Dietary Protein Restriction in the Management of Chronic Kidney Disease

a report by

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The number of patients with chronic kidney disease (CKD) – especially with diabetic nephropathy – is expected to grow significantly in the future.[1,2] CKD is associated with substantial morbidity and mortality, and the consequence of this emerging public health problem is considerable consumption of medical and financial resources. This epidemic has led to the development of therapeutic and management guidelines to improve overall health in patients with CKD, e.g. the Kidney Disease Outcomes Quality Initiative (KDOQI). Dietary management is a tried and true method of helping to maintain the health of CKD patients. In this article, we will discuss the metabolic effects of dietary protein and the essential role of dietary protein restriction in the management of patients with CKD.

The Metabolic Effects of Dietary Protein Intake

Similar to patients with liver disease or hereditary diseases of nitrogen metabolism, patients with CKD develop 'protein intolerance' when they eat too much dietary protein.[3] Dietary protein has multiple fates. First, the breakdown of dietary protein yields amino acids, which are required for the synthesis of new body protein stores. Second, protein digestion yields nitrogen-containing waste products, which must be excreted or they will accumulate to cause the symptoms of uraemia. These waste products include guanidines, aromatic/aliphatic amines and other compounds that exert toxic effects when they are present at a high level. Urea – the major nitrogen-containing metabolite arising from dietary protein – serves as a marker for the degree of accumulation of other toxins. Specifically, a high serum urea nitrogen (SUN) level is consistent with the accumulation of many other waste products.[4–6] When CKD patients eat protein-rich food they also accumulate other compounds, including phenols, uric acid, acids and phosphates.[7] For example, the biochemical parameters of 911 CKD patients followed with minimal dietary attention revealed that patients with a serum creatinine >5mg/dl had several abnormalities. Over 30% of the patients had severe acidosis (serum bicarbonate <15mmol/l), severe hyperphosphataemia (serum phosphate >7mg/dl) and severe azotaemia (blood urea nitrogen values >120mg/dl).[8] Collectively, the accumulation of these compounds is responsible for many of the harmful features seen with uraemia. A high-protein diet can also lead to hyperuricaemia, which not only increases the risk of gout but has also been implicated in the development of the metabolic syndrome, hypertension and, potentially, endothelial dysfunction with vascular disease.[9–12]

As long ago as 1931, Lyon and colleagues identified another problem associated with many uraemic symptoms: the accumulation of acids.[13] The development of metabolic acidosis leads to many hormonal abnormalities (including decreased action of thyroid hormone, an increase in parathyroid hormone (PTH), suppression of growth hormone responses and insulin resistance) plus disorders of bone metabolism.[14] Persistent metabolic acidosis also activates mechanisms that stimulate muscle–protein catabolism and cause negative protein balance.[14–16] Protein-rich diets can also lead to hyperphosphataemia that causes hyperparathyroidism. Even in the early stages of CKD, the presence of mild hyperphosphataemia is associated with an increase in mortality.[8,17] Moreover, hyperparathyroidism can develop when the creatinine clearance decreases below 80ml/min.[18] Even this can occur in the absence of a rise in serum phosphorus, but the pathogenesis still depends on the inability to excrete dietary phosphates causing a secondary increase in PTH, which raises phosphate excretion. The normal values of serum phosphorus in these patients reflects the serum values after an overnight fast plus the phosphaturic influence of PTH. These findings indicate that protein-rich diets have a detrimental metabolic effect in the earliest stages of kidney disease. Lastly, protein intake likely can have an adverse influence on the progression of the underlying kidney disease. For example, a high-protein diet can augment the degree of proteinuria in CKD patients, and this has been associated with worsening of the progression of CKD.[19] Taken as a whole, patients with CKD have 'protein intolerance', and a protein-rich diet can lead to various harmful metabolic effects, some occurring even in the early stages of kidney disease.

