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DOUBLE-STRENGTH KETOANALOGUES IN CHRONIC KIDNEY DISEASE: BRIDGING THE GAP BEYOND CONVENTIONAL THERAPY

Nephrology

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ABSTRACT

Objective: Nutritional therapy is central to chronic kidney disease (CKD) management. Low-protein diets (LPD), when supplemented with ketoanalogues (KA), help delay disease progression by controlling uremia while preserving nutritional status. However, conventional KA regimens often require a high daily tablet load, creating a well-recognized barrier to adherence. Double-strength KA (DS-KA) formulations have been introduced to deliver the same dose with fewer tablets, aiming to improve compliance without compromising efficacy. This review evaluates whether DS-KA offer advantages over conventional KA in CKD care. **Data Sources:** A systematic search of PubMed, Scopus, Embase, and Google Scholar (2005–2025) identified clinical trials, observational cohorts, meta-analyses, and consensus guidelines relevant to KA and DS-KA. **Summary of Findings:** Numerous studies demonstrate that LPDs and very-low-protein diets (VLPDs) supplemented with KA reduce eGFR decline, delay dialysis initiation, and improve metabolic control compared with diet alone, without impairing nutrition. Meta-analyses confirm these benefits and suggest a dose–response effect: daily KA intake exceeding ~12–15 tablets are associated with reduced risks of long-term dialysis and mortality. Yet, adherence diminishes as pill burden increases, underscoring a major, modifiable barrier to treatment success. DS-KA formulations directly address this challenge by halving the number of tablets required for equivalent dosing. This approach is both biologically sound—since the active content remains unchanged—and behaviorally relevant, as simplified regimens are consistently linked to better patient adherence in chronic therapies. **Conclusion:** DS-KA represent a promising evolution in KA therapy for CKD by reducing pill burden, thereby potentially improving adherence and real-world effectiveness. While mechanistic rationale and early observations support their clinical value, robust comparative trials are still needed to confirm superiority over conventional KA and to guide formal integration into practice guidelines.

KEYWORDS

Chronic Kidney Disease (CKD), Double-Strength Ketoanalogues (DS-KA), Pill burden, Adherence

INTRODUCTION

Chronic kidney disease (CKD) is a major global health problem with an estimated prevalence of 9–13% worldwide, affecting over 850 million individuals[1,2]. In India, the burden is particularly alarming, with population-based studies reporting CKD prevalence rates ranging from 10–17%, driven by rising diabetes and hypertension[3,4]. This epidemiological load translates into escalating health-care costs and increased risk of progression to end-stage kidney disease (ESKD), which often requires dialysis or transplantation.

Nutritional therapy is a cornerstone of conservative CKD management. Low-protein diets (LPD; 0.6–0.8 g/kg/day) or very-low-protein diets (VLPD; 0.3–0.4 g/kg/day) are recommended in selected patients to mitigate uremic symptoms, reduce nitrogenous waste accumulation, and slow kidney function decline[5]. However, stringent protein restriction can increase the risk of protein-energy wasting (PEW) and malnutrition if not carefully balanced.

To overcome this, ketoanalogues (KA) of essential amino acids have been used for more than four decades in nephrology practice. First introduced in the 1970s, KA supplementation with LPD/VLPD allows for protein restriction while maintaining nitrogen balance and adequate nutrition by transamination into essential amino acids[6,7]. Clinical evidence has shown that KA use in conjunction with LPD can delay dialysis initiation, preserve nutritional status, and improve metabolic control[8,9].

The recommended dose of conventional KA is typically 1 tablet per 5 kg body weight/day, taken with meals to optimize absorption and nitrogen recycling[10]. For a 60-kg adult, this translates to 12–15 tablets per day, resulting in a high pill burden. Such a regimen poses significant challenges to patient adherence, especially in elderly individuals, those with multiple comorbidities, or those already on complex drug regimens[11]. Poor adherence undermines the potential clinical benefits of KA therapy and remains a critical barrier to their optimal use.

