Nutrition and chronic kidney disease

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The incidence of malnutrition disorders in chronic kidney disease (CKD) appears unchanged over time, whereas patient-care and dialysis techniques continue to progress. Despite some evidence for cost-effective treatments, there are numerous caveats to applying these research findings on a daily care basis. There is a sustained generation of data confirming metabolic improvement when patients control their protein intake, even at early stages of CKD. A recent protein–energy wasting nomenclature allows a simpler approach to the diagnosis and causes of malnutrition. During maintenance dialysis, optimal protein and energy intakes have been recently challenged, and there is no longer an indication to control hyperphosphatemia through diet restriction. Recent measurements of energy expenditure in dialysis patients confirm very low physical activity, which affects energy requirements. Finally, inflammation, a common state during CKD, acts on both nutrient intake and catabolism, but is not a contraindication to a nutritional intervention, as patients do respond and improve their survival as well as do noninflamed patients.

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After the first hemodialysis sessions in the early sixties,[1] Dr Scribner rapidly pointed out key questions that emerged after these first treatments: how to better control blood pressure, how to manage chronic anemia, and which nutrients should be recommended to these patients. Fifty years later in 2010, the two first issues have been largely solved. By contrast, there is still much to do to fight protein–energy wasting as present epidemiological studies report between 30 and 50% of patients with signs of malnutrition.[2–5] What are the signs or protein–energy wasting? Are these symptoms already present before dialysis? Is this possible to correct these abnormalities and how? In this review, we will try to answer some of these important points.

CHRONIC KIDNEY DISEASE: WHICH PROTEIN INTAKE BEFORE MAINTENANCE DIALYSIS?

There is now evidence that patients with chronic kidney disease (CKD) should control their protein intake to reach optimal body protective values.[6] After an extensive review of the literature, most of the scientific societies worldwide recommend a daily allowance of 0.6–0.8 g protein/kg/day for CKD patients with or without diabetes.[7–11] Clinical trials confirmed by meta-analyses on large numbers (e.g., more than 2000 patients) show that it is effective and safe to reduce protein intake from the western-type diet, which contains about 1.3–1.4 g protein/kg/day to a nutritionally and metabolically optimal intake of 0.6–0.8 g protein/kg/day.[12,13] This is particularly important in patients with proteinuria, including those with diabetic nephropathy, as any increase in protein intake will increase proteinuria, which *per se*, is a risk factor for CKD progression.[14,15] Furthermore, reducing protein intake decreases proteinuria as efficiently as angiotensin-converting enzyme inhibitors,[16,17] improves serum lipid profile,[18] and has an additional effect on proteinuria reduction to that of angiotensin-converting enzyme inhibitors.[19] Thus, based solely on proteinuria, there is a strong rationale to control protein intake.

Limiting protein intake is associated with an instant decrease in wasted products and uremic toxins, blood urea nitrogen levels, and acid load. Metabolic consequences of restricted protein diet have been extensively reviewed:[6] reduction in oxidative stress, amelioration of insulin resistance, better control of metabolic bone disorders in response to a reduced phosphate load, and subsequent improvement in anemia control.[20–23]

Nutritional safety of a controlled protein intake

As CKD is associated with protein–energy wasting,[24] the nutritional safety of such a protein reduction has been questioned.[25] Muscle wasting is associated with CKD and increases dependency, mortality, and morbidity in this population.[26] From a basic point of view, one should find a direct relationship between reduced protein intake and muscle wasting. Unfortunately, this approach is not clinically relevant: muscle wasting in chronic diseases is mainly due to an imbalance between protein synthesis and degradation, and is further worsened by inactivity.[27] In addition, acidosis and activation of the ubiquitin–proteasome pathway associated with inflammation and insulin resistance represent the main factors of muscle wasting.[26,28] Reducing protein intake has been shown to improve all these catabolic conditions. Indeed, a better control of metabolic acidosis due to a lower acid load leads to a normalization of the adaptive responses to dietary protein restriction, as it has been clearly demonstrated in animals models, CKD, and dialysis patients,[29–31] and seems beneficial on the progression of CKD.[31] Insulin resistance is associated with muscle protein breakdown in end-stage renal disease patients[32] and rapidly improves after 3 months of low-protein diet (LPD).[22] Recent experimental data suggest that an increase in blood urea nitrogen induces reactive oxygen species production and enhances insulin resistance.[33]

Protein intake and oxidative stress

Oxidative stress and upregulation of oxidative metabolism are among the main factors responsible for sarcopenia in chronic disease and in aging. Recent data suggest that oxidative stress is associated with severe disturbances of muscle function even without muscle atrophy.[34] Moreover, oxidative stress is probably one of the main factors that aggravate glomerulosclerosis and fibrosis during CKD. A low-protein intake confers a protection against oxidative stress in experimental studies.[35,36] Finally in CKD patients treated with LPD or supplemented very low-protein diet (SVLPD), long-term studies on body composition did not find any adverse effect of such diets on muscle or lean body mass.[37–39]