Dietary Protein Restriction in Chronic Kidney Disease

The World Health Organization (WHO) recommends that the minimal daily requirement (MDR) of dietary protein for normal adults is 0.6g protein/kg per ideal bodyweight (IBW). The recommended daily allowance is 0.8g protein/kg IBW. Note that the MDR produces a neutral nitrogen balance in all normal adults of different ethnic backgrounds,

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Table 1: Characteristics of Patients Treated with a Supplemented Very-low-protein Diet

Characteristics	Before VLPD[33]	With VLPD[33]	Minimal Diet Manipulation[8]
Patient number	165	165	Not available
Bodyweight (kg)	64.2±12.1	64.6±12.1	Not available
Body mass index (kg/m²)	22.4±3.3	22.5±3.4	Not available
Protein intake (g/kg/d)	0.86±0.22	0.48±0.13	Unrestricted
Serum creatinine (µm)	458±123	748±183	433–884
Serum urea nitrogen (mg/dl)	63.3±19.3	46.5±17.9	85±15
Serum bicarbonate (mM)	22.4±3.6	24.1±2.9	20.4±0.1
Serum albumin (g/l)	38.7±4.4	38.8±4.8	39.2±0.4
Parathyroid hormone (pg/ml)	211±49	206±193	Not available

Clinical and biological characteristics at the beginning and end of treatment by supplemented very-low-protein diet (VLPD) of the 165 patients (103 male, 62 female) after follow-up of 29.8±23.1 months.

and patients with uncomplicated CKD have the same MDR for protein.[20,21] Normally, dietary protein restriction results in the activation of two major metabolic pathways. First, the degradation of essential amino acids is decreased, leading to increased amino acid stores required for protein synthesis and subsequent neutral nitrogen balance.[22] When the suppression of amino acid degradation is insufficient to produce neutral nitrogen balance, a second mechanism is activated: namely, protein degradation is suppressed. Dietary protein restriction activates these same pathways in patients with uncomplicated CKD, or even those with the nephrotic syndrome.[23–25] Thus, patients with uncomplicated CKD have the same dietary protein requirements as normal adults, activate the same metabolic responses and are capable of maintaining protein stores when dietary protein is restricted. Consequently, an intake of protein above the recommended amount does not lead to increased protein stores and muscle growth because the excess protein will be converted into urea and other nitrogen-containing waste products that produce uraemic symptoms.

The benefits of dietary protein restriction for patients with CKD were established over 100 years ago. In 1869, Beale and colleagues showed that the uraemic symptoms in patients with kidney failure were ameliorated by reducing foods rich in protein.[26] The benefits of dietary protein restriction are multifactorial. First, restricting protein in the diet provides favourable metabolic parameters. The typical biochemical profile (acidaemia, hyperphosphataemia, azotaemia) seen in CKD patients who receive minimal attention to their diet is not typically seen when proper dietary counselling is emphasised. Moreover, dietary protein restriction has been shown to improve insulin resistance and osteodystrophy.[27–30] Patients with CKD (with an average glomular filtration rate (GFR) of 18ml/min) were given a protein-restrictive diet along with amino acid analogue supplements, and were found to maintain a neutral nitrogen balance without the development of acidaemia or hyperphosphataemia.[31] Walser and Hill evaluated 76 patients with CKD (GFR <15ml/min) and prescribed a low-protein diet. During the course of treatment (median time one year) there was no change in the average bodyweight, and serum HCO_{3^-}, phosphorus and albumin levels remained well controlled.[32] Reports by Aparicio and colleagues from France have yielded similar outcomes. They studied 239 CKD patients followed over a two-year period. Serum albumin was maintained (average albumin was 3.9g/dl), acidaemia was controlled (average serum HCO_{3^-} was 24mM) and, despite protein restriction, there was no decline in weight or body mass index (BMI) (see *Table 1*).[33]

Patients from the National Institutes of Health (NIH)-sponsored Modification of Diet in Renal Disease (MDRD) study who were assigned to low-protein diets also maintained acceptable nutritional parameters.[34] Interestingly, a study by Bellizzi and colleagues revealed that protein-restricted diets are associated with improved blood pressure control. They evaluated CKD patients (average GFR <20ml/min) who were given a low-protein diet supplemented with ketoanalogs of amino acids and found a significant decrease in mean blood pressure (103±11–95±7mmHg) over six months compared with controls. There was also a decrease in the average number of antihypertensive medications used.[35] We emphasise the importance of these data, given the detrimental effect of hypertension on the progression of CKD.

