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Unlocking the Therapeutic Potential of Hypocritic Nutrition in Chronic Kidney Disease: A Critical Examination and Novel Approaches

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Abstract

This editorial aims to underscore the therapeutic value of hypoproteic nutrition in chronic kidney disease (CKD), often misconstrued as genuine therapy. Key properties include preventing the deterioration and rapid progression of residual renal function (RRF), delaying the need for replacement treatment, mitigating the production of highly toxic nitrogenous compounds, such as protein-bound uremic toxins, and achieving a phosphorus balance for improved control of uremic osteopathy and reduced cardiovascular events, ultimately enhancing survival rates in end-stage renal disease (ESRD) patients. Additionally, we introduce a novel concept termed "incremental dialysis," leveraging lower protein intake for patients with limited RRF and strong dietary compliance. This approach, which we advocate as part of a combined diet dialysis program (CDDP), has the potential to reduce dialysis frequency, including once-weekly hemodialysis (HD). While the term incremental HD (IH) is sometimes confused with "infrequent dialysis," we emphasize the importance of a hypoproteic diet for medium-advanced stages of CKD to avoid unnecessary and detrimental dialysis excess. Furthermore, we highlight the imperative role of administering amino acids and propose a serious consideration of treating uremic dysbiosis, a significant factor impacting the microbiota in CKD.

Keywords: Hypoproteic nutrition; Chronic kidney disease; Incremental dialysis; Combined diet dialysis program; Uremic dysbiosis.

Introduction

In contemporary healthcare, optimizing conservative treatment for Chronic Kidney Disease (CKD), particularly in the pre-dialytic stage (CKD5), is imperative. Initiating dialytic treatment remains a subject of debate, generally considered when the glomerular filtration rate (GFR) falls within a range of 6-12 ml/min/1.73 m2. However, dialysis becomes necessary when uremic symptoms become unmanageable, irrespective of renal function levels, or when comorbidities demand replacement therapy. Clinical manifestations of untreated uraemia include anorexia, hyperazotaemia, hyperphosphataemia, metabolic acidosis, hydro-saline retention, and malnutrition. The prescription of a hypoproteic diet in CKD5 aims to postpone dialysis initiation by better controlling uremic symptoms. This diet requires adequate energy intake, careful phosphorus control, sodium regulation, and an emphasis on essential amino acids to prevent metabolic acidosis [1-8].

Practical Measures

Advancements in food production methods, including the development of various pasta types with added fibers, contribute to more palatable options. New nutritional regimens for CKD5 and dialysis patients involve reduced protein intake (0.3-0.6 g of protein/kg of body weight) integrated with essential amino acids (EAAs) and ketoacids mixtures. The very low protein diet (VLPD) emphasizes a contribution of less than 0.3 g of vegetable-

based protein/kg of body weight, motivating patients with good compliance and metabolic stability. However, ideal adherence to VLPD regimens is challenging, and standard low protein diets (LPD) based on 0.6 g of protein/kg of body weight may ensure better compliance among CKD5 patients. Noteworthy observations for CKD5D hemodialysis (HD) patients include protein-free diets on HD days, higher protein intake on dialysis days to compensate for hypercatabolism, and the necessity for tailored nutritional treatments based on individual patient characteristics. HD patients experience significant amino acid loss, particularly in thrice-weekly HD schedules, highlighting the need for more precise studies on amino acid loss in the dialysis fluid [9-13].

This comprehensive approach to conservative treatment and dietary management underscores the importance of individualized care in CKD, contributing to better patient outcomes and delaying the need for dialysis initiation.

The New Frontier in CKD: Microbiota

In End-Stage Renal Disease (ESRD), a pronounced state of dysbiosis in the intestinal microbiota leads to functional disruptions in the intestinal barrier permeability. This dysbiosis manifests as a qualitative and quantitative imbalance in the microbial flora, resulting in decreased levels of beneficial molecules such as amino acids and an increased production of uremic toxins like p-cresol and indoxyl sulphate [14-25]. Despite their strong binding to circulating blood albumin, these toxins, only 10% of their free form, can be eliminated, contributing to an accelerated deterioration of Residual Renal Function (RRF) and cardiovascular damage [26,27]. Improvement in dysbiosis is observed by incorporating plant-based diets rich in fibers (30-40 g/day), with careful attention to potassium levels [28]. The associated microbiota-related illness presents as severe malabsorption, marked by reduced saccharolytic fermentation, lower short-chain fatty acids, weakened immunological defenses, and elevated uremic inflammation with increased nitrogen compounds.

Impact of Hypoproteic Nutrition and Residual Renal Function

Numerous publications support the efficacy of a hypoproteic diet in preventing the worsening progression of renal function across all stages of Chronic Kidney Disease (CKD), with particular emphasis on CKD5 and CK5D patients. The reduction in protein intake proves effective in mitigating glomerular and tubular damage by lowering proteinuria [29]. In a selected group of patients maintaining a good metabolic steady state with an RRF of approximately 5-10 mL/min/1.73 m2, a tailored hemodialytic program can be initiated. This involves reducing hemodialysis (HD) frequencies, avoiding pathologies associated with extracorporeal treatments, and preventing an HD "overdose." Such ethical measures provide a substantial advantage in initiating an "incremental HD" program.

