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EDITORIAL

Approach to Integrative Management of Chronic Kidney Disease: Whose Time has Come

Narinder Pal Singh[1], Anish Kumar Gupta[2], Dinesh Khullar[3], Sonu Gupta[4]

[1,2]Faculty of Medicine and Health Sciences, Shree Guru Gobind Singh Tricentenary University, Gurugram, Haryana, India
[1,3] Department of Nephrology & Renal Transplant Medicine, Max Super Speciality Hospital, Saket, Delhi
[4] Department of Medicine, University of Augusta GA & Core faculty, North East Georgia Medical Center, Gainesville, GA
Corresponding Author: Prof. Narinder Pal Singh, Advisor Research (Medical Sciences), FMHS, Shree Guru Gobind Singh Tricentenary University, Gurugram, Haryana, India. Dean Research, Eternal University, Baru Sahib, Himachal Pradesh, India Consultant, Academic Program in Nephrology, Max Super Speciality Hospital, Saket, New Delhi, India E-Mail: Nanu_singh@yahoo.com

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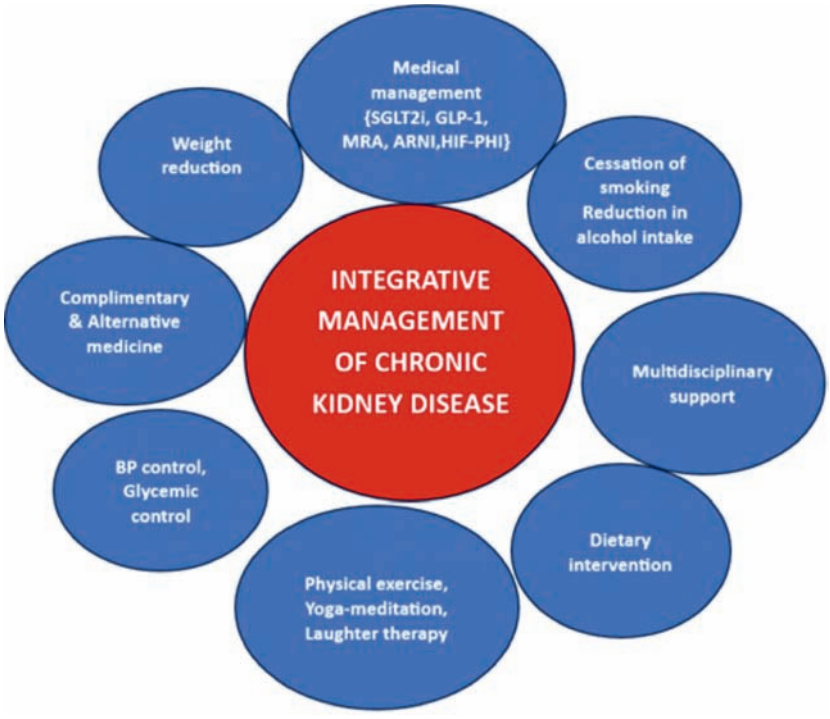
Chronic kidney disease (CKD) is a complex condition affecting millions globally [1]. CKD impacts multiple organ systems and various aspects of patients' lives, requiring an integrated multidisciplinary approach for comprehensive care. Human resources required to manage CKD involves the collaboration of various healthcare professionals such as primary care physicians, nephrologists, nursing officers, dieticians, pharmacists, clinical psychologists, social workers, and physiotherapists. This collaborative approach aims to optimize patient outcomes, enhance their quality of life, and slow disease progression by addressing the diverse needs of CKD patients holistically. Here, we discuss the integrative role of lifestyle modifications such as dietary intervention, weight management, physical activity, and exercise, complementary and alternative medicine, the role of mind-body intervention, blood pressure control, glycaemic control, and advances in the medical management of chronic kidney disease. It also explores the utilization of technology in CKD care.