Quality of protein intake (and not only quantity) should also be addressed. First, despite debate and controversies, clinical studies in patients receiving LPD (0.6–0.8 g/kg/day) or SVLPD (0.3–0.6 g/kg/day, supplemented with amino acids or keto-analogs) are nutritionally safe. No case of malnutrition occurred, in response to an adequate metabolic adaptation.[13,17] In the Modification of Diet in Renal Disease study, 9 months after completion of the study, the mean serum albumin was 42 g/l, and in the 239 patients of the Bordeaux cohort, only two patients stopped an SVLPD diet for reason of malnutrition, whereas the mean cohort serum albumin at start of renal replacement therapy was 39 g/l.[40,41]

Beneficial effects of a nutritional support

Most patients who start renal replacement therapy without prior dietary follow-up do present symptoms of malnutrition, for example, loss of body weight, altered anthropometry, and laboratory nutritional parameters.[42] The occurrence of a previous nutritional care plan appears to be the main protective factor against this progressive wasting. First, nutritional support and patient information are key factors to ensure motivation and adherence to the diet. This fact has been clearly demonstrated by Campbell *et al.*,[43] using body composition analysis and subjective global assessment. Second, in clinical studies, an LPD is usually composed of 50% protein of high biological value (such as meat, fish, or egg). In the case of SVLPD, no malnutrition occurred and long-term survey during or after the start of renal replacement therapy did not show a greater relative risk of death.[41]

Third, animal experiments and studies in elderly patients renewed attention on protein quality and the importance of essential amino acids intake. Indeed, in the elderly, a protein intake higher than 0.8 g/kg/day is recommended to avoid sarcopenia due to a relative resistance of muscle to the anabolic effect of an amino-acid load.[44] However, this resistance could be inhibited using amino-acid mixtures, particularly those enriched in branched-chain amino acids, that is, leucine, isoleucine, and valine.[45] An indirect evidence of the effect of amino acids on CKD-associated sarcopenia is reflected by the observation that, in dialysis patients, resistance training effect on muscle metabolism is enhanced when combined with intradialytic parenteral nutrition.[46] In elderly, sarcopenia is partly explained by enhanced oxidative stress. In nephrectomized rat, increased oxidative stress caused by protein malnutrition impairs the glomerular filtration barrier and a supplementation with ketoacids reduced kidney and oxidative stress injury.[35]

Finally, clinical studies using LPD or SVLPD bear a great attention on energy intake. Specific dietary survey is provided to ensure a sufficient amount of calories, for example, $\sim$35 kcal/kg/day. This is not always the case in most renal units where time of dietitian is lacking. In conclusion, the beneficial effects of reducing protein intake to optimal values are obscured by the lack of physician confidence, dietitian time, and patient education. Although immediately costly and sometimes tricky to set up, nutritional support should be provided for the patient's sake and is clearly cost-effective over the long term.[47]

PROTEIN–ENERGY WASTING: HOW TO MONITOR NUTRITIONAL RISKS AND IMPROVE OUTCOME?

One of the major side effects of kidney disease is the subtle development of anorexia and the concurrent reduction of protein–energy intake, already present at stage III of CKD[48] and during dialysis.[49–51] A number of orexigenic or anorexigenic hormone dysregulations (leptin, ghrelin, peptide YY, and obestatin) have been proposed to explain anorexia in healthy adults and patients.[52–54] Administering recombinant ghrelin during 7 days has been showed to increase meal energy intake by $\sim$25% in malnourished hemodialysis patients.[55] Interestingly, Cheung *et al.* suggested a dysfunction of hypothalamic appetite-regulating sensors,

such as the melanocortin-4 receptor.[56,57] Chronic renal failure mice knockout for this receptor ate normally, whereas their wild-type melanocortin-4 receptor counterparts severely reduced their food intake as a response to kidney failure.[56] When a melanocortin-4 receptor antagonist (such as NBI-12i) was administered to uremic mice, they gained lean and fat mass while lowering their energy expenditure, resulting in a net nutritional improvement. These findings may represent an interesting field to explore in order to improve patients appetite and food intake.

