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High-protein diet is bad for kidney health: unleashing the taboo

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How often have you been told to eat more protein and less carbohydrates to stay healthy? This is not an emerging food culture but rather a prevailing dogma in our society. Physicians, dietitians and other health care professionals tell us constantly about the advantages of a high-protein diet (HPD), such as losing weight rapidly, burning calories, diminishing appetite, preventing obesity, managing metabolic syndrome and treating diabetes. This contemporary creed has gone so far that we feel continuously pressured to eat more protein and less carbohydrates, including even less fruits and vegetables. We feel compelled to eat only the meat patty of the sandwich and leave behind the bun when eating in front of others, otherwise we may lose credibility among friends and peers. If somebody dares to recommend a 'low-protein diet' (LPD) or, even worse, to imply that 'HPD may cause harm', then it would be considered a serious aberration to health and a taboo.

Is high-protein dieting a biologically appropriate nutrition for human physiology? For some 10 000 years, since the end of the Paleolithic age until after World War II, mankind ate a low-energy diet not >2500 cal/day on average, with protein comprising <10–15% of the total energy [1]. In the 10-century-old agriculture era, the total protein intake of our ancestors was <1 g/kg body weight/day, most likely in the 0.6–0.8 g/kg/day range. Carbohydrates and plant-based fats provided >85% of the daily dietary energy intake. Obesity was never a problem and type 2 diabetes used to be a rare disease until recently, that is, as late as the 1960s. As postwar economic prosperity flourished across the globe in the 1970s and thereafter, increasingly more processed carbohydrates and more animal-based fats entered our daily diet. The worldwide pandemic of obesity and diabetes ensued, first in the developed countries, followed by the developing nations and emerging economies. No region on earth was spared from the ravages of overnutrition. To save ourselves from an obese and diabetic destiny, we accepted the emerging data suggesting that we can lose weight by eating more protein. Subsequently, high-protein regimens such as the Atkins, Zone, South Beach and Ketogenic diets emerged in which daily protein intake increased to 20–25% or more of the total daily energy intake. We are being told that getting plenty of protein is the revival of our hunter–gatherer ancestral spirit and it will help maintain our lean muscle and reduce fat mass. This trend has led to the ingestion of more meat and other animal-based foods, and the high-protein culture has emerged as the preferred, healthy and safe way of eating at the dawn of the 21st century.

Is HPD safe for kidney health or not? Evidence suggests that the ingestion of a high-protein meal leads to increased glomerular filtration rate (GFR), resulting in 'glomerular hyperfiltration' as a result of the amino acid surge, which leads to dilatation of the 'afferent' arteriole and increased intraglomerular pressure. Inversely, a lower intake of dietary protein leads to more constriction of the afferent arteriole, resulting in decreased intraglomerular pressure and lowered GFR, as shown in Figure 1. Hence LPD is recommended to those with chronic kidney disease (CKD) or at risk of CKD such as diabetic or obese patients with microalbuminuria and even those with a solitary kidney [2], given consistent data in both animal models and human studies of glomerular physiology. To that end, emerging data across individuals and populations suggest that glomerular hyperfiltration associated with a high-protein diet may lead to higher risk of *de novo* CKD or may accelerate progression of preexisting CKD. Whereas persons with healthy intact kidneys may not be affected by this harmful impact of HPD, those with limited nephron endowment and at risk of CKD may be more vulnerable, such as diabetic and obese persons, as well as those with reduced kidney reserve such as solitary kidney or earlier stages of CKD.

