techniques, we hope to find concordance between the clinical and molecular events that occur in LN. Molecular characterization of renal lesions present in LN will provide clinicians the tools necessary to more accurately classify disease, predict outcomes and appropriately apply novel therapeutics.

CONFLICT OF INTEREST STATEMENT

None declared.


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Low-protein diets in chronic kidney disease: are we finally reaching a consensus?

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In the history of medical sciences, few topics have been the focus of so many clinical trials, reviews/speculation, conference proceedings (Figure 1) and discussions than the question of what constitutes an optimal protein intake for patients with kidney diseases. Indeed, clinical evaluations from 1869 plus experimental investigations from the 1930s concluded that excess dietary protein adversely affected the symptoms of patients or the survival of uraemic rats [1, 2]. Such reports led to creative efforts in the 1940s to design regimens like the egg-potato diet based on meals that were poor in the amount of proteins for patients with chronic kidney disease (CKD). The goal was to reduce uraemic symptoms because dialysis was not an imaginable treatment for patients with CKD. Besides lowering the levels of uraemic products, new benefits
of low-protein diets were rapidly uncovered. Experimentally, Brenner et al. [3] in the 1980s showed that dietary protein restriction was even found to slow the progression of experimental CKD. These new benefits were attributed to the hyperfiltration hypothesis and the future of patients with CKD was no longer considered the death knell associated with progressive CKD. Extensive studies identified that inhibitors of angiotensin-converting enzymes also corrected hyperfiltration and could reduce the loss of kidney function and this benefit was confirmed in clinical trials [4]. In contrast, clinical trials investigating the outcomes of restricting dietary protein (or whether spontaneous intake of proteins was reduced), were less convincing of a protective effect. This conclusion was responsible for an undeniable imbroglio and many reasons were proposed to explain the apparent discrepancy from animal studies. These reasons included methodological caveats (insufficiently powered trials with too few patients or trials of too short a duration), inadequate assessment of the primary outcomes (creatinine-based markers for estimating renal function), too small a difference between normal and reduced protein intakes when compared with experimental studies and difficulty in controlling the dietary intervention (i.e. overlap in protein intakes between the control and interventional groups of patients). Not surprisingly, the conclusion was that humans are not rats and that new methods of research into complex clinical problems may still be in its juvenile age. To counteract these limitations, meta-analyses were performed, providing an increase in statistical power so that the influence of dietary protein restriction on progression could be tested in a new fashion. With the new technique, a protective benefit of lowering protein intake in patients with various degrees of renal impairment was strongly suggested. Specifically, the number of renal ‘deaths’ (i.e. the number of patients who died or had to begin dialysis treatment) was reduced by 32% [5]. Although meta-analyses cannot be accepted as definitive proof of efficacy, these analyses have uncovered a higher level of evidence than most of the reported studies of this clinically important question.

What is the current biological and clinical evidence for beneficial effects of a low-protein intake in patients with CKD? There are at least three important issues. Firstly, it has been known for many decades, that the metabolism of protein generates waste products that accumulate in the body even in patients with early stages of CKD. For example, it was recently uncovered that P-cresyl-sulphate, a catabolic by-product of the amino acid, tyrosine, is at least in part responsible for the well-known insulin resistance that occurs in many patients even in early stages of CKD [6]. Secondly, increasing protein in the diet substantially increases the intake of phosphates, salt and the generation of acid. Each of these ions contribute to the uraemic syndrome: phosphate retention leads to hyperparathyroidism, dietary salt raises blood pressure and acid generation causes loss of muscle mass and bone and may even aggravate progression of CKD. For example, the ratio of dietary phosphorus to protein is ~1/0.013, so 100 g dietary protein contains 1300 mg phosphorus. This leads to a series of complicated, physiopathological cascades such as a rise in fibroblast-growth factor-23. The latter is reportedly a cardiac toxin [7]. Third, it has been reported that increases in dietary protein or in the salt content of the diet eliminate the beneficial effects of ACEi on the progression of CKD [8, 9].