Growth hormone has also been associated with improved food efficiency in CKD. Indeed, Mehls *et al.*[58] reported that uremic rats receiving recombinant growth hormone gained more weight per gram food intake than uremic rats receiving vehicle. Combining growth hormone and insulin-like growth factor-1 improved food utilization and anabolic response in experimental[59] and clinical CKD.[60]

Muscle wasting is a predominant feature of CKD and is particularly present in long-term maintenance dialysis patients. Low muscle mass is associated with increased mortality.[61] Muscle wasting results partly from reduced physical activity (see section below) but also because of resistance to anabolic factors. The impaired action of growth hormone and/or insulin-like growth factor-1 has been studied in detail during maintenance dialysis in children and adults as well.[62–64] Short-term therapeutic interventions have been successful in improving body composition,[65,66] however side effects request long-term studies that are not yet available. As there is a testosterone deficit, which is associated with superimposed mortality in men,[67] it may be interesting to test short courses of androgen support in case of severe cachexia and muscle wasting,[68] in association with physical training. Indeed, most anabolic factors will not be efficient if they are not associated with a rehabilitation program.

In order to clarify the definition of kidney-associated protein–energy wasting, the International Society for Renal Nutrition and Metabolism released in 2008 a nomenclature paper focused on the causes, consequences, and diagnostic criteria of impaired nutritional status in CKD patients.[24] Four groups of parameters were examined (Table 1): serum chemistry, body composition, muscle mass, and dietary intake. For each parameter, a threshold was given based on the most recent epidemiological studies in CKD patients. Protein–energy wasting is then identified if at least one parameter is found below recommendation in three of the four marker groups,[24] and this simple estimation can be performed at bedside. The next steps are to validate this classification and identify a protein–energy wasting score that can predict mortality. A preliminary approach has been recently reported by de Mutsert *et al.*[69] using the 7-point subjective global assessment scale, which is a combination of clinical symptoms of malnutrition and biological abnormalities. In this prospective cohort of 1601 maintenance hemodialysis patients followed in the NECOSAD-II study, the increase in 7 years mortality was clearly linked to a point-by-point decrease in subjective global assessment.[69]

Table 1 | Criteria for clinical diagnosis of protein–energy wasting (PEW), from Fouque *et al.*,[24] with the permission of Nature Publishing

Criteria
Serum chemistry
Serum albumin <3.8 g/dl (Bromcresol Green)[a]
Serum prealbumin (transthyretin) <30 mg/dl (for maintenance dialysis patients only; levels may vary according to glomerular filtration rate level for patients on CKD stages 2–5)[a]
Serum cholesterol <100 mg/dl[a]
Body mass
BMI <23 kg/m^2 [b]
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
Total body fat percentage $<10\%$
Muscle mass
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
Reduced mid-arm muscle circumference area[c] (reduction $>10\%$ in relation to 50th percentile of reference population)
Creatinine appearance[d]
Dietary intake
Unintentional low-dietary protein intake <0.80 g/kg/day for at least 2 months[e] for dialysis patients or <0.6 g/kg/day for patients on CKD stages 2–5
Unintentional low-dietary energy intake <25 kcal/kg/day for at least 2 months[e]

Abbreviation: BMI, body mass index.
At least three out of the four listed categories (and at least one test in each of the selected categories) must be satisfied for the diagnosis of kidney disease–related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–3 weeks apart.
[a]Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, to liver disease or to cholesterol-lowering medicines.
[b]A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, postdialysis dry weight. See text for the discussion about the BMI of the healthy population.
[c]Measurement must be performed by a trained anthropometrist.
[d]Creatinine appearance is influenced by both muscle mass and meat intake.
[e]Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (normalized protein nitrogen appearance or normalized protein catabolic rate) as determined by urea kinetic measurements.

WHAT IS THE OPTIMAL PROTEIN INTAKE IN MAINTENANCE HEMODIALYSIS?

In the seventies, a number of metabolic studies were performed in dedicated research wards to better characterize protein and energy requirements of maintenance dialysis patients. Most of these studies were by the same teams, including a limited number of patients due to the time-consuming nature of research: every time one nutritional parameter is modified (for example, testing 1.0 g protein/kg/day in six patients), a new metabolic equilibrium is to be reached only after 2–3 weeks. Thus, testing three different protein intakes after a baseline period will need at least 2 months of full hospitalization for each patient with daily collection of blood, urine, feces, and dialysate output.[70–72] These constraints explain why so few patients were studied and why some large interindividual needs were identified. As a consequence, the optimal protein and energy needs were defined above the minimal requirements observed in the patient who requested the highest level, whereas some other did well for slightly lower values (safety principle). From these experimental studies, a protein intake between 1.0 and 1.1 g/day (as measured by direct food intake) was associated with neutral nitrogen balance,[70–72] and a general agreement was made upon requirements of 1.2 g/kg/day in maintenance hemodialysis and 1.2–1.3 g/kg/day in peritoneal dialysis. These values were enforced in 2000 by the Kidney Disease Outcome Quality Initiative Nutritional guidelines.[9] However, after some months or years, physicians who started to evaluate their patients' intakes were uncommonly able to reach these values and felt these targets were inadequate.