In this issue of the *Nephrology Dialysis Transplantation*, there are two studies that suggest the potential harm of high dietary protein intake (DPI) on kidney health across large populations. In the first study, Esmeijer *et al.* [3] analyzed dietary and kidney data from the Alpha Omega Cohort, which is a prospective study of 4837 Dutch patients ages 60–80 years with a prior history of myocardial infarction, after subjects took part in a clinical trial of low-dose omega-3 fatty acids [4]. Esmeijer *et al.* studied 2255 patients with available blood samples at baseline and after 41 months of follow-up and also examined dietary data from a biomarker-validated 203-item food frequency questionnaire, determining estimated GFR (eGFR) values using serum cystatin C and creatinine measures. Whereas the mean baseline eGFR was 79–82 mL/min/1.73 m^2, the investigators found that for each 0.1 g/kg ideal body weight per day (g/kg/

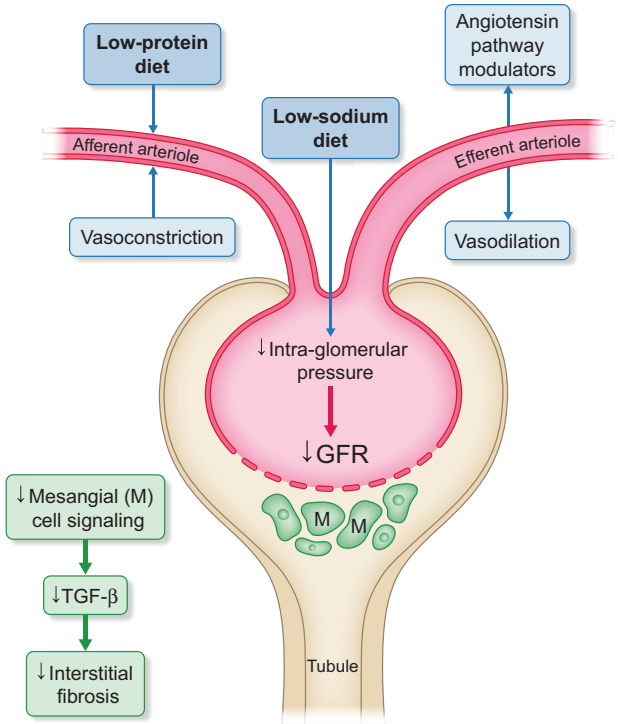

FIGURE 1: The effects of a low protein and low salt diet on the 'afferent' arteriole. (Adapted from Kalantar-Zadeh and Fouque [2].)

day) higher DPI, the annual GFR decline was accelerated by −0.12 mL/min/1.73 m^2/year. The restricted cubic spline analyses showed a strictly linear association such that the lower the DPI, the slower the rate of eGFR decline over time. Additional analyses showed that patients with a daily total protein intake ≥1.2 g/kg/day had a 2-fold faster annual kidney function decline compared with <0.8 g/kg/day, that is, a decline of −1.60 compared with −0.84 mL/min/1.73 m^2, respectively. These data did not find a superiority of plant- versus animal-based proteins, which may be related to the fact that two-thirds of the average ingested protein was animal-based, making differential analyses less reliable. It is important to note that persons with higher versus lower DPI >1.2 versus <0.8 g/kg/day had a higher versus lower eGFR of 82 ± 18 versus 75 ± 19 mL/min/1.73 m^2, respectively [3]. This makes sense, given that higher protein intake increases GFR in the short term, whereas it accelerates kidney function loss in the long term, although regression to the mean may not be fully excluded.

In the other study by Jhee *et al.* [5] in 9226 South Koreans from a large national contemporary (2001–14) cohort, the multivariate adjusted likelihood of kidney hyperfiltration was 3.5-fold higher in the highest versus lowest quartile of the DPI. As in the Dutch study by Esmeijer *et al.* [3], in the Korean study, the loss of renal function was faster across higher quartiles of DPI and the persons with the highest protein intake quartile exhibited 1.3-fold higher risk of a faster decline in kidney function over time. Jhee *et al.* [5] took two additional steps to substantiate their findings. First, they divided the cohort into those with and without kidney hyperfiltration and found that the faster drop in renal function happened only among those with preexisting hyperfiltration. Second, they reexamined their analyses in another, even larger, cohort of 40 113 people from the Korean National Health and Nutrition Examination Survey (2008–15) and found that the higher dietary protein quartile exhibited a higher risk of kidney hyperfiltration. Of note, Jhee *et al.* [5] defined kidney hyperfiltration as an eGFR with adjusted residuals greater than the 95th percentile and rapid renal function decline as a decline rate in eGFR >3 mL/min/1.73 m^2/year. These definitions are population-based arbitrary, and here again a regression to the mean can be a potential reason behind these findings. Nevertheless, the baseline association of renal hyperfiltration with higher protein intake makes sense (see Figure 1) and the faster decrease in eGFR in the latter group is biologically plausible.