Dietary Intervention

The Kidney Disease Outcomes Quality Initiative (KDOQI) 2020 recommends routine nutrition screening every six months for adults with CKD stages 1-5D or post-transplantation to identify those at risk of protein-energy wasting [2]. A comprehensive nutrition assessment, including factors such as appetite, dietary history, weight, biochemical markers, and physical indicators, should be conducted within the first 90 days of initiating dialysis and annually thereafter or as prompted by screening or provider referral. For patients on maintenance hemodialysis (MHD), bioimpedance, particularly multi-frequency bioelectrical impedance (MF-BIA), is suggested for body composition assessment, ideally post-dialysis. Dual-energy X-ray absorptiometry (DXA) is recommended when feasible as the gold standard for measuring body composition. Regular monitoring of body weight/BMI and composition is advised, varying by clinical stability and CKD stage. Biomarkers such as normalized protein catabolic rate (nPCR), serum albumin, and serum prealbumin complement nutritional assessment but should not be interpreted in isolation. Handgrip strength and composite nutritional indices like the 7-point Subjective Global Assessment and Malnutrition Inflammation Score (MIS) are useful in assessing nutritional status in CKD 5D patients. To evaluate the effectiveness of Medical Nutrition Therapy (MNT), monitoring involves observing changes in appetite, dietary intake, body weight, biochemical data, anthropometric measurements, and nutrition-focused physical findings [2].

Protein restriction, Mediterranean Diet adoption, and increased fruit and vegetable intake are recommended dietary approaches. For adults with CKD, protein restriction under close supervision, aiming for 0.55-0.60 g/kg/day or 0.28-0.43 g/kg/day with supplements, is recommended to reduce the risk of end-stage kidney disease and improve quality of life, while those with diabetes may follow a protein intake of 0.6-0.8 g/kg/day to maintain nutritional stability and optimize glycemic control, and CKD patients on maintenance dialysis are advised to consume 1.0-1.2 g/kg/day to sustain nutritional status, with considerations for higher intake levels for diabetic patients at risk of glucose fluctuations.

Before suggesting a low-protein diet for Indian adults with CKD, particularly those on maintenance HD, it's essential to note that the average protein intake among Indians is lower than recommended. Therefore, assessing the nutritional status of CKD patients is crucial before recommending guideline-directed protein restriction. The prescribed diet should be personalized to individuals' preferences, habits, and nutritional needs [3].

For CKD stage 5D patients with persistent inadequate dietary intake, supplementation with multivitamins containing water-soluble vitamins and essential trace elements is reasonable. Including fiber-rich foods like vegetables and fruits and incorporating millets in the diet for essential micronutrients is advisable. Opting for healthy fats from sources like avocados, nuts, seeds, and olive oil balances nutrient intake and cardiovascular health.

Weight Management

Regular anthropometric measurements are advised to monitor body composition changes, and hemodialysis patients should maintain a BMI between 20 and 30 kg/m2. Weight management should involve a multidisciplinary approach, considering nutritional needs, comorbidities, and promoting physical activity with behavior change techniques. After transplantation, a BMI target of d"25 kg/m2 is recommended, and bariatric surgery can be considered for those with morbid obesity (BMI > 40 kg/m2) to reduce weight [4].

Smoking and Alcohol intake

While establishing a clear cause-and-effect relationship is challenging, smoking is linked to worsened progression in individuals with existing CKD. Current smokers face a greater risk of CKD progression compared to former or non-smokers. Conversely, studies suggest that quitting smoking can delay CKD progression compared to continuous smoking [5,6]. It is suggested that CKD patients avoid all recreational drug use and quit smoking.

Moderate alcohol **(2 drinks or less in a day for men or 1 drink or less in a day for women)** consumption appears unrelated to CKD progression but binge drinking heightens the risk. There are many inconsistencies between experimental and clinical studies on alcohol consumption and kidney damage. Alcohol consumption can lead to adverse events, we do not advise non-drinkers to start to drink [5,7].

Physical Activity and Exercise

Encouraging physical activity and exercise in the CKD population is recommended, provided there are no contraindications. Patients should aim for 150 minutes of moderate intensity activity per week or 75 minutes of vigorous activity, which may include interdialytic or intradialytic exercise for patients on hemodialysis. However, exercise should be avoided within three months of initiating hemodialysis or in the presence of certain medical conditions, such as uncontrolled infections, recent myocardial infarction, or symptomatic hyper- or hypotension. Monitoring safety is suggested, including assessing patients' feelings and vital signs before and during exercise, and monitoring for symptoms such as pain, fatigue, altered consciousness, and chest discomfort [4].

Complementary and Alternative Medicines

The popularity of complementary and alternative medicines, particularly from indigenous systems like Unani/Siddha, homeopathy, or Ayurveda, is increasing both in India and globally. Recent studies by various researchers have highlighted the effectiveness of Chinese herbal medicine in treating chronic kidney disease (CKD) and its complications [8-10]. These studies demonstrate its ability to address inflammation, oxidative stress, apoptosis, autophagy, and fibrosis, all of which are key factors in CKD progression. Herbal formulas have shown promise in mitigating mitochondrial dysfunction, treating anemia associated with CKD, and managing specific types of CKD such as idiopathic membranous nephropathy and autosomal dominant polycystic kidney disease. Overall, these findings support the clinical use of herbal medicine in CKD treatment and provide valuable insights for future drug development.