More recent epidemiological research provided slightly different information. Large prospective reports on thousands of patients showed that survival or body composition did not impair when nutritional intakes were lower than recommended.[73–75] In a French cohort of more than 3000 maintenance hemodialysis patients followed during 30 months between 2007 and 2009 (ref. 76), mortality was increased only when normalized protein nitrogen appearance was lower than 0.7 g protein/kg/day (Figure 1), whereas no additional mortality was observed for normalized protein nitrogen appearance values greater than 1.5 g protein/kg/day, by contrast to Shinaberger's report.[73] Thus, there is little doubt that low-protein intakes should be avoided in maintenance hemodialysis, whereas larger intakes do not clearly impair survival in these patients.

It is interesting to note that body composition will not further improve when patients eat above 1.0–1.1 g protein/kg/day. Indeed, in a prospective cross-sectional Japanese study in 129 maintenance hemodialysis patients, lean body mass or subcutaneous/visceral fat was not improved when patients had intakes greater than 0.9–1.1 g protein/kg/day.[74] In another study, two different protein intakes were tested in a crossover design for 40 weeks each (normalized protein nitrogen appearance of 1.01 ± 0.18 vs 0.9 ± 0.14 g/kg/day).[75] Fifty-eight patients were randomized and their energy intake was 28–30 kcal/kg/day. Actual dietary protein intake was

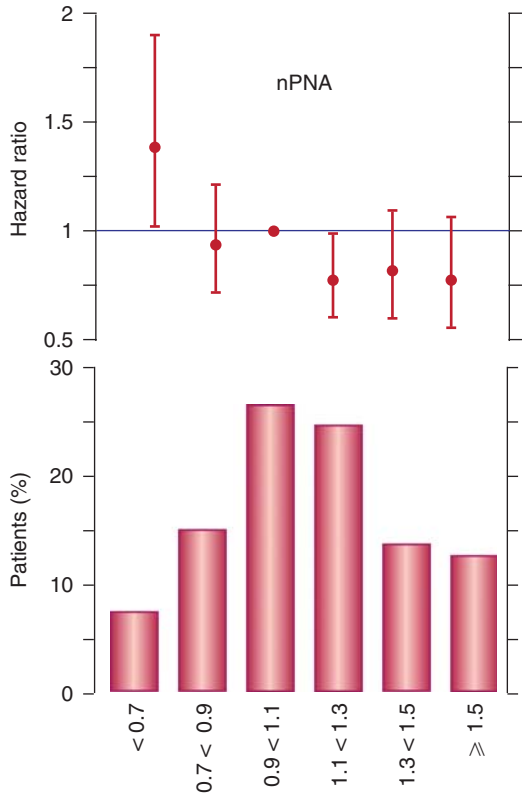

Figure 1 | Mortality rate of hemodialysis patients based on protein intake. Protein intake (g/kg/day) and 30-month hazard ratio for mortality in a prospective cohort of French hemodialysis patients from June 2007 to December 2009 ($n = 3000$, adjusted for age, gender, serum albumin, body mass index, cardiovascular history, and diabetes; from Fouque *et al.*,[76] with the permission of the National Kidney Foundation). nPNA, normalized protein nitrogen appearance.

1.15 g/kg/day and normalized protein nitrogen appearance 1.0 g/kg/day in the high-protein intake period vs 0.94 and 0.90 g/kg/day, respectively, during the low-protein intake period. There was no change in body weight, lean body mass, and fat mass in either group, nor was any change in serum albumin during the different intakes for 40 weeks each, a sufficient time exposure to reveal wasting. Thus, in this report, an intake of 0.95 g protein/kg/day or a normalized protein nitrogen appearance greater than 0.9 appeared sufficient to maintain adequate body composition and laboratory values, and there was no greater nutritional benefit from a higher protein intake.[75] With this in mind, recent guidelines have therefore slightly reduced protein requirements to 1.1 g/kg/day based on dietary interviews or 1.0 g/kg/day based on normalized protein nitrogen appearance.[68]

WHAT IS THE OPTIMAL PROTEIN INTAKE IN PERITONEAL DIALYSIS?

Data are more limited and still discussed regarding the optimal protein intake in peritoneal dialysis patients. Peritoneal dialysis is associated with albumin and amino-acid losses in the spent dialysate, which can reach 5–15 g/day,

seven times per week as compared with hemodialysis losses that only happens three times weekly.[77,78] These losses may represent ~15% of the net daily protein intake. Interestingly, new dialysis regimen, such as automated peritoneal dialysis, does not appear to modify these losses.[78] Anorexia may occur in response to intraperitoneal glucose load and abdominal filling, and actual protein intakes of 1.0 g/kg/day or less are often reported.[79] Studies in metabolic ward in rather young adults have shown in the eighties that a protein intake of about 1.2 g protein/kg/day was associated with neutral or positive protein balance in all patients; however, most patients were already in balance for intakes equal or greater than 1.0 g protein/kg/day.[70,72] Current guidelines therefore mention that protein intake should be 1.0–1.2 g/kg/day[9,80,81] and not below 0.8 g/kg/day in any patient.[80] As most patients will not be able to reach 1.2 g protein/kg/day, an intake of 1.0 g/kg may be acceptable if the patient does not express a decline in nutritional status.[80]

