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EPIDEMIOLOGY OF DIETARY NUTRIENT INTAKE IN ESRD

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Abstract

Protein-energy wasting (PEW) is one of the strongest risk factors of adverse outcomes in patients with chronic kidney disease (CKD) including those with end stage renal disease (ESRD) who undergo maintenance dialysis treatment. One important determinant of PEW in this patient population is an inadequate amount of protein and energy intake. Compounding the problem are the many qualitative nutritional deficiencies that arise because of the altered dietary habits of dialysis patients. Many of these alterations are iatrogenically induced, and albeit well intentioned, they could induce unintended harmful effects. In order to determine the best possible diet in ESRD patients, one must first understand the complex interplay between the quantity and quality of nutrient intake in these patients, and their impact on relevant clinical outcomes. We review available studies examining the association of nutritional intake with clinical outcomes in ESRD, stressing the complicated and often difficult-to-study interrelationship between quantitative and qualitative aspects of nutrient intake in nutritional epidemiology. The currently recommended higher protein intake of 1.2 g/kg/day may be associated with a higher phosphorus and potassium burden and with worsening hyperphosphatemia and hyperkalemia, whereas dietary control of phosphorus and potassium by restricting protein intake may increase the risk of PEW. We assess the relevance of associative studies by examining the biologic plausibility of underlying mechanisms of action and emphasize areas in need of further research.

Patients with end stage renal disease (ESRD) on dialysis experience exceptionally high mortality rates, mainly from causes related to cardiovascular disease (CVD) and infections.(1) Multiple novel risk factors have been invoked to explain the large excess mortality seen in ESRD patients, but measures of nutritional status have invariably emerged as some of the strongest predicators of adverse outcomes in this patient population.(2–9)

In order to alleviate the nomenclatural confusion arising from this complexity an expert panel has recently recommended the use of the term *protein-energy wasting* (PEW) to incorporate all the different aspects of malnutrition and other metabolic or nutritional derangements such as inflammation in patients with CKD.(10) Based on this definition a diagnosis of PEW can be made by using the following criteria: (1) biochemical measures (serum albumin, prealbumin, transferrin and cholesterol); (2) measures of body mass (body mass index [BMI], unintentional weight loss and total body fat), (3) measures of muscle mass (total muscle mass, mid-arm muscle circumference and creatinine appearance); (4) measures of dietary intake (dietary protein and energy intake) and (5) integrative nutritional

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scoring systems (subjective global assessment of nutrition and malnutrition-inflammation score).

The impact of PEW on outcomes is considered to be complex, and in spite of the strong associations with mortality it remains unclear if some or all aspects of it are a direct cause of the poor outcomes, or if they are merely surrogate markers of other clinical conditions portending a poor survival.(11) Because of this complexity the various aspects of PEW have to be carefully studied in order to determine which, if any of them could be considered as truly causally related to adverse outcomes, and to thus determine which of them should be considered as targets of interventional clinical trials. Of the five major PEW criteria nutrient intake is most difficult to study, as the direct assessment of what and how much a person ingests over extended periods of time can only be feasibly done in small numbers of subjects and under carefully controlled circumstances. To bypass such impracticalities the use of surrogate markers of nutrient intake has become wide spread in clinical practice and has also allowed for the studying of this parameter on a broader scale in research studies.

We have reviewed epidemiological aspects of nutrient intake in ESRD patients, focusing on observational studies to describe the outcomes associated with deficiencies in nutritional intake in this patient population.

Nutrient intake in ESRD

The ingestion of food is a basic activity that is meant to provide the body with macro- and micronutrients needed in order to maintain tissue growth and structure and to provide fuel for energy-requiring processes. Anorexia-induced inadequate nutrient intake is an important cause of malnutrition in CKD and ESRD patients,(12–16) and a decline in protein and calorie intake becomes gradually manifest typically once the glomerular filtration rate declines to approximately <25–38 ml/min.(15) The causes of anorexia in CKD and ESRD are multiple.(17) The retention of uremic toxins and various comorbid conditions can lead to lowered appetite and a decrease in protein and energy intake, which is often compounded by the ill-advised imposition of various dietary restrictions.

