

Low-protein diet in chronic kidney disease: from questions of effectiveness to those of feasibility

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A low-protein diet (LPD) as a therapeutic measure in chronic kidney disease (CKD) was suggested by Beale as early as 1869 [1], and the first attempt to evaluate experimentally LPD in humans was fulfilled by Smith in 1926 [2].

In the mid 1960s, Giordano and Giovannetti were the first to show that LPD, supplemented with essential amino acids to achieve neutral nitrogen balance, was able to reduce almost all uraemic signs and symptoms [3, 4]. By lowering blood urea and other nitrogenous waste products, LPD has favourable effects on secondary hyperparathyroidism [5], peripheral resistance to insulin [6], hyperlipidaemia [7], hypertension and acid–base disorders [8]. For instance, Goraya *et al.* [8] have shown that a vegetarian diet in CKD patients Stage II (60–90 mL/min) significantly decreased the 8-h urine net acid excretion, potential renal acid load, urine albumin-to-creatinine ratio, urine *N*-acetyl- β -D-glucosaminidase-to-creatinine ratio and the urine transforming growth factor- β -to-creatinine ratio at 30 days, as compared with a control group. They also showed a 30-day greater decrease in systolic blood pressure, plasma and urine excretion of potassium, aldosterone, endothelin and urine excretion of sodium in the vegetarian group. As maintenance dialysis is generally initiated when uraemic symptoms begin, the need to start it may be deferred by LPD [9]. For instance, Walser *et al.* [10] found that dialysis can be safely deferred by LPD for a median of 1 year after patients reach a glomerular filtration rate (GFR) level of 10 mL/min among non-diabetics and 15 mL/min among diabetics.

In the 1980s, the rapid development of kidney replacement therapies led to an enormous increase in expenditure, but mortality and morbidity remained high for patients receiving dialysis. This observation further raised the interest of health providers and researchers in interventions for slowing the deterioration of kidney function in order to delay end-stage renal disease (ESRD).

Since that time, many experimental and observational studies have addressed the question of the ability of LPD (protein intake ≤ 0.8 g/kg/day), or very LPD (protein intake ≤ 0.3 g/kg/day), to retard the progression of CKD towards

ESRD. Fouque *et al.* [11] identified 46 studies conducted between 1975 and 1991 that addressed this issue in non-diabetic CKD patients, and Pan *et al.* [12] identified 26 studies published up to 2008 in diabetic CKD patients. Despite the many studies performed over more than 30 years, the effectiveness of LPD in preventing ESRD among diabetic or non-diabetic CKD patients remains uncertain, with largely conflicting results. The Modification of Diet in Renal Disease (MDRD) was the largest randomized clinical trial to test the hypothesis that LPD slows the progression of kidney disease among 1840 patients with various stages of CKD. The primary results published in 1994 were not conclusive with regard to the effectiveness of this intervention [13]. However, following secondary analyses undertaken later, the authors concluded that ‘the balance of evidence is more consistent with the hypothesis of a beneficial effect of protein restriction than with the contrary hypothesis of no beneficial effect’ [14]. Five meta-analyses of studies of the effects of LPD on CKD progression in diabetic and non-diabetic patients have been performed since the early 1990s, four in favour of a beneficial effect [9, 11, 15, 16] and one not [12]. The reasons for the discrepancies between the results of studies conducted to evaluate LPD are of particular interest. Comparison of their designs reveals great heterogeneity:

First, the interventions evaluated vary considerably in terms of protein restriction (0.28–0.80 g/kg/day) and supplementation or not with amino acids and/or keto-analogues;

Second, the patients enrolled encompass diverse age groups, diverse aetiology of CKD, and various degrees of kidney failure (CKD Stages III–V);

Third, the major end point used to evaluate the effectiveness of the intervention differ between studies, ranging from serum creatinine increase to creatinine clearance, GFR decrease over time and kidney death;

Fourth, the duration of patient follow-up is also variable; indeed, one explanation for the failure of the MDRD study

to demonstrate a beneficial effect of LPD was its short duration (2.2 years of follow-up on average);