What should be done about dietary protein? What level of dietary protein is nutritionally safe? These questions have been addressed in explorative studies of healthy adults and CKD patients. In both cases, the evidence indicates that an intake of 0.6 g protein/kg ideal body weight/day is sufficient to maintain body composition in most normal adults or patients with CKD, provided that proteins in the diet are of high biological value (e.g. 50% from animal source in order to include sufficient essential amino acids to support synthesis of proteins in the body) [10]. This amount of dietary protein can be reduced further to 0.3 g protein/kg ideal body weight/day if a ketoanalog supplement is added to dietary proteins as long as the amounts of essential amino acid skeletons are sufficient to synthesize body proteins [11, 12]. Obviously, the supplemented diets will reduce nitrogen intake but an adequate intake of essential amino acids will be achieved by transamination of ketoanalogos. It is important to underline that limiting the intake of animal proteins does prompt a superior nutritional profile because there will also be a reduced intake of phosphates and salt plus precursors of metabolic acidosis; there can also be a more beneficial intake of lipids [13, 14].

In this issue of NDT, Bellizzi et al. [15] have reported results of dietary manipulation in a cohort of Italian patients with CKD. Specifically, they retrospectively compared three groups of CKD patients: one was assigned a very low-protein diet (actual intake of 0.58 g protein/kg/day) supplemented with ketoanalogos (s-VLPD, n = 184) while another group from

FIGURE 1: The extensive literature on the low-protein diet issue in chronic kidney disease.
the same clinic was not treated with the s-VLPD diet and had a protein intake of 0.83 g/kg/day (n = 334). These patients were compared with results from a control group of CKD patients who had no intensive dietary follow-up; they began maintenance dialysis therapy according to patients throughout Italy (n = 9092). No information on protein intake was provided for this later group. The primary outcome of the investigation of Bellizzi et al. was survival of patients after they began renal replacement therapy. To improve the match of patients in those beginning dialysis, the results were subjected to a propensity score analysis. The survival curve shown in Figure 1 of their report [15] revealed that both experimental groups of patients had improved survival compared with results from the control group. In particular, no increase in mortality was observed in the s-VLPD group.

The question of survival during maintenance dialysis treatment is critically important to nephrologists, especially in patients who were matched to characteristics of adults of the same age. The conclusion is that pre-dialysis care obviously impacts mortality after patients start dialysis. This conclusion was challenged some months ago by Menon et al. [16] following a retrospective analysis of results gathered during the Modification of Diet in Renal Disease study. Menon et al. concluded that patients receiving an s-VLPD had a higher mortality rate compared with that of control patients who were enrolled to eat un-supplemented amounts of dietary protein. Flaws in this analysis and conclusions are reported by Bellizzi et al. in the present paper [15] as well as others who have treated patients with s-VLPD [17]. To address their conclusion in greater detail, Bellizzi et al. examined subgroups and found out that patients younger than 70 years and those without cardiovascular disease benefited from s-VLPD to a greater degree (P < 0.01). Notably, patients in this group had a longer exposure to s-VLPD before starting maintenance therapy [15]. We recognize that the post hoc nature of the analysis of Bellizzi has limitations; however, their use of a propensity score analysis helped to reduce biases. Certainly, this hypothesis should be explored further.

Have we reached a consensus? First, we believe the assiduous efforts of nephrologists around the world to search for a protective effect of reducing protein intake in CKD patients should be commended. Second, the beneficial effects of reducing the generation of uremic toxins are time-tested [1, 3] so the remaining concern is that with excessive reduction in dietary protein there would be a risk of protein wasting. Thanks to Bellizzi et al. [15] and others [18, 19], there is abundant information confirming that diets reduced in protein are nutritionally safe. Since they are superior (in terms of mortality) to no nutritional education or intervention in patient care, we suggest that guidelines for the pre-dialysis treatment of patients with CKD worldwide introduce efforts as outlined by Bellizzi et al. Finally, the cost-effectiveness of introducing this type of CKD care should be monitored by comparing outcomes achieved by maintenance dialysis [20].

CONFLICT OF INTEREST STATEMENT

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