Protein restriction: a revisited old strategy with new opportunities?

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When dialysis facilities were not widely distributed, protein intake had been a hot topic for many years to delay, for as long as possible, the need for dialysis in patients with advanced chronic kidney disease (CKD). The seminal paper by Giovannetti and Maggiore [1], which was published in the *Lancet* exactly 50 years ago, was a strong message for the nephrological community: many patients were given a low-protein diet with apparently great success, despite the lack of a true control group. Strong believers to this approach had to match with new opportunities. 


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lack of effective renoprotective strategies and by the fact that little was known about the role of hypertension and proteinuria on CKD progression at the time. The first trials showed positive findings in slowing down CKD progression but had a small sample size or inadequate methodology [3]. Given these uncertainties, the Italian Cooperative Study was designed to compare either a low-protein diet (0.6 g/kg body weight daily) or a ‘normal’ controlled-protein diet (1.0 g/kg daily) in a large sample of CKD patients [4]. Although a very low rate of CKD progression in both groups could have reduced the statistical power, when considering the doubling of baseline plasma creatinine levels or the need for dialysis as end points, the effect of the low-protein diet on renal survival was modest and only of borderline significance. While compliance was good in the controlled-protein group, it was poor for the low-protein diet one, leading to a difference in protein intake between groups that were substantially less than that required by the protocol (0.2 instead of 0.4 g/kg day). This underlines that compliance to demanding diets is difficult in the setting of a randomized clinical trial. The findings of the study had a great clinical and social impact, allowing CKD patients to follow a standard Italian diet without useless restrictions and, even more importantly, without protein-free foods. However, many nephrologists gave a misleading interpretation of these findings and confused a controlled-protein diet with no control in protein intake. This aspect is crucial, considering that in general, protein intake is much higher than that recommended by the World Health Organization in many countries [5]. Indeed, in the paper by Cirillo et al. [6], the participants of the Gubbio study had a protein intake of 1.34 ± 0.57 g/day/kg of ideal weight at baseline. The Modification of Diet in Renal Disease (MDRD) Study gave the final confirmation that a low-protein diet has little effect on CKD progression [7]. Following stratification according to glomerular filtration rate (GFR), 840 patients were randomized to usual-protein diet or a low-protein diet (1.3 or 0.58 g/kg/day; Study 1) and to either a low-protein diet (0.58 g/kg/day) or a very low-protein diet (0.28 g/kg/day) with a keto acid–amino acid supplement in Study 2. At primary analysis, the mean decline in GFR at 3 years did not differ significantly between the diet groups. A 28% less decline in GFR rate in the low-protein group than in the usual-protein group was observed after the fourth month of follow-up (P = 0.009) at a secondary analysis only of Study 1; this is a rather small benefit on CKD progression despite statistical significance.

The effect may be grossly quantified as the time gained free from dialysis: after having followed a low-protein diet (0.58 g/kg/day) for nearly 10 years, the advantage is of nearly 1 year [8]. The calculation of the number needed to treat (number of patients to be treated) is in line with a modest clinical effect: 56 patients have to follow the diet for 1 year without significant benefits to avoid renal death in one patient. Differing from previous studies, the MDRD trial had the methodological advantage of measuring GFR on the basis of the renal clearance of $^{125}$Iiothalamate, thus avoiding the confounding effect of changes in creatinine production by muscle masses.

The decrease in popularity of the low-protein diet went together with the understanding of the nephroprotective actions of the renin–angiotensin system (RAS) inhibitors [9, 10]. The advantage of taking an ACE inhibitor for years is substantial, especially in proteinuric nephropathies, and certainly less demanding to the patient than the low-protein diet [6].

Cirillo et al. [6] reported interesting results from the cohort of the Gubbio study showing an association between protein intake and GFR. At baseline the higher is the protein intake, the higher is the level of GFR. However, after a mean follow-up of 12 ± 0.9 years, the association reverses: those having a higher protein intake at baseline had a faster decline in GFR. The interpretation of these data is not easy. At first glance, it seems that the high-protein intake causes hyperfiltration and thus a high GFR at the price of a faster deterioration of the renal function in the long term. Unfortunately, we do not know the renal reserve of the patients, especially of those with lower protein intake. Theoretically, the deterioration of renal function may be faster in the patients with higher protein intake at baseline just because they were already using their renal function reserve from the beginning and thus the deterioration of renal function was clearly evident and more detectable.

Another point to consider is that the level of deterioration of renal function was not impressive during the study follow-up, even in the patient population with the faster progression rate, with an estimated glomerular filtration rate decrease ranging between 1.24 mL/min/year in the group with the higher protein intake at baseline and 0.75 mL/min/year in those with a protein intake of <1 g/kg of ideal body weight. This is not very different from the physiological renal function deterioration of the healthy population (~1 mL/min/year).

With this rate of decline in GFR, a middle-aged person would need ~40 years before reaching end-stage renal disease. From the clinical point of view, it means that even a higher protein intake, as in this study [6], is not so important in causing a significant deterioration in renal function in the long term. However, we should avoid the mistake of misinterpreting the message of the study and claim that a high-protein intake is safe. Even if the rate of decline in renal function is minimal, there are other potential advantages in not being excessive with protein intake because proteins go together with salt, phosphate and acid uric and many other uraemic toxins. Phosphate and uric acid levels are recognized as factors affecting cardiovascular morbidity and mortality in the general population [11, 12]. According to the National Health and Nutrition Examination Survey III study, there is a clear relationship between a higher phosphate intake and a higher all-cause mortality risk in individuals who consumed >1400 mg/day [13]. Evidence from several studies have shown that high salt intake not only increases blood pressure but also plays a role in endothelial dysfunction, cardiovascular structure and function and cardiovascular morbidity and mortality in the general population [14].

