[Frontiers in Bioscience S3, 1432-1442, June 1, 2011]

Low protein diets are mainstay for management of chronic kidney disease

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1. ABSTRACT

Low protein diets, made either of natural foods or of L-essential amino acids and/or their nitrogen-free ketoanalogues, are feasible, safe, and efficient means to reduce disease progression in patients with chronic kidney disease and do not prejudice patient outcomes once they get into Renal Replacement Therapy. They ameliorate symptomatology, grant a positive nitrogen balance, reduce proteinuria, improve osteodystrophy and lipid profile, reduce serum concentrations of uric acid, phosphate, and maintain plasma bicarbonate within normal limits thus preventing metabolic acidosis. They also reduce the number of hypotensive drugs and the quantity of erythropoietin to be administered to achieve target hemoglobin concentrations, and do not deteriorate quality of life. On the contrary, they retard progression of chronic kidney disease. There is a need to motivate patients to increase adherence to prescription and dietitians to escape the risks of malnutrition.

2. TIMELINE OF THE HISTORY OF RENAL NUTRITION

The history of nutrition in renal disease usually starts with a reference to L.S. Beale (1869) who suggested a that a reduction of protein intake might be beneficial in reducing the kidney work load in renal disease (1). However low protein nutrition was administered to patients with Bright disease by Mariano Semmola (2), a medical student who studied the effect of a low protein diet and published them in the proceedings of the Academy of Naples in 1850. The data were also discussed and published in the proceedings at the Academy of Medicine in Paris at the time Semmola worked under Claude Bernard, Trousseau and Rayer. He demonstrated that a vegetable diet or a regimen without protein reduced urinary albumin excretion. In the subsequent 42 years he wrote 25 additional full papers in Italian and international journals on the topic of primary albuminuria which were appreciated by the expert of his time including Jean-Matrie

Charcot, Frédérich Labadie-Largrave, Sigismund Jaccoud, Henri Hallopeau, E. Lechorché, Ch. Talamon, and Georges Dielafoy and were confirmed in many subsequent experiments of Gubler, Parkes and Lépine, that is the cream of the clinical investigators of those days (2). Semmola made experiments in humans using protein poor and protein rich diets. He used a soup of greens and bread and compared with the effects of 600 grams of boiled meat. He also studied the effects of a diet containing 200 g of fat, 1500 g of bread and 1 kg of chestnuts (2).

The next significant step was made by Franz Volhard (3) who in 1918 observed a reduction in body urea nitrogen, improvement of symptoms and prolonged survival following the administration of a vegetarian low protein diet and a normal energy intake (2000 kcal/d). Thirty years later, in 1948, Kempner (4) strongly supported a low protein diet to reduce progression of renal failure and toxicity by suggesting the use of a 20 g protein diet with low sodium content (150 mg/d), an adequate caloric intake (2,000 kcal/d). However the diet carried the risk of reducing body weight. Then Borst introduced a protein free diet, poor in sodium but providing adequate energy. The diet was effective in reducing symptoms of patients with chronic kidney disease (5). Bull *et al.* administered 10 g of proteins/d and allowed the usual caloric intake (6). Addis in turn supported a protective effect of low protein diets in the diseased kidney because of the reduced workload that had emerged in studies in rats (7). Smith (8) was skeptic on the real benefit of a low protein diet and Peters and van Slyke disclosed (9) its potential for malnutrition.

In the years 1949-1954 Theodore N. Pullman performed seminal work on the effects of dietary protein intake on GFR, renal plasma flow, and maximum tubular secretory capacity for PAH. In particular it was observed that a high protein intake increased GFR, ERPF TmPAH in comparison with average protein intake and low protein intake (10, 11). Pullman was also kind enough to historically review those data for the 1995 September issue of Seminars in Nephrology which one of us (N.G. De Santo) dedicated to Renal Reserve (12). In that paper Pullman also reviewed data available from 1932 to 1950 that included nephrotic children, patients with renal disease, hypertensive, and various cases of nephritis (12).

Finally, John P. Merrill, professor of medicine at the Harvard Medical School and physician in chief at the Peter Bent Brigham Hospital in Boston (13) in 1955 suggested a diet containing 0.5-0.6 g/Kg of high biological value proteins along with adequate energy.