There are other similar studies that have suggested the deleterious effects of an HPD on kidney health [6]. A recent study showed that among African Americans with diabetes, higher protein intake as a percentage of total energy intake was associated with a greater decline in eGFR [7]. A large cohort study of ∼1800 healthy adults [8] showed that the highest versus lowest tertile of low-carbohydrate HPD was associated with a 48% greater risk of incident CKD. As to what types of protein are

Table 1. Recommended protein intake for different stages of kidney disease

	Normal kidney function (eGFR >60[a]) and no proteinuria but at higher CKD risk, for example, diabetes, hypertension or solitary kidney[b]	Mild to moderate CKD (eGFR 30–<60[a]) without substantial proteinuria (<0.3 g/day)[c]	Advanced CKD (eGFR <30[a]) or any CKD with substantial proteinuria (>0.3 g/day)[c]	Transitioning to dialysis therapy with good RKF, including incremental dialysis preparation[c]	Prevalent dialysis therapy or any CKD stage with existing or imminent PEW[d]
Dietary protein (g/kg/day based on IBW[e])	<1.0 g/kg/day, increase proportion of plant-based proteins	<1.0 g/kg/day (consider 0.6–0.8 if eGFR <45 mL/min and fast progression)	0.6–0.8 g/kg/day including 50% HBV or <0.6 g/kg/day with the addition of EAA/KA	0.6–0.8 g/kg/day on nondialysis days (e.g. incremental dialysis) and >1.0 g/kg/day on dialysis days	1.2–1.4 g/kg/day, may require >1.5 g/kg/day if hypercatabolic

Adapted from Kalantar-Zadeh and Fouque [2].
[a]The unit for eGFR is mL/min/1.73 m^2 body surface area.
[b]Solitary kidney can be congenital, acquired or surgical, including status after donor or cancer nephrectomy.
[c]Prevalent renal transplant recipients are often in the two categories of eGFR 30–<60 mL/min and >30 mL/min or transitioning to dialysis and can be approached similarly.
[d]PEW according to the International Society of Renal Nutrition and Metabolism criteria [16].
[e]The IBW is to be used for kilograms in the denominator of all dietary recommendations, especially in persons with a body mass index >30 kg/m^2. IBW can be estimated in kilograms in males (= 50 kg + 2.3 kg for each inch >5 feet) and females (= 45.5 kg + 2.3 kg for each inch >5 feet).
RKF, residual kidney function; HBV, high biologic value protein; EAA, essential amino acids; KA, ketoacids (keto-analogues of amino acids).

safer for kidneys, that is, plant- versus animal-based proteins, there have been ongoing debates [9]. A recent study suggested that red and processed meats are associated with higher CKD risk, while nuts, low-fat dairy products and legumes appear to be protective against the development of CKD [10]. There are studies suggesting that lower intake of meat- and animal-based foods may be more beneficial to kidney and cardiovascular health, given that the intake of animal fat is associated with albuminuria and given that other components related to meats, such as choline and carnitine, are converted by gut flora into trimethylamine (TMA) and TMA *N*-oxide, which are associated with atherosclerosis and renal fibrosis [11].