Several studies explore the renal protective effects of herbal medicine in diabetic animal models, suggesting potential therapeutic strategies for diabetic kidney disease [9,11-13]. These include interventions like Bu-Shen-Huo-Xue, Tang Shen, and Yiqi Jiedu Huayu herbal decoctions, as well as Huidouba, Zhen-Wu-Tang, Orthosiphon stamineus extract, and I-BET151, each showing promise in addressing various kidney ailments through different mechanisms.

Many researches have explored the active ingredients in herbal medicine for treating CKD [14-16]. Fucoidan from Laminaria japonica targets the FGF23-Klotho axis, alleviating mineral and bone disorder. Genistein restores renal fibrosis by regulating m6A modification. Emodin nanoparticles enhance stability and colon adhesion for CKD therapy. Rhein and curcumin synergize in CKD treatment. Total flavones from A. manihot inhibit

microinflammation via gut microbiota modulation. Saikosaponin D from Bupleurum falcatum attenuates peritoneal fibrosis. Astragaloside II protects podocytes in diabetic rats. Oleuropein from Ilex pubescens mitigates AKI via toll-like receptor suppression. Glycyrrhetinic acid from Glycyrrhiza uralensis defends renal tubular cells against oxidative damage.

However, concerns regarding renal safety are significant due to limited regulatory control. Often herbal products can lead to toxicity due to undocumented adverse effects, misidentification of herbs, contamination with heavy metals from faulty manufacturing processes, or concomitant nephrotoxins with conventional drugs known for renal adverse effects. Aristolochic acid nephropathy, for instance, found in Chinese medicinal herbs like Guang Fang Ji or wild ginger (Xi Xin), illustrates this, causing chronic interstitial nephritis and urothelial malignancies due to the formation of toxic DNA adducts in renal tissues [9,17].

Mind-body Interventions

Relaxation techniques, spiritual healing/prayer, laughter therapy, yoga, and meditation, once classified as Complementary and Alternative Medicines, have now gained mainstream acceptance, along with support groups and cognitive-behavioral therapy [18. In a study conducted by Sharma et al. in South Delhi, significant enhancements in health parameters and overall well-being were observed among CKD patients following three months of laughter treatment and lifestyle adjustments. This underscores the importance of holistic care, highlighting the potential advantages of laughter therapy and exercise in reducing the necessity for dialysis [19]. Exercise training improves vascular function in CKD patients and should be considered in their management, but more research is needed to confirm its impact on cardiovascular diseases [20]. Future initiatives may prioritize preventive education initiatives and the promotion of mind-body intervention as strategies for effective CKD management.

Blood Pressure Control

Blood pressure target recommendations vary among guidelines, with KDIGO [21] suggesting a goal of less than 120 mmHg for CKD patients, ACC/AHA [22] recommending ≤130/80 mmHg, and the European Society of Hypertension-European Society of Cardiology advising less than 140/90 mmHg, emphasizing individualized goals. However, the CKD population has shown a tendency for mask hypertension or nocturnal hypotension. For more accurate BP monitoring, home BP monitoring and 24-hour ambulatory BP monitoring are preferred to in-office measurements.

Glycaemic Control

Current guidelines advise tailoring glycemic control goals to individual patients with diabetic kidney disease by selecting a personalized target HgbA1c level within the range of <6.5% to 8.0%, considering the balance between renal and cardiovascular benefits and the risk of hypoglycemia [23].

Guidelines advise starting with non-pharmacological interventions or used in conjunction with pharmacological therapy to lower blood pressure and in CKD patients. These include a low-salt diet (<2g/day), moderate exercise (150 mins/week), treating sleep apnea, weight loss, and avoiding nonsteroidal anti-inflammatory drugs.

Medical management in chronic kidney disease

The demand for innovative CKD therapies arises from limitations in current treatments, including the progressive nature of the disease and the desire for more effective, targeted drug delivery and patient-centered interventions. While Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are standard care, their efficacy may be limited due to varied responses, adverse effects, and tolerability issues. Innovations in medical science offer promising avenues for developing therapies that minimize side effects, improve cost-effectiveness, and provide tailored solutions to individual patients, reflecting a more holistic and personalized approach to CKD management.