3. THE ADVENT OF THE GIORDANO-GIOVANNETTI DIET

All started with one experiment on a single healthy subject (Carmelo Giordano). The experiment was published in 1961 (14). The healthy subject in the course of 53 days utilized various diets: i) essential amino acids + 3 g of N as glycine; ii) essential amino acids + 0.5 g N as glycine, and iii) essential amino acids + 2 g of N as ammonium citrate and D essential amino acids + 2 g N as urea. Urea and ammonium were utilized to maintain nitrogen balance. In the same year (15) Giordano studied 2 patients with advanced renal failure given a diet with essential amino acids equivalent to 2 g of N, associated with an energy input of 2,500 Kcal/d. Blood urea was reduced. A third Giordano's paper was published in 1963 (16) and summed up data in one healthy subject, and 8 patients with a eGFR in the range 3-26 ml/min, 7 of them were hypertensive. They underwent for 7 weeks a diet providing L-essential amino acids (2 g of N) associated with 2300 calories in women and 3,100 cal in men. Subsequently they were switched to a low protein diet providing 23 g of proteins of high biological value. Blood urea was reduced under amino acids, nitrogen balance started to be positive after 3 weeks. In the same year at the Second International Congress of Nephrology that took place in summer in Prague, Giordano had an oral presentation (17). He discussed data obtained in: A) 5 patients with a plasma creatinine in the range 2.6-6.0 and studied for a total of 79 months; B) 10 patients with a plasma creatinine in the range 6.3-9.0 mg/dl followed-up for 117 months and C) 8 patients with a plasma creatinine > 9.0 mg/dl followed-up for 40 months. Patients received a low protein diet of 3.8 g of N (week 1 and 5) and an amino acid diet (weeks 2-4) providing 2.0 g of N associated with diets of normal-high caloric content (2,300-3,000 kcal). Blood urea was reduced by the amino acid diet which normalized N balance after 1 week. At the meeting there were no other presentation on low protein alimentation in renal disease. It should be stressed that all studies in references 1-4 were supported by NIH, which continued to support Giordano's research until 1985.

In 1964 Giovannetti and Maggiore (18) reported in Lancet data on 9 patients with eGFR of 3-4 ml/min fed for 15-20 days a basal protein deficient diet (1.0-1.5 g of N), followed by a diet with L-essential amino acids (1.74 gN) and finally a restricted protein diet with egg proteins or egg albumen (2.2 g N/d) making a total experience of 48 months. Blood urea was normalized and N balance turned positive when the essential amino acids were administered. The positivity was kept by the egg-protein diet. In that year a monograph of Giordano (19) prescribed for CKD patients L-essential amino acids for 2-3 weeks (2 g of N), followed by 3.8 g of N as high biological value proteins. At the Italian Congress of Nephrology, which took place in Fiuggi in September 1964, Monasterio *et al.* (20) reported on 34 CKD patients, 32/34 hypertensive, followed for 1-8 months (for a total of 213 months). Plasma creatinine was in the range 4 to 6 mg/dl in 11 patients, 6 to 9 mg/dl in 11 patients, and > 9 mg/dl in 12 patients. They were given 20 days of a basal protein deficient diet (1.0-1.5 g of N) followed by a diet providing 2 g of N as egg proteins. Calories were provided as protein poor spaghetti, pizza and wafers. Patients remained on diet up to 18 months (1 patient). Giordano *et al.* at the same meeting provided data on 67 patients followed for a total of 469 months (21). Their plasma creatinine concentrations were either in the range 2.8-6,0 mg/dl (16 patients, Group A); or in the range 6.7-9.0 mg/dl (16 patients, Group B), or > than 9 mg/dl (35 patients, Group C). They received a pudding providing 2 g of N as essential amino acids for 15-20 days,

Table 1. Nitrogen balance studies in 25 patients undergoing various protein intakes for periods of 14 days for a total of 1012 days (25)

Protein intake	Patients no.	% with positive N balance
Free	4	0
Essential AA (8-11 g)	14	57.1
LPD, 17-g	18	16.6
LPD, 20-g	13	46.1
LPD, 23-g	10	60
LPD, 25-g	14	85.7%

and low protein diets (24 g of proteins) subsequently. In Group A, followed for 135 months, there were 4 deaths, in Group B, followed for 160 months, there were 7 deaths, and in group C, followed for 174 months, there were 29 deaths.