Second, protein-restricted diets generally improve uraemic symptoms and, therefore, offer the possibility of delaying initiation of renal replacement therapy.[36–41] This occurs because most uraemic symptoms are dependent on the accumulation of nitrogenous waste products and correlated with SUN, and these problems can be limited by protein restriction.[37] For example, the MDRD study showed that a lower protein intake delayed the need for dialysis therapy by decreasing the rise in SUN and the occurrence of uraemic symptoms, despite having higher serum creatinine levels and lower GFR compared with patients with a higher protein intake.[42] Reports of long-term therapy indicate that dietary protein restriction can postpone the need for dialysis therapy by one year or more in patients with a typical progression rate of 0.3ml/min/month.[43,44] Walser and Hill showed in a study of patients with end-stage kidney disease (ESKD) (GFR <10ml/min in non-diabetics and <15ml/min in diabetics) were safely managed with a supplemented low-protein diet for a median of one year before the initiation of dialysis therapy.[32] These findings are substantial given the high morbidity/mortality and costs associated with dialysis, not to mention the lack of readily available dialysis in many parts of the world.

When the suppression of amino acid degradation is insufficient to produce neutral nitrogen balance, a second mechanism is activated: namely, protein degradation is suppressed.

Finally, a low-protein diet may limit the progression of kidney failure in CKD patients. The largest study to address this question was the MDRD study. It did not demonstrate a significant decrease in the loss of GFR in patients randomly assigned to a prescribed low-protein diet.[43] However, a sub-analysis of subjects participating in the MDRD study showed that those who adhered to a lower-protein diet (0.2g/kg/day lower) achieved a 1.15ml/min/year slower mean decline in GFR and a 41% increase in time to dialysis or death.[42] Other problems with the design of the MDRD study include an average follow-up of only 2.2 years and the unregulated use of angiotensin-converting enzyme inhibitors (ACEi). The MDRD study excluded patients with insulin-dependent diabetes mellitus (IDDM), but an earlier report by Zeller and colleagues found that protein restriction in patients with IDDM slowed the decline in iothalamate-measured GFR.[45] A meta-analysis of 1,524 non-diabetic adults showed

Table 2: Specific Dietary Requirements for Patients with Chronic Kidney Disease[3]

Patients	Minimum Protein Requirements	Notes
Normal adults	0.6g of protein/kg per day	30–35kcal/kg per day needed to utilise dietary protein efficiently
Those with uncomplicated chronic kidney disease (CKD)		Adjustments for specific problems (diabetes, hyperphosphataemia)
CKD patients with muscle mass loss	0.8g of protein/kg per day	Ensure 30–35kcal/kg per day
CKD patients with proteinuria	<0.8g of protein/kg per day plus 1g protein per gram of proteinuria	This is the maximum needed

that lowering protein intake in patients with CKD reduced the occurrence of renal death by 31% compared with patients receiving higher-protein diets.[46] The benefits of protein-restricted diets on independent predictors of kidney failure are highly suggestive of a beneficial effect. For example, hypertension and proteinuria are two major factors associated with the progressive loss of kidney function.[47]

> Although diet implementation can increase therapy costs, the costs associated with dietary counselling are lower than the costs of dialysis therapy.

Protein restriction has been shown to decrease the degree of proteinuria[19,48] and it can suppress proteinuria synergistically with ACEi.[49] Protein-restricted diets have also been shown to reduce intra-renal and systemic hypertension.[35,50] Further studies delineating the effects of protein restriction on the progression of CKD are warranted. Regardless of the limitations of the MDRD study and other reports, we conclude that the benefit of a low-protein diet on the progression of kidney failure is not yet proved.

Barriers to Protein-restricted Diet Implementation

Implementation of a low-protein diet in the management of CKD is often neglected and its value in the planning care of CKD patients is underestimated.[51] There are a significant number of 'perceived barriers' to implementing dietary strategies, but none should supersede over 100 years of experience with low-protein diets in the management of CKD. The first impediment to using dietary strategies is the conclusions of the MDRD study that a low-protein diet does not alter the progression of kidney failure. As noted, this study had significant limitations and it does not address the the other major beneficial metabolic effects of dietary-protein restriction. Second, dietary counselling as a part of the management of patients is severely underused,[52] perhaps due to cost or the lack of availability of such services. However, in the US the cost of dietary counselling is reimbursed by Medicare. *Table 2* outlines the dietary requirements for patients with CKD. The MDR of protein intake and calories in normal adults or those with uncomplicated CKD is 0.6g of protein/kg/d and 30–35kcal/kg/d.[3] The recommended amount of protein intake rises up to 0.8g of protein/kg/d when there are concurrent illnesses, use of steroid therapy or proteinuria above 5g protein/d.

