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Perspective

Very low-protein diet to postpone renal failure: Pathophysiology and clinical applications in chronic kidney disease

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Abstract

The uremic syndrome is a metabolic disorder characterized by the impairment of renal handling of several solutes, the resulting accumulation of toxic products and the activation of some adaptive but detrimental mechanisms which all together contribute to the progression of renal damage. In moderate to advanced renal failure, the dietary manipulation of nutrients improves metabolic abnormalities and may contribute to delay the time of dialysis initiation. This commentary focuses on the physiopathological rationale and the clinical application of the very low-protein diet supplemented with ketoanalogs for the management of chronic kidney disease.

Keywords: Low-protein diet; Ketoanalogs; Renal failure; Chronic kidney disease

Renal adaptation during chronic kidney disease and effects of dietary protein restriction

The progressive reduction of functioning renal mass along with chronic kidney disease (CKD) leads to the reduction of renal excretion of several solutes, metabolic waste products and toxins, inducing retaining of these molecules and metabolic imbalances. The residual nephrons in the attempt to maintain neutral body balances increase the solutes excretion by activating some compensative mechanisms (i.e. the so called

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"*Trade-off hypothesis*") which, however, are detrimental for the kidney and the whole body. Hence, during the progressive CKD the renal adaptations allow maintaining the balance of major body solutes, but also contribute to the negative progression of renal damage toward the end-stage renal disease.

The principal solutes retained during CKD are the protein related products which cause hyper-azotemia, acidemia, hyper-phosphatemia; phosphate and sodium also play a relevant role in the renal adaptation causing hyper-parathyroidism and extracellular volume expansion, respectively. The low-protein, low phosphate, low salt diet, by counterbalancing both the accumulation of uremic solutes and the renal adaptive mechanisms, represents a rational physio-pathological approach to manage the metabolic disturbances in CKD.[1] Indeed, in CKD the nutritional treatment focusing on protein and sodium restriction allows metabolic and fluid control[2]; even during the advanced CKD stages, a very restricted dietary treatment may reduce signs and symptoms of uremia and possibly the CKD progression by counteracting the nutrient waste products accumulation and the related adaptive mechanisms.[3]

Historical background of low-protein diets in chronic kidney disease

In the early 19th century, it was first reported that in renal failure a low protein intake ameliorates the retention of waste products resulting from protein catabolism, improving the uremic syndrome. In experimental studies, Giordano[4] demonstrated that in advanced renal failure the body uses the endogenous urea for the protein synthesis and a very small amount of exogenous urea (around 3 grams of nitrogen per day) is sufficient to lower the serum urea levels and maintain a neutral body nitrogen balance and a stable body weight. Giovannetti and Maggiore[5] observed in a clinical setting that a high energy diet very restricted in proteins (less than 2 grams of nitrogen from high biological value proteins per day) dramatically improved the uremic symptoms and prolonged survival in patients with end-stage renal failure. These seminal studies suggested dietary restriction of proteins as a therapy for advanced CKD.

Thereafter, it was suggested that a low-protein diet (LPD) may lower the glomerular filtration rate (GFR) decline rate and delay the initiation of renal replacement therapy. In experimental CKD models, Brenner et al[6] demonstrated that the amount of dietary proteins influences glomerular hemodynamics, the high proteins induce glomerular hyper-filtration, hypertrophy and result in glomerular sclerosis and proteinuria; inversely, the low protein intake protects the residual renal mass and slows down the CKD progression. Nonetheless, many studies evaluating the clinical effectiveness of LPD in CKD failed to demonstrate the same effects in the clinical setting.

As a consequence, the implementation of the dialysis technique which was considered the best treatment for kidney failure is spreading; this approach conveyed a negative connotations to the conservative treatment for CKD and the use of LPD lost popularity while the overuse of dialysis arose.[7] Nevertheless, many studies showed that dialysis may not prolong survival or provide an acceptable quality of life in most patients. Consequently, the conservative care for CKD is again gaining credit as a rational treatment alternative to dialysis,[8] with some major LPD strategy issues remaining to be defined.