From 1965 on Berlyne and his associates treated over 100 patients with chronic renal failure on the Manchester modification of the Giordano Giovannetti diet (22-24), a diet containing 18-g of proteins + 250 mg of L methionine, providing 2300 kcal, 1300 as liquid glucose, protein poor spaghetti and biscuits and 1000 as cream and oil. Thirty of the patients had a CaxP product of 96.4. The diet prolonged a comfortable existence.

At the third International Congress of Nephrology, in Washington 1996, Giordano and his associates reported on 221 patients followed up to 60 months (25). They started with 0.3g/Kg of HBV proteins associated with 35 kcal/kg and were followed-up by assessing the nitrogen balance. When the N balance was negative, 2-3 g of proteins were added in total 24 g for a 70 kg man. The study reported on more than 1000 days of N balance in 25 patients given various dietary intakes (free intake, 8-11-g L-essential amino acids, and low protein diets providing 17-g, 20-g, 23-g and 25g, as outlined in Table 1. Eighty-five per cent of the patients were in positive nitrogen balance with 25 g of proteins (Table 1). The study also disclosed a reduced phenylalanine to tyrosine ratio and a loss of 10-20 g of amino acids and peptides during a dialysis session of six hours.

Giovannetti on the same occasion reported data in more than 500 patients given initially a nitrogen poor diet (6 g of protein of vegetal origin and fruits) and subsequently 12 g of protein/d as egg protein (2g N). The longest observation lasted 3 years (26).

In 1968 Kopple *et al.* (27) provided a controlled comparison of 20-g and 40-g protein diets in the treatment of chronic uremia. The latter diet showed superiority in terms of nitrogen balance and patient's acceptance. It also provided similar symptomatic improvement to the 20-g diet. Kluthe and Quirin introduced the German modification of the Giordano-Giovannetti diet that was based on potatoes and eggs (28). It provided 20-25g of protein/d, 40% of which of vegetable origin and 60% of animal origin. Energy derived from butter, margarine, for a total of 2000-2400 kcal. The diet that supplied 10-30 mmol of sodium, in one study provided a positive nitrogen balance in 11 of 14 patients (29).

Finally in 1981, at the 8th international congress of Nephrology in Athens, Giordano discussed the impossibility for nutrition to compete with the enthusiasm generated by dialysis and transplantation and made the point that appropriate alimentation had to be used very early in the course of chronic kidney disease. Therein he was finally able to compound discords emerging from available studies with the use of ketoacids and accepted them as a definite modality of nutrition in chronic kidney disease (30).

The experimental data of Brenner *et al.* disclosed the glomerular adaptation of the kidney to renal injury (31), which mediated by sustained elevation in glomerular capillary pressure and flows. Brenner *et al.*, speaking at conference organized to celebrate Morgagni 300 years after birth, pointed out (32) the relevance of the data of Maschio *et al.* and of Giordano al. who had showed that the rate of progression can be effectively retarded in a variety of renal disorders by prolonged control of dietary protein intake (33,34). In 1982 the group of Maschio *et al.* provided an extensive study, that although non randomized, generated important insights in the feasibility and success of long lasting dietary management (35) and nurtured additional interest for renal nutrition.

4. THE ADVENT OF KETOANALOGUES

The concept began with a paper on the effects on nitrogen balance of D-isomers of essential amino acids in uremia (36). It was hypothesized that it was the ketoacid of the D-isomers of aminoacids to be utilized. Two seminal papers were published in 1971 showing the feasibility of a low protein diet based on ketoanalogues (37,38). Ketoacids of the essential amino acids valine and phenylalanine could be utilized in studies with nitrogen balance and ^{15}N incorporation. It was shown that phenylalanine and valine may be synthesized by healthy and uremic individuals (37,38). Walser *et al.* brought strong additional evidence (39). However since anoxic infants on ketoacid formulations failed achieve catch-up growth whereas they amino acid formulations did (40) a new reference pattern was proposed (41). For the subsequent 30 years Walser and his associates have continuously investigated on the problem and concluded that a very low protein diets supplemented with ketoacids was superior to an amino acid formulation(42-44). A conclusion which was a subject of controversy with the Neapolitan group.