Another perceived barrier to dietary strategies is the notion that CKD patients are unwilling to adhere to the diet. A change in life-long dietary habits is difficult, but compliance with any therapeutic intervention can be difficult. A skilled dietician can formulate a balanced diet that is acceptable to most patients, and even in a gastronomic country such as France a report by Aparicio et al. showed that nearly two-thirds of French patients with CKD complied with low-protein diets.[53] Kanazawa and colleagues reported that there was no correlation between dietary protein restriction and the health-related quality of life responses of patients. They also noted that an appropriate social support structure is associated with better patient compliance.[54] Although diet implementation can increase therapy costs, the costs associated with dietary counselling are lower than the costs of dialysis therapy.[55]

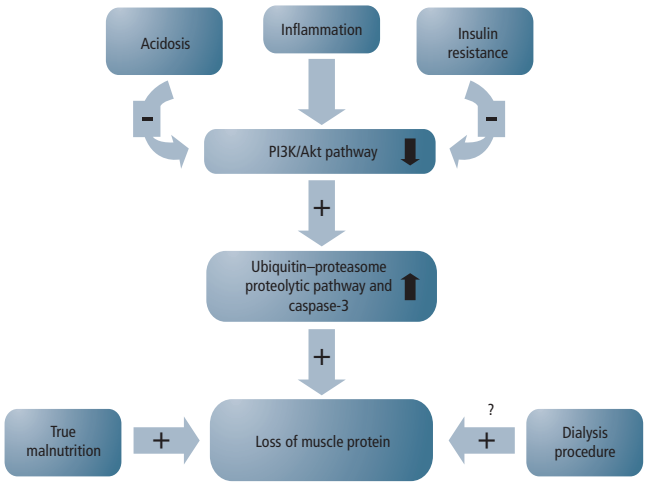
Low-protein Diets and 'Malnutrition'

Many nephrologists and other physicians are reluctant to implement low-protein diets because they are concerned that dietary protein restriction is unsafe and/or will lead to diminished muscle mass and 'malnutrition'. In addressing this concern, investigators have shown that the use of low-protein diets to treat CKD patients has no effect on their survival after the start of dialysis.[56,57] We concur that physicians should be concerned about patients who are losing muscle mass and serum proteins, but several reports document that these problems have little to do with dietary protein restriction or protein intake. In fact, the efficacy of low-protein diets in maintaining nutrition has been well documented.[31,34,40,58] This occurs because a well-planned low-protein diet will provide an adequate intake of energy, and because CKD patients without complicating illnesses will activate the same protective/adaptive mechanisms as normal adults.[23–25] For these reasons, patients with uncomplicated CKD have the same protein requirements as normal adults.

> The weight loss, fatigue and muscle wasting seen in chronic kidney disease (CKD) have often been misdiagnosed as malnutrition, but it is the metabolic consequences of CKD, not dietary insufficiency, that cause muscle wasting in CKD patients.

The term malnutrition deserves special mention. It is defined as abnormalities caused by insufficient caloric intake or imbalanced diet, so malnutrition should be corrected by increased dietary protein/caloric intake. However, CKD-induced muscle wasting is a catabolic process that occurs because cellular pathways are

Figure 1: The Phosphatidylinositol 3-kinase/Akt Pathway



Chronic kidney disease (CKD) and other catabolic conditions activate a common proteolytic pathway leading to muscle protein catabolism. Malnutrition rarely leads to a loss of lean body mass in CKD. The underlying mechanism of how the dialysis procedure causes muscle atrophy is unclear.

activated independently of dietary intake. Unfortunately, the erroneous term of malnutrition is used for two reasons: there is concern that hypoalbuminaemia is due to an insufficient protein intake; and certain clinical features of CKD mimic the problems associated with malnutrition.