SGLT-2 inhibitors have emerged as a significant breakthrough in CKD management, demonstrating robust protective effects on both the heart and kidneys regardless of diabetes status. Trials such as CREDENCE, DAPA-CKD, and EMPA-KIDNEY revealed approximately 30% reduction in kidney-related risks, even in patients with low baseline kidney function [24-26]. These benefits were observed alongside ACE inhibitors or ARBs, suggesting additive effects. The DAPA-CKD trial extended these findings to patients with IgA nephropathy, though evidence for focal segmental glomerulosclerosis was limited. Ongoing investigations explore SGLT-2 inhibitors' use in other CKD populations.

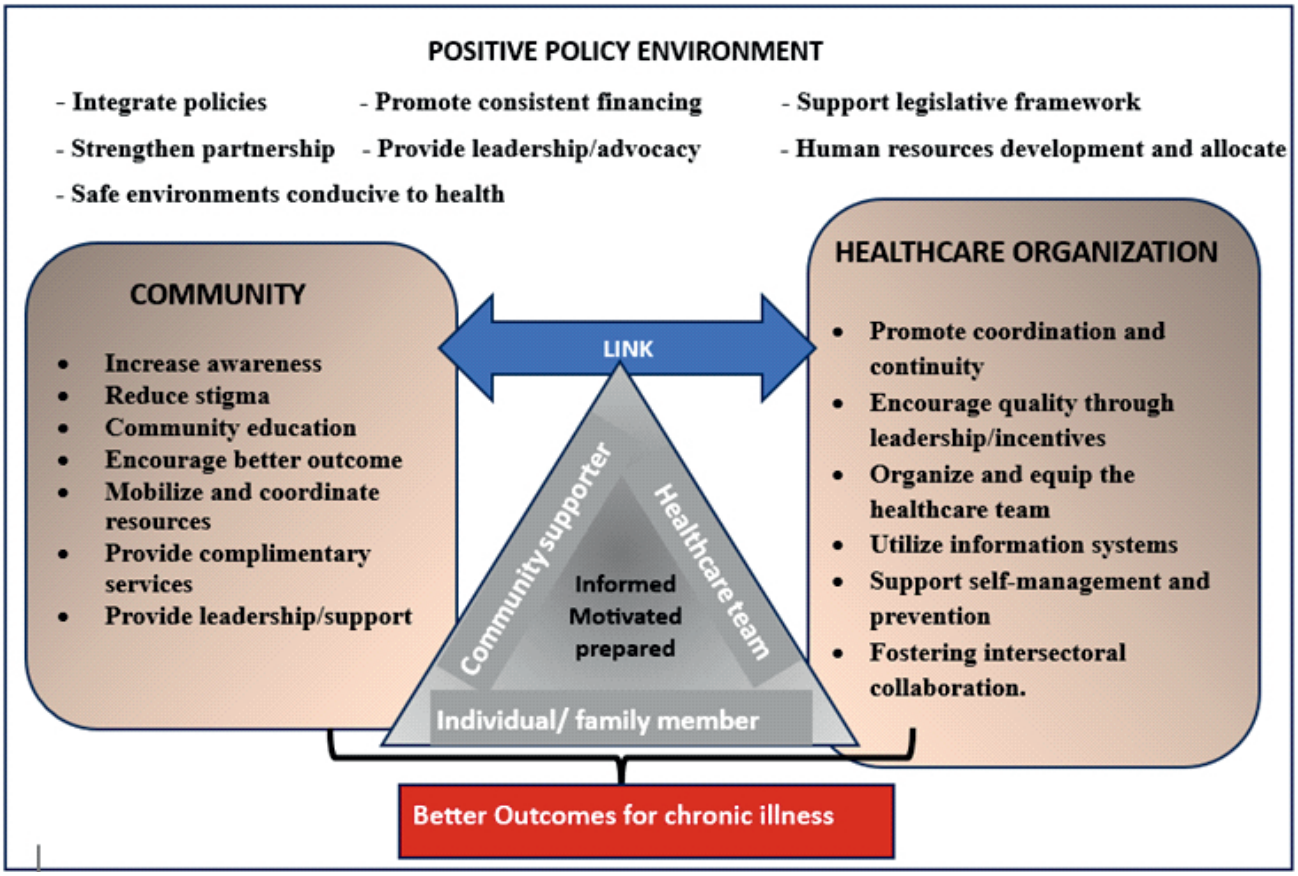
GLP-1 receptor agonists have shown effectiveness in improving kidney outcomes, though their precise mechanisms remain unclear. The FLOW trial aims to evaluate semaglutide's impact on CKD progression, addressing a critical research gap [27].