Complicating the problem is the concomitant increase in protein and energy requirements in advanced CKD and ESRD due to the combined catabolism-inducing effects of dialytic therapies and various metabolic alterations such as metabolic acidosis. In order to maintain an even or positive nitrogen balance dialysis patients are advised to ingest a daily amount of protein of approximately 1.1–1.3 g/kg/day (18–21) and a daily amount of energy of approximately 35 kcal/kg/day.(22) In contrasting to these ideal levels derived from experimental studies, the actual protein intake of patients receiving maintenance hemodialysis (MHD) or peritoneal dialysis (PD) appears to be approximately 0.95–1.0 g/kg/day(12–14;16;23) and the actual energy intake is approximately 23–28 kcal/kg/day,(13;14;16) suggesting an inadequate average protein and energy intake in dialysis patients. Such deficient intake, be it due to diminished appetite or other pathophysiological or psychosocial constellations, can be causally linked to the development of PEW. Nevertheless, it remains unclear to what extent the resultant lower-than-ideal protein and/or energy intake can be causally linked to increased mortality and morbidity.

Outcomes associated with quantitative deficiencies in nutrient intake

Due to the difficulties in obtaining direct information about protein and energy intake, there is a paucity of data about the outcomes associated with these variables. Anorexia, a major reason for the low nutrient intake in ESRD has been associated with 4-times higher risk of death and with increased morbidity in a study of 344 maintenance hemodialysis (MHD) patients in the US(24); these findings were recently replicated by a similar study in 233

European MHD patients (25)(Table 1). However, reduced appetite can only be considered an indirect measure of dietary nutrient intake. Studies examining risks associated with dietary protein and/or calorie intake obtained from diet diaries have been few in number, small in size and failed to provide conclusive evidence on the risks associated with these parameters (Table 1).(26;27) Evidence from these studies needs to be interpreted with caution as their small size makes these studies susceptible to type II statistical errors.

An indirect way to assess dietary protein intake is by measuring urinary urea appearance, assuming that the amount of excreted urea in urine is mainly determined by the amount of dietary protein intake.(28;29) A large observational study of 5,059 incident MHD patients examined the association between total dietary protein intake (calculated from urine urea nitrogen reported on Medicare Form 2728) and mortality, and found a significant association between lower total protein intake and increased mortality (Table 1).(30) This study also highlighted the difficulties in examining the impact of the normalized amount of protein intake (defined as total protein intake divided by body weight), which is a reflection not only of protein intake but also of the various other conditions affecting body weight. In spite of the significant association between lower total protein intake and higher mortality this study found that the association between normalized protein intake and mortality was in fact reversed (lower normalized protein intake was associated with lower mortality).(30)

The advent of urea kinetic modeling in dialysis patients has made it possible, albeit with certain limitations, to indirectly assess on a large scale daily protein intake, expressed as normalized protein nitrogen appearance (nPNA, also known as normalized protein catabolic rate or nPCR). Two important conditions have to be met for the validity of nPNA: the metabolic stability of the studied individual (not being overtly catabolic or anabolic) and his/her closed status (no urinary loss of urea). Stable maintenance dialysis patients with minimal residual urine usually meet these criteria.

Data gathered from large clinical trials and especially from the databases of large independent dialysis chains has allowed for large scale assessment of outcomes associated with estimates of dietary protein intake. Such studies have invariably linked a lower nPCR to higher mortality and morbidity in a variety of patient populations (Table 1).(30–39) The largest such study examined 53,933 MHD patients receiving chronic dialysis between 2001 and 2003.(38) In this study, patients with time-varying nPNA of 1.0–1.4 g/kg/day experienced the lowest mortality rates. Interestingly, higher mortality was associated both with nPNA levels of <1.0 g/kg/day and >1.4 g/kg/day (Figure 1). Possible explanations for the higher mortality seen in those with the highest nPNA levels were outcome-associated confounding effects of body weight in smaller patients, the toxic effect of a very high-protein diet, a highly catabolic state caused by inflammation, or residual confounding by a behavior pattern of poor compliance in those with the highest levels of protein intake.