Practical application of the very low-protein diet in chronic kidney disease

The lower "normal" intake of proteins suggested for the general population is 0.8 grams per kilo of body weight (BW) per day; this amount of proteins also represents the initial dietary protein level at the early CKD stages. Several protein-restricted dietary regimens have been proposed for moderate to advanced CKD: a typical LPD provides around 0.6–0.7 $g \cdot kgBW^{-1} \cdot d^{-1}$; a very low-protein diet (VLPD) provides around 0.3–0.4 $g \cdot kgBW^{-1} \cdot d^{-1}$ and it is basically a vegetarian diet which has to be supplemented with essential aminoacids to satisfy the body nitrogen need and with nitrogen-free ketoanalogues to recirculate the endogenous urea [supplemented very low-protein diet (sVLPD) or ketodiet]. These different dietary regimens could be adapted along the course of CKD.[1–3,9]

Renal and cardiovascular effects

In moderate to advanced CKD, a small reduction of protein intake can lead to substantial improvement of the uremic metabolic disorders. The prescription of a standard LPD (0.6 $g \cdot kgBW^{-1} \cdot d^{-1}$) compared with the lower-normal protein intake suggested for the general population (0.8 $g \cdot kgBW^{-1} \cdot d^{-1}$), provides a better control of hyper-azotemia and metabolic acidosis in all patients, including those with non-optimal adherence to diet prescription.[10] A VLPD, given a good adherence, is much more beneficial than standard LPD on either metabolic disorders or several renal and cardiovascular risk factors present in advanced CKD, such as

phosphoremia, proteinuria, hypertension, anemia, metabolic acidosis, hyper-parathyroidism and dyslipidemia.[11–16] The VLPD contains less phosphate as compared with standard LPD and these phosphates which are mainly present as phytate have a lower intestinal absorption rate; consequently, the phosphate burden is markedly lower and the serum phosphate levels are reduced.[17] The lower the dietary protein intake in CKD is, the higher the impact on proteinuria; with the sVLPD such an effect is further enhanced by the lowest levels of serum phosphates due to the lower phosphate intake.[14] In advanced CKD patients with uncontrolled hypertension, the sVLPD induces a marked and sustained decrease in blood pressure not related to dietary proteins but directly dependent on the characteristic of the VLPD (type of proteins, cholesterol and phosphate content, ketoanalogs, salt intake).[16]

Overall, in moderate to advanced CKD, a VLPD supplemented with ketoanalogs improves the metabolic control and reduces the magnitude of the major clinical signs and symptoms of uremia allowing the patient to delay the initiation of dialysis and reach this critical phase of the disease with less cardiovascular complications.[18]

Nutrition

A possible drawback related to the restricted dietary regimens during CKD is the risk of protein-energy wasting (PEW). The minimum amount of protein to maintain the daily nitrogen balance is around 0.55 $g \cdot kgBW^{-1} \cdot d^{-1}$ and most CKD patients get it, including patients on VLPD supplemented with ketoanalogs; to maintain the nitrogen balance, however, an energy intake higher than 30 $kcal \cdot kgBW^{-1} \cdot d^{-1}$ is needed, but in CKD it is often difficult to reach this threshold.[19,20] Therefore, the key point to maintain a proper nitrogen metabolism and avoid PEW in CKD is the strict adherence to the dietary energy prescription during LPD[21]; indeed, in patients on VLPD supplemented with ketoacids and adequate energy intake, malnutrition is not observed during either the pre-dialysis or after dialysis initiation periods.[22,23]

As a result, though a careful nutritional monitoring is mandatory in all CKD patients, the VLPD supplemented with ketoanalogs provides adequate protein and energy intakes.[1] A consensus from the International Society of Renal Nutrition and Metabolism advised an algorithm for quarterly nutritional monitoring for CKD patients.[24] Changes of the nutritional parameters over time represent a key component of the observation and a close monitoring is associated with the maintenance of a steady nutritional status.[21,25] Overall, while the sVLPD in malnourished CKD patients is not suggested,[3,17] the ketodiet can even improve the nutritional status in all well-nourished CKD patients under regular nutritional monitoring.[26]

Progression of renal disease

In experimental CKD models, higher protein intake induces glomerular sclerosis and proteinuria.[6] As a consequence, the LPD has been supposed to protect against the progression of CKD and to preserve the residual renal function, slowing down the GFR decline toward the end-stage renal disease. However, the larger study designed to evaluate this effect in CKD patients, the Modification of Diet in Renal Disease (MDRD) study, showed that the standard LPD did not significantly affect the GFR decline.[27] Nevertheless, the level of kidney function at which patients start the renal replacement therapy is variable; it mainly depends on the degree of the uremic symptoms and clinical complications, independently of the GFR degree. Accordingly, in CKD the sVLPD may delay the initiation of dialysis by reducing the uremic symptoms and complications. Walser et al[28] first evidenced that in compliant CKD patients the sVLPD postpones the initiation of dialysis for a median time of one year. This early evidence was confirmed by a Cochrane review which showed the effect of LPD on prolonging the renal survival in non-diabetic CKD patients and this effect was mostly due to the VLPD.[29]