Mineralocorticoid receptor antagonists, particularly finerenone, offer promising alternatives, with trials demonstrating significant reductions in kidney-related risks. Ongoing studies like FIND-CKD (ClinicalTrials.gov: NCT05047263) and CONFIDENCE further explore finerenone's efficacy [28].

Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) represent a novel class of medications showing promise in managing anemia in CKD, though concerns regarding cardiovascular safety prompt further investigation.

Chronic kidney disease and heart failure (HF) often share common risk factors and frequently coexist [29]. The management of CKD patients with HF concentrates on addressing both symptoms and enhancing overall survival. For patients with eGFR 30–60 mL/min/1.73 m2, triple therapy with a low-dose beta-blocker, RAAS inhibitors or **ARNI (angiotensin receptor neprilysin inhibitors),** and a full dosage of SGLT-2 inhibitors is suggested. Low-dose MRAs may be added during follow-up if creatinine levels remain stable or increase by less than 30%, and potassium levels are below 5 meq/L. In those with eGFR 15–30 mL/min/1.73 m2, initiating low-dose beta-blockers and SGLT-2 inhibitors first, followed by RAAS inhibitors, is recommended after uptitration of the initial two agents. In cases of severe renal dysfunction, a cautious multi-drug approach may be considered, starting with lower doses of beta-blockers and subsequently adding ACE-I without uptitration. Treatment discontinuation is warranted if serum creatinine increases by more than 50% or exceeds 3.5 mg/dL [30, 31].

Hyperkalemia is the most common cause for drug discontinuation, and adjustments are advised based on potassium levels. Novel potassium binders such as **patiromer and sodium zirconium cyclosilicate** can be employed in individuals with normal renal function and isolated potassium elevation to facilitate the maintenance of RAAS inhibitors and ARNI therapy. Additionally, before altering the dose of neurohormonal blockers, including MRAs, the possibility of haemolysis with falsely elevated potassium should be excluded.



World Health Organization Innovative Care for Chronic Conditions framework [adopted from WHO ICCC].

Multidisciplinary integrated approach to managing chronic kidney disease:

The WHO's ICCC model [32], initiated in 2002, targets the global surge in chronic diseases. It emphasizes collaboration among patients, healthcare teams, communities, and policymakers at micro, meso, and macro levels. A multidisciplinary approach to managing CKD involves the collaboration of various healthcare professionals specializing in nephrology, primary care, nursing, dietetics, pharmacy, social work, exercise physiology, mental health as well as family/community involvement. Nephrologists lead the diagnostic process, treatment planning, and monitoring of disease progression, while primary care physicians coordinate overall health management and comorbidity care. Nurses provide essential patient education, medication management, and support, while dietitians develop personalized nutrition plans to optimize kidney function and manage related complications. Pharmacists ensure proper medication dosing, monitor for interactions, and educate patients on adherence. Social workers assess psychosocial needs, provide counseling, and coordinate community resources. Exercise physiologists and physical therapists design tailored exercise regimens to improve cardiovascular health and muscle strength. Mental health professionals offer counseling and support to address emotional challenges associated with living with a chronic illness. This collaborative approach aims to optimize patient outcomes, improve QoL and slow disease progression by addressing the diverse needs of CKD patients holistically.

Role of technology in integrative CKD management

Advancements in technology are driving the transition of traditional nutrition care models to virtual and digitally supported ones, yet the readiness, practices, and policies for mobile health (mHealth) in nephrology are not fully optimized. While mHealth presents opportunities for improved efficiency and convenience, several challenges need to be addressed, including ensuring universal access, enhancing assessment quality, validating applications, addressing cybersecurity, conducting comparative effectiveness research, and maintaining equitable reimbursement for digital services [33].

Medical practice is advancing from empirical and evidence-based methods to intelligent diagnosis with AI-directed medicine. Despite being in its early stages, AI shows promise in developing prediction algorithms for routine clinical use by leveraging diverse real-world data. Challenges include data quality, standardization, and privacy concerns. While AI has the potential to enhance clinician efficiency and alleviate pressure in clinics, further research is needed, especially in applying AI to kidney diseases, due to limited large-scale studies.

Conclusion

An integrated approach to CKD management is crucial for addressing the complex and multifaceted nature of the disease. From early detection and diagnosis to lifestyle modifications, medication management, and psychosocial support, a comprehensive strategy enhances patient outcomes and QoL. The collaborative efforts of a multidisciplinary healthcare team, coupled with patient education and empowerment, form the foundation for effective

CKD management. By addressing the various dimensions of CKD, healthcare professionals can optimize treatment strategies and improve the overall well-being of individuals living with this chronic condition.

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