INCREASING PROTEIN INTAKE IN DIALYSIS: THE PHOSPHATE PARADIGM

If there is no clear nutritional advantage to increase protein intake, is there a metabolic risk to do so? This question arises as protein is linked to phosphate in a strong and accurate relationship: 1 g protein brings 13–15 mg phosphate, of which 30–70% is absorbed through the intestinal lumen. Thus, a 80 kg-patient eating 90 g protein/day may absorb 600–700 mg phosphate daily, which results in a net balance of 1200–1400 mg every other day, an amount that cannot be eliminated through dialysis as a single regular hemodialysis session can only clear 500–600 mg phosphate every other day and 1-day peritoneal dialysis clears ~300 mg phosphate. However, this theoretical calculation is not fully confirmed by clinical observation. Indeed, in a randomized controlled trial, Kloppenburg *et al.*[75] tested, during 40 weeks twice, two different levels of protein intake (0.94 vs 1.15 g protein/kg/day) that did not result in a variation of serum phosphate (1.89 vs 1.88 mmol/l, respectively, P = nonsignificant), despite a difference in protein intake of 20 g and phosphate intake of 250 mg/day.[75] In a subsequent report, Shinaberger *et al.*[82] showed that, in more than 50,000 maintenance hemodialysis patients, serum phosphate slightly increased from 5.8 to 6.3 mg/dl when patients' normalized protein nitrogen appearance increase from 1.0 to 1.4 g/kg/day (Figure 2, top). However and more importantly when analyzing patients' survival, the more they ate protein, the more they survived, until reaching a protein intake of 1.4 g/kg/day or above (Figure 2, bottom).[82] In a *post hoc* analysis of the HEMO study, Lynch *et al.*[83] also reported that the patients who received no prescribed dietary phosphate restriction had the best survival. In a current follow-up of more than 3000 maintenance hemodialysis patients in France, survival at 30 month was best for the highest protein intakes, without a trend for a J-curve (Figure 1).[76] Taken together, these recent studies indicate that the optimal protein intake in maintenance hemodialysis, based on nPNA, should be targeted from 1.0 to 1.4 g/kg/day. There is no such survival data based on protein intake in peritoneal dialysis patients.

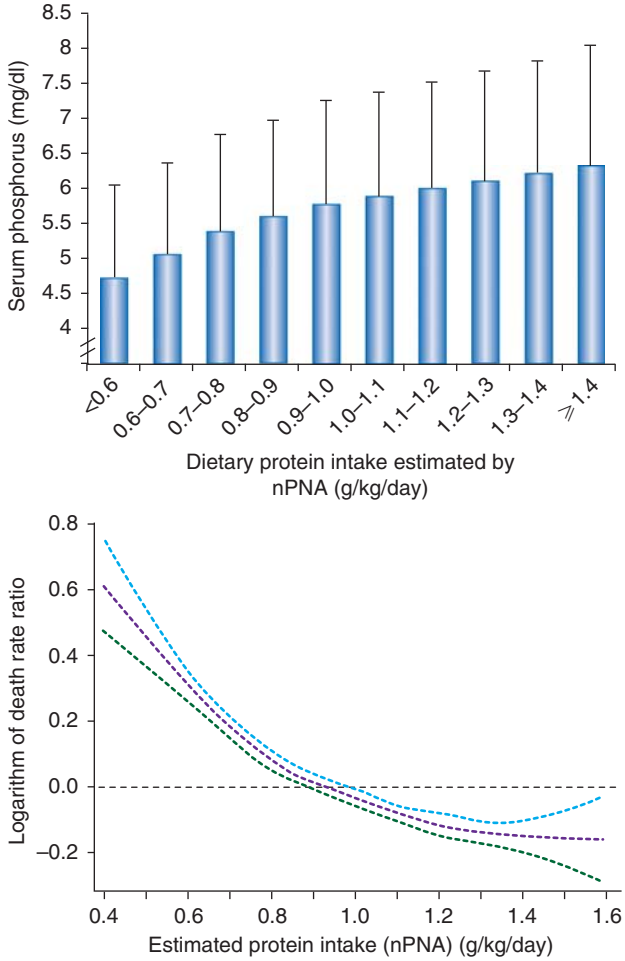

Figure 2 | The phosphate and protein intake paradigm. Mortality decreases when protein intake increases up to 1.4 g/kg/day (lower panel), despite a slight increase in serum phosphate (upper panel; from Shinaberger *et al.*,[82] with the authorization of the American Society of Nutrition). nPNA, normalized protein nitrogen appearance.