For example, hypoalbuminaemia is commonly seen in patients with CKD, especially those on dialysis. However, a decrease in serum albumin is likely due to the presence of circulating cytokines and inflammation, not from an inadequate diet (i.e. malnutrition).[59] The weight loss, fatigue and muscle wasting seen in CKD have often been misdiagnosed as malnutrition, but it is the metabolic consequences of CKD, not dietary insufficiency, that cause muscle wasting in CKD patients.[60,61] Increasing protein intake in such patients will only lead to the detrimental metabolic consequences of CKD, rather than increasing muscle mass.

Specifically, increasing protein intake can lead to the development of acidosis, which has been shown to accelerate the destruction of muscle protein through activation of the ubiquitin–proteasome proteolytic (UPP) system, in conjunction with caspase-3.[62] The UPP has been identified as the proteolytic system that causes muscle protein catabolism in a number of catabolic states, including burns and traumatic injury.[63] Metabolic acidosis has been demonstrated to cause negative nitrogen balance and a loss of protein stores.[62] Correcting acidosis can suppress the UPP and lead to an increase in bodyweight.[61,62]

A major consequence of CKD is insulin resistance, and defects in insulin and insulin-like growth factor (IGF-1) signalling will activate muscle breakdown. The mechanism involves suppression of the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, leading to activation of caspase-3 and UPP. This pathway is suppressed in the muscle of experimental models of uraemia/CKD, diabetes mellitus and other catabolic conditions (see *Figure 1*), suggesting that the suppression of the PI3K/Akt pathway is the trigger for the muscle protein degradation and muscle atrophy that occurs in uraemia, diabetes mellitus and other conditions associated with insulin resistance.[62,64–67] Besides these problems, the dialysis procedure *per se* can stimulate muscle protein catabolism. Interestingly, the negative protein balance stimulated by the dialysis procedure is transiently corrected by intra-dialytic paranteral nutrition (IDPN), but the benefits are not sustained and net muscle catabolism re-appears when IDPN is discontinued even after the dialysis procedure has finished.[68–70] These findings demonstrate that the dialysis procedure stimulates muscle catabolism through mechanisms not yet understood.

We do not dismiss the possibility that CKD patients can develop true malnutrition because CKD can induce a decrease in appetite, especially when the SUN is high and/or with a large numbers of medicines. In the case of uraemia, it is ironic that the implementation of a low-protein diet may decrease the levels of retained uraemic products and this, in turn, would improve a patient's appetite. The cause of anorexia is complex, however, because there is evidence for circulating factors in CKD that act via the central nervous system to decrease appetite.[71] For this reason, the protein and caloric intakes of patients with CKD should be regularly monitored. If intake is adequate, the term malnutrition should be used with caution and other causes for muscle wasting should be sought, including the activation of proteolytic cellular pathways in muscle.

For over a century, the implementation of a protein-restricted diet has been shown to yield improvements in blood pressure control, uraemic symptoms and the harmful metabolic profile seen with advanced kidney failure.

Conclusion

The medical community must use all safe therapeutic strategies to improve the overall health of CKD patients, slow the progression of their renal insufficiency and stall the need for renal replacement therapy. Dietary management is an integral strategy in managing patients with CKD. For over a century, the implementation of a protein-restricted diet has been shown to yield improvements in blood pressure control, uraemic symptoms and the harmful metabolic profile seen with advanced kidney failure. There are suggestive results indicating that low-protein diets may slow the progression of kidney failure in some subjects. Any therapeutic intervention that forces a significant change in patient lifestyle may be met with resistance and therapy non-compliance. Low-protein diets are no different, but several studies have shown that a well-designed diet in conjunction with a strong dietary counselling programme and support structure are acceptable and tolerated by patients. More importantly, a protein-restricted diet is safe and does not lead to diminished muscle mass, fatigue or malnutrition, as some would suspect. The term malnutrition is used erroneously when describing these findings in patients with CKD. In fact, more recent experimental data show that the muscle atrophy and decreased protein stores associated with CKD are due to activation of proteolytic pathways and not to diminished caloric/protein intake. More studies are necessary to reveal other pathways associated with the anorexia of CKD or dialysis-related muscle catabolism. ■

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