Of course, not all the CKD patients may benefit from a VLPD supplemented with ketoacids. Recent advances in clinical research definitely demonstrated that the ketodiet is highly effective in reducing the renal death in selected, well-nourished, progressive CKD, proven diet adherent, low-comorbidity patients.[30] On the other hand, the prescription of an sVLPD to unselected CKD patients does not reduce the risk of renal death in the whole population, mainly due to low diet adherence but also to age, diabetes, cardiovascular comorbidities and the previous GFR low decline rate.[31] Therefore, the sVLPD is effective in reducing the decline rate of GFR and deferring dialysis initiation but the selection of subjects and the high adherence to the diet are mandatory.[30] A further key-point is the continuous nutritional counseling to maintain the high adherence.[10]

Patient survival

A major concern on the LPD and particularly on the ketodiet is about a possible negative impact on the

patient survival. A solitary paper from the MDRD group found that the prescription of an sVLPD to CKD patients increases the risk of death after the initiation of dialysis.[32] This paper has several drawbacks, such as the very long time without dietary treatment prior to the study observation, the presence of several confounders and the absence of any information on the death events; additionally, a reliable hypothesis for the relation between the sVLPD and the worst outcomes is not provided and this relation seems to be spurious.[33] In opposite, a controlled study evaluated at the start of chronic dialysis treatment a group of CKD patients previously treated with an sVLPD for a long period; the study had two control groups, CKD patients treated in tertiary nephrology care but without a VLPD prescription and unselected CKD patients starting dialysis without any previous information.[34] In this study, the sVLPD was not associated with a higher mortality during the dialysis period with respect to both controls, allowing the conclusion that the sVLPD during CKD does not increase the mortality in the dialysis period. Also, a trial in elderly CKD patients came to the same conclusion.[35] Overall, the sVLPD is safe during either the predialysis period or along the following dialysis phase.

Initiation and modalities of nutritional treatment in chronic kidney disease: guidelines and consensus

The role of the LPDs in the comprehensive treatment of CKD is worldwide recognized but specific criteria to implement this treatment in the clinical practice are still debated. Basically, current guidelines only suggest to use a 0.6–0.8 $g \cdot kgBW^{-1} \cdot d^{-1}$ of proteins and high energy (35–30 $kcal \cdot kgBW^{-1} \cdot d^{-1}$) diet in advanced CKD stages; no guideline gives advices for earlier CKD stages or ideal diet composition.

Recently, it has been published a consensus obtained with the Delphi methodology on some open questions about the nutritional treatment in non-dialysis CKD, highlighting a broad consensus among nephrologists on starting the nutritional treatment early in CKD and using the LPD or sVLPD starting from CKD stage 3, also in diabetic patients.[36] These statements agree with a previous expert consensus about the sVLPD in CKD[3]; briefly, patients should be advised since the early CKD stages to reduce the protein intake to 0.8 $g \cdot kgBW^{-1} \cdot d^{-1}$, which is the lower level of recommended intake for the general population; at CKD stage 3, the LPD should be started; at a GFR below 30 ml/min (CKD stage 4), the sVLPD can be introduced.[3] This incremental approach may educate the patient to a proper nutrition since the early stages of the disease allowing a better adaptation and adherence to the dietary treatment.

Summary

In the last decades, the CKD progressively increased worldwide and the number of patients requiring dialysis is estimated to double by 2030, mostly in the developing countries. In addition, the end-stage renal disease was among the primary causes of mortality in the world.[37,38] Hence, in addition to population-based strategies, an efficacious conservative treatment for non-dialysis CKD patients is mandatory to prevent the epidemic of end-stage renal disease.

In the comprehensive conservative treatment for non-dialysis CKD, the nutritional treatment represents a crucial point and the LPD is the cornerstone of the treatment, impacting on the signs and symptoms of the uremic syndrome, on the renal and cardiovascular risk factors related to uremia and on the progression of renal disease.[39]

The optimal level of protein intake to slow the progression of renal damage is unknown, but a VLPD supplemented with ketoanalogs is effective (in ideal condition) in delaying CKD progression, being efficient in selected CKD patients (young, no diabetes, no comorbidity, CKD progressors, diet adherent) in which it significantly reduces the risk of renal death. In non-selected CKD patients, this treatment has reduced effectiveness, is burdened by low adherence and has a low impact on renal death. Anyway, the sVLPD is safe along the whole CKD course and does not worsen patient survival. An individualized approach may further enhance the impact of the sVLPD in CKD.[40,41]

Conflicts of interest

The authors declare that they have no conflicts of interest.

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