WILL PROTEIN REQUIREMENTS CHANGE IN THE FUTURE? THE IMPORTANCE OF DIALYSIS MEMBRANES AND TECHNIQUES

Dialysis membranes and techniques have dramatically evolved. High-flux membranes tend to clear solutes more rapidly and efficiently, in an attempt to reduce dialysis time. Hemofiltration techniques, including hemodiafiltration (pre- or postdilution) are designed to better remove middle molecules. However, a number of nutrients such as amino acids, vitamins, and trace elements may also be lost to a greater extent with these recent highly efficient techniques, and limited research is available to date to document this question.

For example, a polysulfone superflux dialyzer has been shown to induce an albumin loss of approximately 2.5 g per session during standard hemodialysis condition. When this

filter is used during predilution hemodiafiltration, albumin loss is about 8 g per session, and during postdilution hemodiafiltration, albumin loss reaches 25 g per session.[84] Such an important albumin loss is hardly compatible with a balanced protein metabolism and cannot be restored by food intake. In a previous randomized control trial on high-flux dialyzer and anemia control,[85] 74 patients were allocated to two different membranes, a high-flux polymethyl methacrylate membrane and a low-flux cellulose one. After a 3-month follow-up, when looking at nutritional parameters, there was a significant decrease in serum albumin from 3.88 ± 0.55 to 3.64 ± 0.55 g/dl and in serum creatinine from 10.3 ± 2.0 to 9.4 ± 2.9 mg/dl in the high-flux membrane group, whereas dialysis dose did not change, which could be viewed as deleterious on a nutritional point of view.[85] In another study comparing predilution hemodiafiltration with a high-flux polysulfone dialyzer vs standard hemodialysis with a low-flux membrane, Beerenhout *et al.*[86] observed a gain of 1.4 kg of muscle mass at 1 year in the hemodialfiltration group vs 1.2 kg in the hemodialysis group ($P<0.05$), whereas there was no other nutritional or body composition change. Thus, data are lacking to predict if these emerging dialysis techniques will improve or may be at risk for patients' nutritional status. Further research should be encouraged.

ENERGY NEEDS AND PHYSICAL ACTIVITY: A WORRYING PATTERN

It is cumbersome to estimate an individual's energy requirements, as energy metabolism depends on many variable factors, such as age, gender, lean body mass, climate, inflammation, thyroid and parathyroid function. Obviously, in a balanced state, energy requirements correspond to energy expenditure, thus a patient should adapt intakes to his/her expenses. Total energy expenditure is made up from three separate components: resting energy expenditure, thermic effect of meals, and physical activity energy expenditure.[87] The accurate estimation of total energy expenditure in chronic kidney patients is essential to allow an adequate provision of nutrients; however, it is a challenge to collect actual physical activity and resting energy expenditure in these patients.[88–91] There are conflicting results on resting energy expenditure during dialysis,[92] and there is no data on total energy expenditure because physical activity is hardly monitored.

We have therefore evaluated total energy expenditure during a 7-day period using a new device called SenseWear Armband (Body Media, Pittsburgh, PA), which uses sensors that continuously record movement, heat flux, and skin temperature allowing a detailed estimation of the wearer's energy expenditure, duration of physical activity, and number of steps walked.[93] We monitored 24 maintenance hemodialysis patients and compared their results to 18 age-matched healthy individuals. Total energy expenditure of maintenance hemodialysis patients was lower (29.5 ± 6.6 kcal/kg/day) when compared with healthy individuals (31.8 ± 7.0 kcal/kg/day), $P=0.02$. There was a major reduction in physical activity between patients (4810 ± 3706 steps/day) and healthy individuals (8712 ± 5287 steps/day), $P=0.008$. Total energy expenditure was positively correlated with the steps number ($r=0.84$, $P=0.001$; Figure 3).[93]

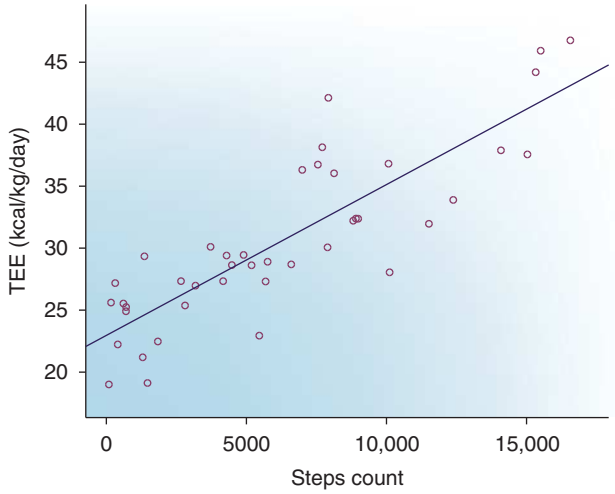

Figure 3 | Daily walking and total energy expenditure. The relationship between total daily energy expenditure (TEE) estimated by the SenseWear Armband and patient steps number (mean of 7-day recording, $n=24$, $r=0.84$, $P=0.001$). Healthy subjects with moderate activity usually walk more than 8000–10,000 steps per day.