To address this challenge, double-strength ketoanalogues (DS-KA) have been developed, providing equivalent active ingredients in half the tablet count. By reducing pill burden, DS-KA are hypothesized to enhance adherence and real-world effectiveness, while preserving the established benefits of KA in slowing CKD progression.

Physiological Role of Ketoanalogues in CKD

Ketoanalogues (KA) are nitrogen-free analogues of essential amino acids (EAA) that undergo transamination in vivo, converting into their respective amino acids by utilizing circulating nitrogen from non-essential amino acids or urea. This process promotes nitrogen recycling, thereby reducing the accumulation of nitrogenous waste products and improving nitrogen balance in CKD patients. By enabling adequate amino acid availability at a low nitrogen load, KA supplementation allows for the safe prescription of low-protein diets (LPD) and very-low-protein diets (VLPD), which are proven to slow CKD progression and reduce uremic complications[12-14].

Beyond nitrogen economy, KA-supplemented protein restriction exerts favorable metabolic effects. It has been shown to lower the production of uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which contribute to inflammation, oxidative stress, and cardiovascular complications in CKD[15,16]. Additionally, KA reduce dietary acid load, thereby improving metabolic acidosis, which is a known accelerator of muscle catabolism and CKD progression[17]. Clinical evidence also suggests improvements in calcium–phosphate homeostasis and reduction in secondary metabolic derangements when KA are added to LPD[18].

Importantly, KA play a key role in preserving nutritional status and muscle mass in patients undergoing protein restriction. By supplying substrates for protein synthesis, KA mitigate the risk of protein-energy wasting (PEW) and sarcopenia, which are common in advanced CKD. Long-term use of KA-supplemented diets has been associated with delayed dialysis initiation, stable serum albumin levels, and better maintenance of body composition in CKD cohorts19,20. Together, these mechanisms illustrate how KA optimize the balance between slowing disease progression and maintaining patient nutrition, laying the foundation for improved outcomes in conservative CKD management.

Conventional Formulations vs. Double-Strength Formulations

Conventional Ketoanalogue Formulation		Double Strength Ketoanalogue Formulation	
Each tablet contains:		Each tablet contains:	
αKA to isoleucine	67 mg	αKA to isoleucine	134mg
αKA to leucine	101 mg	αKA to leucine	202mg
αKA to phenylalanine	68 mg	αKA to phenylalanine	136mg

αKA to valine	86 mg	αKA to valine	172mg
αKA to methionine	59 mg	αKA to methionine	118mg
Lysine acetate (l-lysine 75 mg)	105 mg	Lysine acetate (l-lysine 75 mg)	210mg
l-threonine	53 mg	l-threonine	106mg
l-tryptophan	23 mg	l-tryptophan	46mg
l-histidine	38 mg	l-histidine	76mg
l-tyrosine	30 mg	l-tyrosine	60mg
Calcium/tablet	50 mg	Calcium/tablet	100mg

Conventional ketoanalogue (KA) formulations are typically prescribed at a dose of ~1 tablet/5 kg body weight/day, administered with meals to optimize nitrogen reutilization. For an average 60–70 kg adult, this corresponds to 12–15 tablets daily. While clinically effective in preserving renal function and delaying dialysis when combined with low-protein diets (LPD), such high pill burden remains a major barrier to long-term adherence, particularly in elderly patients and those with multiple comorbidities requiring polypharmacy[21,22]. (Table 1)

To overcome this challenge, double-strength ketoanalogues (DS-KA) have been developed. Each DS-KA tablet contains double the active ingredient content of conventional formulations, thereby reducing the required daily tablet number by approximately 50% (6–7 tablets for a 60–70 kg adult) without altering the total dose delivered. This pharmaceutical innovation is designed to maintain therapeutic equivalence while minimizing treatment complexity. Improved adherence with lower pill burden is expected to translate into more consistent nitrogen balance, better metabolic control, and ultimately superior renal outcomes[23,24]. (Table 1)

Although clinical experience with conventional KA is extensive and strongly supportive of their role in delaying CKD progression, head-to-head trials directly comparing DS-KA and conventional KA are lacking. The biological plausibility of DS-KA improving adherence is strong, and early real-world observations suggest enhanced patient acceptability; however, definitive evidence from randomized controlled trials and pharmacoeconomic analyses will be critical to confirm whether DS-KA confer measurable clinical and cost benefits beyond improved convenience.