5. THE EFFECTS OF LOW PROTEIN DIETS IN MULTICENTER RANDOMIZED CLINICAL STUDIES – LESSONS FROM META-ANALYSES

A total of 5 meta-analysis (45-49) have provided in the years 1992- 2007, based on a total of seventeen multicenter, randomized studies (50-66), in non-diabetic (50-55, 60, 61, 65, 66) and diabetic patients (56-59, 62-64).

The first meta-analysis was published by Fouque *et al.* (45) who analyzed 46 trials between 1976 and 1991. Only six of them were randomized and controlled. One study had been published only in abstract form. The study population included 440 patients on low protein diets and 450 controls. There were 61 renal deaths in the treated group and 95 in the control

group. The Relative Risk (RR) was 0.54 (0.37 to 0.79). The conclusion was that low protein diets clearly delay end stage renal disease. No firm conclusion was possible of the effects on progression, the nutritional risks, the benefits on osteodystrophy, anemia, and quality of life. The level of restriction and the needs for supplements were not assessed.

Four years later Pedrini *et al.* (46) published the second meta-analysis. A total of 1413 non-diabetic patients were followed-up for 18 to 36 months (50, 52, 55). The meta-analysis also included five studies on 108 diabetic patients followed-up 9 to 35 months (56-59). Dietary protein reduced significantly the risk for renal failure or death that was 0.67 (C.I. 0.50 to 0.89). It was concluded that a low protein diet had a beneficial effect independent of angiotensin-converting enzyme inhibitors. Effects were also seen on protein excretion, serum creatinine, creatinine clearance, and glomerular filtration rate. Dietary protein restriction delayed progression in diabetic and nondiabetic renal disease independently of an effect on blood pressure. In nondiabetic patients it reduced the risk for renal failure or death. The data were considered robust and led to the suggestion of a low protein diet of 0.6 g/kg. There was indication for awareness of the harmful effects of dietary protein restriction. For diabetic patients the same amount of protein was advised for patients with progressive proteinuria despite good glycemic control.

Kasiske and his associates analyzed data encompassing experience on 23 studies 13 of which were randomized (47). Among those randomized and controlled, eight were related to studies in nondiabetic patients (50-55, 60, 61) and four to studies in diabetic patients (56, 58, 62-64). Nondiabetic patients ate diets providing 0.68 g/kg of protein, the control groups 1.01 g/kg, the control group for diabetic patients ate 1.26 g/kg of protein/d. The difference in protein intake between patients and controls averaged 0.33 g/kg in studies in nondiabetic patients and 0.54 g/kg in studies on diabetic patients. The data demonstrated that protein restriction reduces the rate of decline in renal function by 0.53 ml/min/year (95% CI 0.08 to 0.98 ml/min/yr). By excluding a large study of Locatelli *et al.* (54) the decline increased to 0.66 ml/min. The results of the meta-analysis showed that a reduced protein intake retards the rate of decline in GFR. However the magnitude was too small. The study failed to understand the real value of the MDRD study. The contrast with previous meta-analyses is evident. However, Kasiske *et al.* appropriately suggested that a low protein diet might retard renal death even without a substantial improvement in GFR but through a delayed onset of uremic signs and symptoms. The meta-analysis supported the needs for studies with protein restriction in studies of longer duration (47).

The metanalysis of Fouque *et al.* (48), looking for renal death – a robust endpoint – was based on seven studies in nondiabetic adult patients (50-55, 65, 66). Although the difference in protein intake between control patients and patients on restricted diet was small (from less than 0.2 g/kg bw to 0.35 g/kg bw), a 39% reduction in renal death was disclosed in 753 patients on restricted protein intake compared to 741 controls. It was calculated that the number of patients to be treated (NNT) with the protein restriction to spare 1 renal death is 16, a number to be matched with a NNT of 30 for statins and the NNT of 111 in the Scotland Coronary Prevention study. Interestingly the funnel plot which represents the individual odds ratio corresponding to the study patient number (67) showed that the odd ration of the larger studies (1, 5, 6) were closed to the to the common odd ratio of 0.61, whereas in smaller trials (2,3,16) the odd ratio was in the range 0.29 to 0.38, thus suggesting a stronger effect. However this was discussed in terms of publication bias due to self-censoring.