And fifth, the last source of variability seems to be compliance of patients with LPD, often considered as being poor, or at least suboptimal. In the MDRD study, patient compliance was unsatisfactory, with an estimated protein intake of 0.73–0.77 g/kg/day in LPD (instead of 0.60 g/kg/day) and 0.48 g/kg/day in very LPD (instead of 0.28 g/kg/day). However, the level of compliance varied a lot according to the CKD stage and the patient characteristics, particularly their age [14]. This suboptimal compliance may explain the discrepancies found by the authors between results of intention-to-treat analysis and those of per-protocol analysis. In the eight trials considered in their meta-analysis, Pan *et al.* [12] found that achieved mean protein intake in the LPD groups exceeded by 20% the prescribed protein intake, as assessed by 24-h urinary urea nitrogen excretion or dietary history. Combe *et al.* [17] estimated that 67% of patients were compliant with LPD in a study conducted in 1993, and Kopple reported that in his experience about 15% of CKD patients are able to follow LPD comfortably [18]. In a literature review, Fouque *et al.* showed that the actual mean difference in protein intake between higher and restricted protein intake groups was less than expected (i.e. 0.35–0.70 g/kg/day according to the considered study) and varied from 0.2 to 0.35 g/kg/day [19]. It is then questionable whether, in the face of inconclusive findings, the LPD is truly not effective in slowing the progression of kidney function or whether the LPD is not being appropriately implemented in the intervention groups.

During the same period, the question of the safety of LPD and very LPD, and particularly its potentially deleterious effects on nutritional status and clinical outcome of CKD patients, has raised concern. Some authors have argued that if protein intake falls below 0.8 g/kg/day, the diet may not provide a sufficient amount of daily energy intake in terms of calories and then the risk of malnutrition in predialysis patients is increased, which is a major risk factor for mortality during maintenance dialysis, especially in the elderly [20, 21]. Since then, various studies conducted to address this issue have shown the ability of LPD or very LPD in maintaining nutrition and its lack of deleterious effects on clinical outcome before and after the initiation of dialysis [22–27].

Finally, the safety of LPD and its beneficial effects on uraemic symptoms are now well recognized, but its effectiveness in slowing the progression of kidney disease remains a matter of debate. Moreover, considerations about patient compliance with LPD raise the question of its feasibility in current medical practice. In a clinical trial setting, patients are generally highly selected (patients considered by the physician as being able to follow LPD are more likely to be included), dietary counselling and close monitoring are employed, compliance is regularly assessed by measuring urea excretion and/or by dietary inquiries and, if necessary, measures to motivate patients are used. However, even under these optimal conditions, poor compliance with LPD has been widely described [12, 14, 17, 18]. It is

therefore very likely that compliance is even worse in current medical practice where patients are not selected and benefit from less intensive care than those included in studies.

It must be emphasized that modifying dietary habits is challenging and implies a major change in lifestyle. Indeed, it is more difficult to implement and evaluate dietary interventions than to implement and evaluate drug intervention. To change dietary habits, counselling by a skilled dietitian is highly recommended [28], but it is unlikely to be sufficient as the support of the patient by family members and whoever prepares the food is critical. To maintain this change over time, the LPD prescribed has to be pleasant, varied and not too restrictive.

At present, as the safety of LPD and its beneficial effects on uraemic symptoms are obvious [3–8], its prescription to most CKD patients seems justified, even if its effect on CKD progression remains controversial. Indeed, by reducing uraemic symptoms, late dialysis may be safely considered, which is probably the most important point for the patient in terms of quality of life and mid-term mortality [29]. Consequently, there is a need to help patients to adhere to their LPD: interventions such as patient and family education programmes should certainly be explored, but it is also important to develop simple and attractive approaches to LPD and then evaluate their feasibility in current medical practice. This issue was explored by Piccoli *et al.* in their study conducted in the Nephrology Unit of San Luigi Hospital, University of Torino (Italy). The authors proposed to their patients with CKD Stages IV–V, Stage III with rapid progression and with refractory nephrotic syndrome, a simplified vegetarian LPD supplemented with alpha-keto analogues (LPD-KA). The simplified LPD-KA is based on a concept of forbidden and allowed foods [forbidden: fish, meat, milk, eggs and derivatives (except in the context of the free-choice meals); everything else is allowed]. The diet is vegan, with an average of 0.6 g/kg/day protein intake and of 30–35 kcal/kg/day energy intake, and supplemented with Ketosteril (1 co/10 kg of body weight) [30]. To improve compliance, one to three free-choice meals per week are allowed and the foods are not weighed. A total of 139 CKD patients agreed to adopt this vegan diet for at least 1 month between 2007 and 2012, and the authors evaluate the long-term feasibility of such an approach and report, in parallel, data on CKD progression and all causes mortality of included patients.

In practice, the question of the effectiveness of LPD in slowing the progression of CKD becomes of minor importance if most patients are not able to adhere to it. Therefore, initiatives to simplify and increase the attractiveness of LPD and then evaluate its feasibility are of particular interest. Further research aimed at comparing different approaches of LPD in terms of patient compliance and satisfaction should be encouraged.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Piccoli *et al.* Vegetarian low-protein diets supplemented with keto analogues: a niche for the few or an option for many? *Nephrol Dial Transplant* 2013; 28: 2295–2305.)

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