Another interesting finding of this study was a strong association between a decrease in nPNA over time and increased mortality, and a slightly less pronounced, but still significant association between an increase in nPNA over time and decreased mortality. As the reasons for the temporal changes in nPNA were not evident in this observational study these latter findings require experimental confirmation before one can conclude that an increase in protein intake can cause improved survival.

A significant drawback of the evidence derived from observational studies assessing associations between nPNA and outcomes is the imperfect nature of this variable as a marker of protein intake. Measured nPNA incorporates the estimated permeability of the dialyzer and is also affected by the accuracy of measured blood and dialysate flow rates.(36) Furthermore, as protein intake fluctuates from day to day due to changes in intake and

catabolism,(40) the monthly assessment of nPNA may not be an accurate reflection of true average protein intake, especially if the patient's protein metabolism is not in equilibrium. Further inaccuracies are incurred because of difficulties with assessment of the volume of distribution of urea in obese, malnourished, or edematous patients,(41) and because of overestimation of nPNA caused by delayed equilibrium with subsequent urea rebound after dialysis, which can vary according to patient and dialysis procedure characteristics.(42)

In summary, the evidence from observational studies suggests a robust association between lower nPNA (nPCR) and adverse outcomes in ESRD patients. Much less data are available on outcomes associated with actual protein and energy intake. Self-reported appetite appears to be a very robust predictor of mortality and morbidity, but data on this variable are also scant.

Consequences of qualitative deficiencies in nutritional intake

The aforementioned studies of dietary protein and energy intake described associations with outcomes related to the amount of the studied nutritional characteristics. It is important to recognize, though that in addition to the amount of protein and energy intake there are several other nutritional characteristics that involve the *quality*, rather than the *quantity* of consumed food which could affect the health and well being of patients with ESRD. These include deficiencies in various micronutrients (vitamins and trace elements) and imbalances of macronutrients stemming from incorrect dietary habits or prescriptions.

Deficiencies in many micronutrients may be linked to PEW-related cardiovascular and infectious mortality in ESRD.(11) The lack of arginine, glutamine, zinc, vitamin B6 (pyridoxine), vitamin C, folic acid and levocarnitine may all adversely affect various aspects of immune function and could be instrumental in the high infectious mortality seen in ESRD.(43–50) Cardiovascular outcomes may also be affected by diet characteristics, as an atherogenic diet is imposed upon most individuals with CKD.(51;52) Due to the difficulty of maintaining adequate energy intake on low protein, low potassium diets, patients may tend to rely more on food sources containing high amounts of atherogenic fat. A recent comparative study based on food frequency questionnaires indicated that MHD patients consume significantly lower amounts of potassium, dietary fiber, vitamin C and certain cardioprotective carotenoids.(52) Such patients appear to have a lower intake of dietary nutrients including minerals and vitamins, but a higher intake of cholesterol. Most advanced CKD patients are exposed to traditional restrictions in potassium intake, which may result in reduced fruit and vegetable intake, leaving meat and other high fat foods as the main sources of calories.(52)

In spite of the plausibility of the aforementioned mechanisms of action, the long term consequences of the many qualitative nutritional deficiencies involving micronutrients and trace elements in ESRD remain unknown. Large scale observational studies have not been conducted to determine outcomes associated with the individual deficiencies, and clinical trials involving the supplementation of such nutritional elements are also lacking.

The desire to achieve adequate quantities of protein and energy intake could in itself have unintended consequences if not accompanied by careful planning and supervision to assure that the macronutrient content of the patients' food is appropriate. Higher protein intake can result in increased potassium and phosphorus intake, with resultant increase in the serum levels of these elements. While higher serum levels of both potassium and phosphorus have been associated with adverse outcomes in MHD patients,(53;54) there is a paucity of data regarding the direct association between the dietary intake of these elements and clinical outcomes. Recent results based on data obtained from food frequency questionnaires in 224 MHD patients enrolled in the Nutritional and Inflammatory Evaluation (NIED) study have

indicated that higher amounts of both potassium and phosphorus intake are associated with increased all-cause mortality even after adjustments for markers of nutritional status including protein intake (K Kalantar-Zadeh, personal communication).