Incremental Hemodialysis

Incremental Hemodialysis (IH) encompasses a range of therapeutic options implemented with a schedule of less than thrice-weekly HD sessions, ideally integrated with a moderately low-protein diet (LPD). IH is a strictly implemented program following the assessment of uremic status in pre-dialysis patient settings through a synergic nephrological and nutritional approach. This aims at achieving excellent nutritional status and preserving diuresis with a Glomerular Filtration Rate (GFR) ranging between 5 and 10 mL/min/1.73 m2. In the 1980s and 1990s, the Integrated Dialysis Dietary Program (IDDP) was introduced for patients with a GFR <3 ml/min/1.73 m2, involving a weekly HD session integrated with a very low protein diet (VLPD) equal to 0.3-0.4 g/kg/day, supplemented with Essential Amino Acids (EAAs) and their ketoanalogues [29-32]. While IH was initially considered to delay the start of dialysis, experiences led to the suspension of IDDP in 1998 due to malnutrition risks and neurological peripheral disorders [33-37]. Subsequently, the Combined Diet Dialysis Program (CDDP) was developed, with modified protein intake, patient recruitment criteria, and enhanced estimation of dietary compliance. A controlled, non-randomized study demonstrated significant advantages of CDDP over thrice-weekly HD schedules, highlighting better preservation of residual diuresis, reduced β2-microglobulin levels, and improved phosphatemia control [38]. The cumulative survival rate in the CDDP group remained comparable at 24 months, but at 96 months, a higher cumulative survival rate and significant cost savings were observed [39,40]. The CDDP, tailored to cooperative patients, emerges as a promising "bridge" option to initiate an incremental HD program.

Minimizing Damage from Protein-Bound Toxins and Hyperphosphatemia: A Comprehensive Approach

The hypoproteic nutrition strategy, in conjunction with Residual Renal Function (RRF), results in decreased intake, production, and increased elimination of various toxin compounds in CKD5 and CKD5D patients. Table 1 illustrates a comprehensive list of molecules that can be effectively limited [41].

Protein-bound uremic toxins, if unchecked, can induce endothelial damage, exert direct toxic effects on renal tubules, activate the Renin-Angiotensin-Aldosterone System (RAAS), heighten insulin resistance, trigger apoptosis in various renal cells leading to renal fibrosis, incite oxidative stress, and contribute to cardiac apoptosis [42]. Additionally, the underestimated direct toxicity of hyperphosphatemia significantly correlates with cardiovascular mortality in End-Stage Renal Disease (ESRD) and CKD5D patients, emphasizing its direct impact on kidney function. The primary

culprits of kidney damage are closely linked to the calcification of renal microcirculation and subsequent tubular-interstitial lesions, owing to the accumulation of hydroxyapatite crystals, particularly at the cortico-medullary junction—a phenomenon recognized since the 1980s [43].

An "Incremental HD" approach on a once- to twice-weekly basis, facilitated by RRF and reduced protein intake, holds promise in achieving phosphorus balance [44]. In the conventional thrice-weekly HD sessions for oligoanuric patients, there is a progressive buildup of phosphate in uremic body compartments, particularly in endothelial walls.

Action of Hypoproteic Nutrition: Summarized Insights

- Addressing inadequacies in proteic intake is pivotal in mitigating uremic toxins, metabolic acidosis, calcium and phosphorus mineral metabolism disorders, protein energy wastage, renal failure progression, and general discomfort. In ESRD, especially in CKD4-5 stages and among dialysis patients, specific measures are recommended:
- Prescribe an Ideal Proteic Dose: A prescription of 0.6 g/kg/day is suggested, with ongoing research required to compare Low Protein Diet (LPD) (0.6 g/kg/day) versus Very Low Protein Diet (VLPD) (0.3-0.4 g/kg/day). LPD might enhance patient compliance.
- Administer Amino Acid Mixtures: A mixture of amino acids, particularly essential and branched amino acids, is advised to compensate for compromised absorption, metabolism, and synthesis in ESRD.
- Prolong RRF with Hypoproteic Diet: A hypoproteic diet prolongs RRF and reduces phosphate absorption, minimizing toxin molecules such as protein-bound uremic toxins, leading to improved hydro-electrolytic balance and reduced cardiac overload.
- Tailored Hypoproteic Diet for CKD5 and Dialysis Patients: Prescribe a personalized hypoproteic diet to mitigate the risks associated with frequent weekly treatments, particularly relevant if salt intake reduction is part of the treatment.
- Consider Incremental Substitutive Treatments: In selected collaborative patients, initiate incremental schemes for substitutive treatments in Hemodialysis (HD) or peritoneal dialysis cases.
- Periodically Monitor UNA and RRF: During an incremental dialytic program, regularly check Urea Nitrogen Appearance (UNA) to assess patient adherence and RRF, evaluating through averaged urea and creatinine clearances via 24-hour urine collection.
- Address Intestinal Dysbiosis: Initiate treatment for intestinal dysbiosis, acknowledging its alteration in the uremic milieu. Incorporate fibers, prebiotics, or probiotics to improve diet and reduce the inflammatory uremic status.

While the recognition of the importance of fiber and interventions for intestinal dysbiosis is growing, further extensive studies are imperative to establish preventive measures for RRF and alleviate the inflammatory uremic status.

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