As to whether an LPD with mostly to entirely plant-based protein is adequate [12], it is important to note that the Recommended Dietary Allowance (RDA) for protein is 0.8 g/kg/day and that the estimated requirement is likely even lower, that is, 0.6 g/kg/day, based on metabolic studies, provided adequate essential amino acids are ensured [2], whereas traditionally an LPD for CKD management is defined as daily protein in the 0.6–0.8 g/kg/day range [2]. However, most adults in Western societies eat 1.0–1.4 g/kg/day of protein [13]. Whereas most guidelines recommend that 10–15% of energy be derived from protein, which is consistent with the RDA of 0.8 g/kg/day of DPI, higher intakes of dietary protein, where protein intake may be as high as 20–25% or more of the total energy source, should not be prescribed to CKD patients or persons at high risk of CKD unless there are exceptional circumstances that would necessitate the intake of high amounts of protein for limited periods of time, such as temporary corrective management for protein–energy wasting (PEW) [2]. The recommended DPI for different stages of CKD are shown in Table 1 [2]. The target protein intake for CKD Stages 3B, 4 and 5 as well as those with substantial proteinuria is recommended to be 0.6–0.8 g/kg/day, whereas for persons without CKD but with a solitary kidney or at high risk of CKD, high protein intake >1.0 g/kg/day should be avoided. Indeed, a recent prospective observational study by Metzger *et al.* [14] showed that the lower the DPI, even lower than 0.6 g/kg/day, the slower the progression toward end-stage renal disease, implying that there may be no clear 'sweat spot' in the recommended range of low protein intake. However, it is important to note that in CKD patients, PEW, which is often heralded by a loss of appetite and unintentional reduction in food ingestion, including lowered protein intake, may be associated with worse CKD outcome, including faster CKD progression, as shown in a recent South Korean study [15]. This observational association is different from the causal impact of a proactively implemented LPD regimen on CKD progression. Hence, during a PEW episode, an LPD for CKD management should be temporarily halted (Table 1).

The studies by Jhee *et al.* [5] and Esmeijer *et al.* [3] should be qualified for their epidemiologic nature, given that the association does not equate to causality. The use of a food frequency questionnaire in both studies is another limitation, since these questionnaires tend to underestimate the average daily nutrient intake, although ranking subjects across their food intake such as in the form of quartiles of dietary protein is an effective remedy for the said shortcoming. Furthermore, glomerular hyperfiltration cannot be reliably detected by eGFR values. Notwithstanding these limitations, these studies suggest that a high DPI may have deleterious effects on kidney health in the general population, especially those with preexisting hyperfiltration or with other risk factors, such as a prior history of cardiovascular disease as was the case for the Alpha Omega study [3]. Given these and other data, it is time to unleash the taboo and make it loud and clear that a high-protein diet is not as safe as claimed, as it may compromise kidney health and result in a more rapid kidney function decline in individuals or populations at high risk of CKD. While more studies are needed to shed greater light, and while we expect that discussion will continue on this and other taboo topics [17], it is prudent to avoid recommending high-protein intake for weight loss in obese or diabetic patients or those with prior cardiovascular events or a solitary kidney if kidney health cannot be adequately protected.

CONFLICT OF INTEREST STATEMENT

None declared relevant to this article.

(See related articles by Jhee *et al.* High-protein diet with renal hyperfiltration is associated with rapid decline rate of renal function: a community-based prospective cohort study. *Nephrol Dial Transplant* 2020; 35: 98–106 and Esmeijer *et al.* Dietary protein intake and kidney function decline after myocardial infarction: the Alpha Omega Cohort. *Nephrol Dial Transplant* 2020; 35: 106–115)

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2019 Update in basic kidney research: microbiota in chronic kidney disease, controlling autoimmunity, kidney inflammation and modelling the glomerular filtration barrier

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Recently, NDT published a series of exciting articles in the basic kidney research domain.

In the April issue, the team of Lingyun Sun reported their studies on the therapeutic effects of human umbilical cord-derived mesenchymal stromal cells (UC-MSC) in MRL-Faslpr mice [1]. None of the available rodent models used to study systemic lupus erythematosus adequately mimics human lupus, but MRL-Faslpr mice are frequently used to study lupus nephritis because they develop lupus-like systemic autoimmunity with a robust polyclonal immune complex glomerulonephritis mimicking many morphological aspects of progressive lupus nephritis in humans. The authors isolated MSC from human umbilical cords and transplanted 1×10^6 cells into 6-month-old female MRL-Faslpr mice as a single tail vein injection. A similar number of human embryonic lung fibroblasts or vehicle was injected into mice of two control groups, respectively. All mice were sacrificed 2 months later. Mice transplanted with UC-MSC had lower circulating double-stranded DNA