Another recent study using food frequency questionnaires in 160 kidney transplant recipients indicated that a Mediterranean dietary pattern is associated with a reduced risk of metabolic syndrome in these patients.(55) The long term outcomes of such a diet were not examined in this study and the relevance of these findings to MHD patients is questionable.

The above results underscore a dilemma posed by the interplay between qualitative and quantitative changes of diet in ESRD, where a (desirable) increase in the quantity of protein and energy can result in the (undesirable) increase in the intake of several potentially harmful elements. This is perhaps best exemplified by changes in dietary prescriptions that concomitantly affect protein and phosphorus intake. On the one hand dietary restrictions meant to alleviate increases in serum phosphorus may result in diminished dietary protein intake and could consequently cause or worsen PEW; on the other hand prescriptions meant to increase dietary protein intake in patients with existing PEW could lead to higher phosphorus intake and worsening hyperphosphatemia.

The potential effects of such dietary measures were highlighted in a recent epidemiologic study of 30,075 prevalent MHD patients,(56) which described the risk of death associated with concomitant changes over 6 months in serum phosphorus and protein intake (measured by nPNA). When examined individually both lower protein intake (Figure 2) and a decrease in protein intake over 6 months (Figure 3) were associated with higher mortality in this study. Similar analyses for serum phosphorus indicated that higher serum phosphorus and an increase in serum phosphorus over 6 months were also individually associated with higher mortality. When the two variables (protein intake and serum phosphorus) were examined concomitantly, the best outcomes were found in patients whose decrease in serum phosphorus was accompanied by increased protein intake and worst did those whose phosphorus and nPNA both decreased. Higher mortality was seen in patients whose serum phosphorus and nPNA both increased over 6 months, followed by those whose phosphorus increased but whose nPNA decreased. A limitation of this study was that the reasons for the changes in serum phosphorus and nPNA were unknown and may have been only partially related to dietary intake.

While the foregoing results have to be interpreted with caution, they could indicate that the risk of controlling serum phosphorus by restricting dietary protein intake may outweigh the benefit of controlled serum phosphorus and may lead to greater mortality. Clinical trials will be needed to assess the impact of phosphorus-control measures with neutral or positive impact on protein intake, such as the use of phosphate binders or the implementation of dietary restriction through curbing non-protein containing sources of phosphorus.

Conclusions

Deficiencies in protein and energy intake are an important determinant of PEW in ESRD, and are associated with significantly higher mortality and morbidity. Qualitative dietary changes could add to the burden of diet-related morbidity and mortality through complex mechanisms involving cardiovascular and immunologic mechanisms, but their role in such outcomes is less well defined. Epidemiological studies suggest that interventions targeting an optimal protein and energy intake could have a substantial benefit in ESRD patients. Such interventions will also have to address the complex qualitative changes brought about by increased protein and energy intake. Due to the complex nature of PEW it is also possible that deficient nutritional intake is a surrogate marker of more advanced morbid conditions,

without a direct causal effect on adverse outcomes. A causal effect of nutritional intake on outcomes can only be proven by prospective randomized clinical trials. Due to the significant impact of PEW on mortality in ESRD such trials are eagerly awaited.

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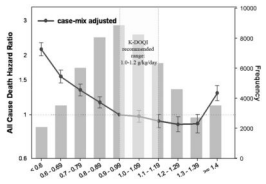

Figure 1.
Case-mix adjusted hazard ratios for all-cause death associated with various levels of normalized protein nitrogen appearance in 53,933 maintenance hemodialysis patients receiving chronic dialysis between 2001 and 2003. Based on data from Reference 38.

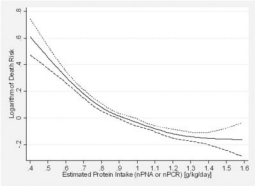

Figure 2.
Multivariable-adjusted hazard ratios for all-cause mortality over a 3 year observation period associated with baseline levels of dietary protein intake (represented by the normalized protein equivalent of total nitrogen appearance) in 30,075 prevalent maintenance hemodialysis patients. Adapted from Reference 56, with permission.

