhances adherence and nutritional status.[45]

7. CONCLUSION

The survival and quality of life of haemodialysis patients are still seriously threatened by hyperkalaemia. A paradigm shift in nephrology practice is seen in the move from traditional management, which focused on dietary restrictions and outdated resins, to a more holistic model that integrates dialysis optimisation, contemporary pharmaceutical agents, and cutting-edge monitoring technologies. For safe and efficient therapy, individualised approaches that take into consideration patient variations in potassium kinetics, comorbidities, and therapeutic objectives are essential.

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