History often repeats itself, and this is true also for nephrology. In recent years, RAS inhibitors are losing some of their appeal as nephroprotective drugs [15]. Today, the majority of CKD patients are older than 65 years and are affected by non-proteinuric nephropathies. In this often frail patient population, the risk of RAS inhibition may outweigh its benefit.
possible advantages of dual blocked have also received a significant stop following the publication of the Ongoing Telmisartan Alone and in Combination with Ramipril Trial first [16], and recently of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints [17] and the Veterans Affairs NEPHROpathy IN Diabetes Study [18].

Furthermore, in very frail and old patients, the start of dialysis raises several ethical and practical concerns [19]. In many instances, life expectancy and quality of life may be rather poor in elderly patients with CKD stage V and the survival advantage offered by dialysis is markedly reduced in those with severe co-morbidities. Hence, the idea of postponing the start of dialysis using a low-protein diet has gained new popularity. As in the 1960s, Italians were again those proposing the use of a low-protein diet. The DODE study is a randomized, controlled study to assess the non-inferiority of a vegan diet (35 kcal, 0.3 g/kg/day of proteins supplemented with keto-analougues, amino acids and vitamins) versus dialysis on survival in 112 patients older than 70 years and with a GFR of 5–7 mL/min [20]. After 1 year, the number of deaths was similar in the two groups but the patients on dialysis experienced a significantly higher hospitalization rate. Two-thirds of the patients in the diet group started dialysis because of either fluid overload or hyperkalaemia at a mean GFR of 4.3 ± 1.1 mL/min. It is worth mentioning that our centre was not able to contribute to study enrolment because at the same GFR level at which the patients receiving the vegan diet in the DODE study started dialysis, in our centre, the patients were still out of dialysis just following a controlled-protein diet without free-protein food. In the 1990s, we tried to postpone the need for thrice weekly haemodialysis by using an integrated diet dialysis programme of once weekly haemodialysis combined with a very low-protein diet in 69 CKD patients with a baseline GFR of 2.54 ± 0.94 mL/min [21]. Despite the fact that the patients entering this programme were well motivated and followed carefully, they developed a certain degree of malnutrition and depurative inadequacy in the long term. Altogether, a well-conducted low-protein diet may be an option in those patients with CKD stage V who are likely to receive little benefit from the dialysis programme or have a very short life expectancy. However, the risk of malnutrition is particularly high in the elderly population, especially in those with stage V CKD, and the very low-protein diet is safe only in the hands of multidisciplinary and well-motivated staff with the constant oversight of a specialized renal dietician.

Data from the MDRD study [7] showed that every effective reduction of 0.2 g/kg/day of protein intake can significantly improve not only serum urea but also phosphate and bicarbonate levels. Recently, the low-protein diet has gained new appeal as an important tool to decrease phosphorus and acid intake in the CKD population. Effectively, phosphorus is increasingly considered a primary player in possibly accelerating CKD progression [22] and favouring the development of secondary hyperparathyroidism and cardiovascular complications. More and more, it has become clear that controlling phosphate intake is extremely important in the management of mineral bone disease, given the large amount of phosphate in Western diets, which is often hidden in foods as an additive.

In 5 of 6 nephrectomy rats, CKD progression is mediated in part by metabolic acidosis through endothelin A receptors [23]; following oral alkali, kidney injury and endothelin-1 levels decreased [24]. Accordingly, a randomized clinical trial showed significant benefit of sodium bicarbonate compared with placebo on renal survival [25]. Similar benefits can also be obtained with a diet rich in vegetables and fruits [26].

Uric acid has also been proposed as one of the culprits of CKD progression, and uric acid-lowering therapy may retard the progression of CKD [27]. It is then possible that a low-protein diet, with a reduced uric acid content and an inhibitory effect of acid uric synthesis may be of benefit in CKD patients [28].

Finally, reduced salt intake is of primary importance in CKD patients, since it not only reduces volume overload and blood pressure values but also increases the anti-proteinuric effect of one RAS inhibitor [29, 30] to a higher extent than that of dual blockade [29]. This aspect is of particular importance, given that the European Medical Agency has recently advised against the use of dual blockade, particularly in patients with diabetes-related kidney problems [31].

To conclude, after decades we are still debating on the true clinical relevance of protein intake, particularly in CKD patients. A common sense approach seems wise: there is no reason why CKD patients should have a higher protein intake than that suggested by the Food and Drug Administration. A low salt and protein intake (just <1 g/kg/ideal body weight), selecting lower phosphate protein content, could be enough for avoiding the majority of CKD complications, favouring patient compliance without interfering too much with everyday life and not negatively impacting the nutritional balance.

(See related article by Cirillo et al. Protein intake and kidney function in the middle-age population: contrast between cross-sectional and longitudinal data. Nephrol Dial Transplant 2014; 29: 1733–1740.)

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