We also evaluated the role of the dialysis session in daily total energy expenditure and observed that patients spent less energy (28.4 ± 4.8 kcal/kg/day) and walked less (3629 ± 3198 steps/day) during the dialysis days when compared with the nondialysis days (30.3 ± 7.8 kcal/kg/day; 5323 ± 4254 steps/day, $P=0.01$). This decrease in physical activity may be caused by the lack of motion during the 4-h hemodialysis procedure, the postdialysis fatigue, and the mandatory commuting time to reach the dialysis facility back and forth. As a matter of fact, Majchrzak *et al.*[94] also observed that physical activity was lower on dialysis days when compared with nondialysis days, suggesting targets for improving physical activity, both during hemodialysis and on nondialysis days. It is therefore mandatory to implement exercise in CKD patients, as underlined by Painter and Johansen.[95] In addition, exercise has been shown to increase nutrient utilization during intradialytic parenteral nutrition.[46] Research is also needed in order to achieve the best tolerance and identify-specific training programs (aerobic and resistance exercise) designed for CKD patients.[96]

Thus, in maintenance dialysis patients, daily energy requirements may fluctuate between 30 and 40 kcal/kg/day based on actual physical activity.[68] However, the best patient outcome will result from an increase in physical activity and a subsequent augmentation in energy intake, and this is a call for action.

INFLAMMATION: A DOUBLE-EDGE CATABOLIC AND ANORECTIC SWORD

Chronic inflammation has been identified in CKD in the mid-nineties[97–99] and was thought to be the primarily cause

for low-serum albumin concentrations in these patients. There is a linear risk between serum C-reactive protein (CrP) and coronary heart disease, stroke and mortality in the general population,[100] and in a healthy elderly population.[101] In maintenance dialysis, Kaysen *et al.*[102] reported a double dependency of serum albumin, positive one with protein intake as a source of amino acids mandatory to protein synthesis, and negative one with serum CrP as a marker of chronic inflammation. More recent reports have confirmed the major interdependency between inflammation, cardiovascular risk, and malnutrition.[103,104] As serum albumin is a strong predictor for mortality, it is tempting to analyze the potential impact of inflammation on CKD patients' survival.[24]

Low-grade chronic inflammation is present in about 30–65% of maintenance dialysis patients.[105] Inflammation seems to increase with age, and in 2008, maintenance hemodialysis patients aged over 75 years had a median CrP of 6 mg/l, which was significantly greater than those aged under 75 years.[106] The CrP threshold used to define inflammation is unclear, and varies between 5 and 10 mg/l among studies. In many reports, other inflammatory markers such as interleukin-1, -6, or tumor necrosis factor-α have been shown to be elevated and elicit comparable side effects.[107,108] However, these markers are more difficult to collect and more expensive to measure, and on a routine basis, it seems acceptable to use CrP. Thus, whatever the cause,[99] inflammation appears to be a common condition of CKD, and until now, no dialysis technique or medication has been successful in correcting or even improving inflammation.

The impact of inflammation on nutritional status is twofold (Figure 4). Inflammation may induce additional catabolism in CKD patients, as shown by Avesani *et al.*[90] Indeed, any 1 mg/l CrP elevation results in a 30 kcal increase in daily energy expenditure.[90] Besides being catabolic, inflammation is also responsible for anorexia. Experimental injection of recombinant interleukin-1 in rats dramatically reduces spontaneous food intake.[109] In maintenance hemodialysis patients, serum CrP is negatively linked with appetite.[49,50] Indeed, Kalantar-Zadeh *et al.*[49] reported in 331 Californian maintenance hemodialysis patients a significant inverse relationship between an appetite score and serum CrP. Visfatin, a new adipocyte-derived factor sensitive to inflammation,[110] may also be involved in anorexia in CKD.[111] Based on an appetite questionnaire in 246 maintenance hemodialysis patients in Sweden, a high-serum visfatin (for example, greater than 40 ng/ml) was associated with poor appetite and a lower plasma amino-acid profile. Appetite was also influenced by visfatin genotype.[111]

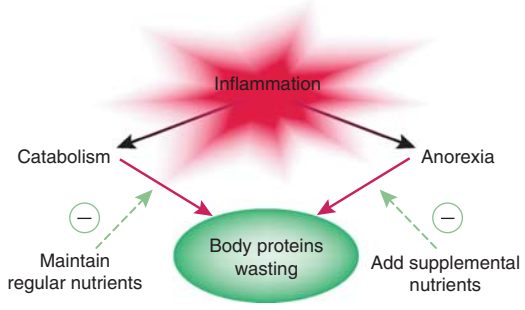

Figure 4 | The double impact of inflammation on wasting. The role of inflammation in chronic kidney disease, responsible for increased catabolism and anorexia, both actions that may induce protein–energy wasting and loss of body proteins, which can be counteracted by nutrients.