Table 1: Conventional Vs. Double Strength Ketoanalogues

Feature	Conventional ketoanalogues	Double strength ketoanalogues
Key Nutrients	Alpha-Ketoanalogue of Essential Amino Acids	Alpha-Ketoanalogue of Essential Amino Acids (Higher Concentration)
Strength	Standard Dose	Double Strength
Recommended dose	1 tablet / 5 kg BW / Day	1 tablet / 10 kg BW / Day
Dosage Requirement	More tablets needed to achieve the required effect (12-15 tablet/day)	Fewer tablets required due to higher concentration (6-7 tablet/day)

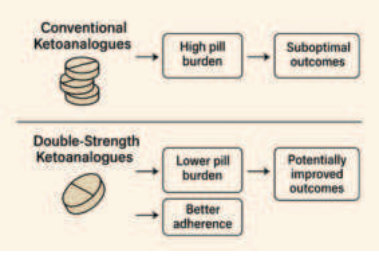

Figure 1: Conventional Vs. Double Strength Ketoanalogues

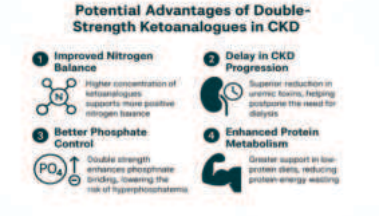

Figure 2: Clinical Benefits of Double Strength Ketoanalogues (DS-KA)

Practical & Clinical Implications

- Adherence: DS-KA could significantly lower pill burden, facilitating better compliance among elderly and polypharmacy patients—improving overall efficacy.
- Quality of Life: Reducing daily tablet load enhances patient comfort and satisfaction.
- Economics: Though DS-KA appears costlier per tablet, the overall treatment cost may be comparable or even lower, as fewer tablets are required. Additionally, improved adherence ensures better clinical outcomes, reducing hospitalization and long-term healthcare expenses.
- Personalized Care: DS-KA align with modern individualized nutrition strategies prioritizing adherence and outcomes.

Limitations of Current Evidence

- No direct randomized controlled trials comparing DS-KA to conventional KA.
- Existing data reflect conventional dosing—clinical outcomes based on tablet count only.
- Need long-term data on survival, cardiovascular outcomes, and actual adherence measures comparing formulations.

Regulatory and Clinical Adoption in India: Implications for Global Practice

India has been at the forefront of adopting double-strength ketoanalogue (DS-KA) formulations, with several products already approved and available in the market. For instance, Renolog-DS is a widely used DS-KA formulation that provides equivalent efficacy at half the pill burden compared to conventional preparations. This shift reflects an important advancement in addressing one of the major barriers to ketoanalogue therapy—patient adherence.

Given these real-world benefits, the Indian regulatory acceptance of DS-KA highlights the need for global nephrology guidelines and policy makers to consider this innovation. Wider international adoption of DS-KA could standardize treatment, reduce therapeutic inertia, and improve long-term patient outcomes across diverse healthcare settings.

Future Perspectives

Head-to-head RCTs comparing DS-KA vs. standard KA are warranted focusing on adherence, nutritional markers, and renal outcomes. Longitudinal studies are required tracking compliance, quality of life, and health economics in CKD patients using DS-KA. If DS-KA demonstrate superior outcomes, integration into CKD nutrition guidelines and consensus statements would follow.

CONCLUSIONS

KA supplementation with LPD is an evidence-based strategy to delay CKD progression while protecting nutrition. Tablet burden is a key compliance barrier. DS-KA, by cutting pill number in half, may offer improved adherence and effectiveness. Nonetheless, dedicated clinical research is essential to validate these advantages.

Conflicts of Interest: Harsh J Shah, Jacky K Pariyani, Kalyani V Shinde & Ankit S Singh are employees of La Renon Healthcare Pvt. Ltd., Ahmedabad, Gujarat, India.

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