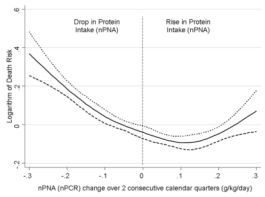

Figure 3.

Multivariable-adjusted hazard ratios for all-cause mortality over a 3 year observation period associated with changes in levels of dietary protein intake (represented by the normalized protein equivalent of total nitrogen appearance) over a six month time period in 30,075 prevalent maintenance hemodialysis patients. Adapted from Reference 56, with permission.

Table 1

Observational studies examining associations between the amount of dietary protein or calorie intake and clinical outcomes in patients with end stage renal disease on maintenance dialysis therapy.

Study	Patient population	Predictor	Results	Comment
Acchiardo et al, 1983(31)	N=120, MHD	PCR and pre-dialysis BUN	Higher morbidity and mortality associated with lower PCR and pre-dialysis BUN.	Exclusively non-diabetic patients.
Harter, 1983(35)	N=160, MHD	PCR	Increased treatment (dialysis) failure in group with lower PCR.	Randomized controlled trial of dialysis dose (National Cooperative Dialysis Study).
Teehan et al, 1990(37)	N=51, CAPD	PCR	Increase in hospitalization associated with lower PCR.	Single center study.
Blake et al, 1991(33)	N=76, CAPD	nPCR	No association between nPCR and mortality.	None of the components of the urea kinetic model correlated with outcomes.
Raja et al, 1992(39)	N=88, MHD	nPCR	Lowest morbidity in the group with Kt/V > 1.0 and PCR > 1.0 g/kg/day.	Examined the concomitant effect of KT/V and nPCR.
Davies et al, 1995(34)	N=97, CAPD	Protein intake, calorie intake, PCR	Dietary protein and calorie intake, but not PCR were associated with higher mortality in univariate, but not multivariate analyses.	Adjustment for comorbid conditions rendered protein and calorie intake non-significant.
Herselman et al, 2000(27)	N=37, MHD	Dietary protein and energy intake, PCR	No association with all-cause or infectious morbidity over 26 months.	Small, single center study. Other markers of nutritional status showed significant association with outcome.
Kalantar-Zadeh et al, 2003(36)	N=122, MHD with KT/V>1.20	nPCR	Lower nPCR associated with high higher mortality and hospitalization rates.	Lower serum albumin, TIBC and creatinine showed similar associations.
Kalantar-Zadeh et al, 2004(24)	N=331, MHD	Appetite (self-rated)	Diminished appetite associated with higher rates of mortality and hospitalizations, and higher levels of inflammatory markers.	Prospective cohort.
Beddhu et al, 2005(30)	N=5,059, incident MHD	Total and dietary protein intake (derived from BUN and urine urea clearance)	18% increase in hazard of death for patients in the lowest quartile of TPI compared to highest quartile. Lower DPI associated with lower risk of death.	Data from USRDS. Lower TPI also associated with lower serum albumin, urine creatinine and BMI.
Araujo et al, 2006(26)	N=344, incident MHD	Protein and energy intake assessed by food diary.	Protein intake <1.0 g/kg/d, and energy intake <25 kcal/kg/d associated with worse survival in univariate analysis.	Low energy intake remained associated with mortality after multivariable adjustment. Single center study.
Shinaberger et al, 2006(38)	N=53,933, MHD	nPCR and change in nPCR	Best survival associated with nPCR of 1.0 to 1.4 g/kg/day. A decrease in nPCR associated with increased mortality and an increase in nPCR	All patients enrolled in DaVita dialysis units between 2001 and 2003.

Study	Patient population	Predictor	Results	Comment
			associated with decreased mortality.	
Carrero et al, 2008(25)	N=233, MHD	Appetite	Poor appetite associated with higher mortality.	Poor appetite also correlated with other markers of malnutrition and inflammation.