Chronic inflammation is linked with more impaired nutritional status. In a 5-year follow-up of 310 Swedish patients, mortality was greater in patients with a CrP >10 mg/l and a subjective global assessment greater than 2, indicating a worse nutritional status.[112] It is interesting to note that, depending on the way inflammation will impact on metabolism, a slow process with muscle and fat loss without hypoalbuminemia may apply if only food intake is reduced as a consequence of anorexia, whereas a more rapid wasting and hypoalbuminemia will occur as a consequence of catabolic events induced by a more active inflammation[112] (Figure 4). This may partly explain why in a maintenance hemodialysis population some inflamed patients may have a less severe wasting state than others.

Is this chronic inflammatory-wasting state an irreversible situation? First, when survival is analyzed according to nutritional status (for example, subjective global assessment, normalized protein nitrogen appearance, or serum albumin) and CrP, patients with a high CrP and a good nutritional status always survive better than those with a low CrP and a more impaired nutritional status, conferring some protection of a better nutritional state to the deleterious effects of inflammation.[112] Second, fortunately, there seems to exist a therapeutic response to this inflammatory-induced wasting. Recent interventional studies have shown anabolic responses to either oral and/or parenteral nutritional supplements in hemodialysis patients.[113–115] Importantly, these responses also occurred in patients with CrP above 10 mg/l.[113–115] In the FINE study after receiving 1 year of supplemental nutrition, serum albumin and prealbumin of the malnourished inflamed patients did respond better than in the noninflamed patients.[114] Thus, after a careful check-up aimed at solving obvious inflammation causes, inflamed patients presenting with protein–energy wasting should be aggressively treated with nutritional supplements as well (Figure 4).

Is nutrition responsible for inflammation? The food content may possibly be responsible for production or additional accumulation of inflammatory compounds. Plasma advanced glycosylated end-products have been shown to increase during advanced CKD and could be increased not only from endogenous metabolism but also from dietary sources.[116] Indeed, about 10% of ingested advanced glycosylated end-products may be absorbed and $\sim$60% of this absorbed amount will be incorporated in tissues.[117] Ingesting food low in advanced glycosylated end-products content resulted in a plasma advanced glycosylated end-products reduction.[118] As a follow-up to this observation, does a

protective diet exist? A potential response may be found in the Mediterranean diet. This diet is rich in vegetables, fruit, olive oil, and fish, and poor in red meat. It has been associated with reduced cardiovascular mortality, increased longevity, and more recently with decreased dementia.[119] A Mediterranean diet possesses anti-inflammatory properties, improves lipid profile and reduces oxidant stress. For example, olive oil has been shown to reduce CrP and oxidized low-density lipoprotein cholesterol.[120,121] Whether this Mediterranean diet possesses protective properties in CKD should be further studied. Indeed, in maintenance dialysis, attention should be focused on potassium intake that could be slightly increased by these diets rich in fruit and vegetables.

In summary, it appears that inflammation is not only catabolic but may also induce protein–energy wasting from a reduction in appetite.[24] Interestingly, by contrast to a generally admitted opinion, inflammation-induced protein–energy wasting can be reversed by nutritional supplements.

CONCLUSION

Fifty years after the first dialysis treatments, nutrition is still a recurrent issue and many disorders are currently not well understood. However, there has been progress in nutritional targets in CKD patients before and during maintenance treatment. Before dialysis, there is good evidence that a long-standing nutritional care plan, with a control of protein intake, is efficient in correcting many metabolic disorders, including proteinuria, and is cost-effective. During dialysis, nutritional targets have gained in understanding and phosphate metabolism does not appear a sufficient issue to reduce protein intake, as compared with the risk of super-imposed mortality when patients' intakes are reduced. New devices recording physical activity report dramatically reduced energy expenditure in dialysis patients and call for sustained physical activity plans as a part of routine treatment. New classification of nutritional disorders in CKD patients may help physicians to more easily identify initial protein–energy wasting. Finally, inflammation, a common CKD disorder, is responsible for anorexia and catabolism, but inflamed patients can respond to supplemental nutrition as well as noninflamed ones.

DISCLOSURE

All the authors declared no competing interests.

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