A recent meta-analysis of Fouque and Aparicio (49), using renal death as endpoint was based on 763 patients on low protein diets and 751 controls from 8 studies (50-55, 65,66) showed a reduction in renal death. The odd ratio was 0.69(95% C.I. 0.55-0.85) suggesting 31% reduction in renal death. Also in this meta-analysis the paper with a small number of patients showed more favorable effects. The authors suggested that in stage 3 and 4 of CKD the Western diet should be reduced to 0.6-0.8 g/kg bw/d, by strictly monitoring compliance and signs of malnutrition. The finding on amelioration of anemia deserves a special consideration. The trial of Di Iorio *et al.* (66) was performed in patients fed very low protein diets supplemented with ketoacid-aminoacid providing 0.5 g/kg of protein and an energy input of 35 cal/kg/d. The trial showed a 35% reduction of the erythropoietin dose required to maintain the hemoglobin levels, which was mediated by a correction of a moderate secondary hyperparathyroidism focusing on PTH and phosphate concentrations (66).

6. DATA FROM SELECTED STUDIES

Rosman *et al.* (50) were the first to perform a controlled prospective randomized study in 228 patients with a creatinine clearance of 10-60 ml/min. They showed that a moderate protein intake (0.4-0.6 g/Kg body weight) the rate of progression of chronic renal insufficiency was reduced in comparison to a usual diet. They used isocaloric diets made of rice, potatoes, protein-free bread, and eggs and did not observe weight loss and significant reduction in serum albumin concentrations. The study thus confirmed retrospective and nonrandomized trials.

Jungers *et al.* (51) performed a randomized controlled study on 31 patients by using a low protein diet and a very low protein diet supplemented with ketoacids in patients with a serum creatinine of 500 to 900 mmol/L and showed that the supplemented diet prolonged the time of renal death by 29%.

Locatelli *et al.* (54) randomized 156 patients either to a low protein diet (0.6g/Kg) diet or to a moderate protein diet (1.0 g/Kg). Renal survival time was more favorable in the low diet, however the loss of renal function was not different in the two studies. The study lacked a significant statistical power and was further weakened by the fact that the moderate protein diet provided 0.9 g/kg per day of protein) whereas the low protein diet provided 0.78 g/kg of proteins. So the real difference was 0.122 g/kg, too small to achieve an effect. In addition the compliance was very poor, but body weight did not change.

For the Modification of Diet in Renal Disease Study, (MDRD Study) financed by the National Institutes of Health of the United States, Klahr *et al.* (55) organized a multi-center, randomized prospective trial to evaluate the effects of two levels of protein intake and two levels of blood pressure (usual blood pressure defined by a mean blood pressure of 103 mmHg and low blood pressure with a mean arterial pressure of 92 mm Hg). In Study A they enrolled 585 patients with a GFR of 25 to 55 ml/min per 1.73 m^2 of body surface area randomly assigned either to a usual protein diet (1.3 g/kg) or a low protein diet (0.58 g/kg). Mean caloric intake was of about 28 kcal/Kg. Klahr *et al.* (55) also enrolled (Study B) 255 patients with GFR in the range 13 to 24 ml/min per 1.73 m^2 either on LPD (0.58 g/kg) or Very Low LPD (0.285g/kg) supplemented with ketoacids and aminoacids providing a protein intake similar to the LPD. Caloric intake was around 25 kcal/kg.

In study A in the first 4 months patients on low protein diet and low blood pressure had a significant higher loss of GFR. Subsequently the rate of decline was 28% less in the LPD and 9% in Low Blood Pressure group. The less steep slopes after 4 months were seen consistent with a small beneficial effect of this intervention on progression of renal disease. Black patients benefitted of low blood pressure as it was the case for patients with proteinuria. Patients with polycystic kidney had the most rapid decline in GFR. The lowering GFR effect in the first four months was interpreted as a hemodynamic response to lower protein intake. In Study B a marginal effect of very low protein diet was seen on GFR. This in contrast with many previous studies.

The conclusion of the study, which did not match the expectations of the promoters, was rather pessimistic and suggested that i) in patients with moderate renal insufficiency dietary intervention was of small benefit; ii) in patients with more severe renal insufficiency the very low protein diet did not significantly slow the progression of renal disease; iii) in patients with proteinuria and low blood pressure the decline of GFR was smaller; iv) the interventional study appeared inappropriately short. The authors, as well the whole community of nephrologists worldwide interpreted the data as results of inadequacy of low protein nutrition to slow the CKD course.

It took some years to understand all the results of the MDRD study (68). In secondary studies it was demonstrated that a reduction in protein intake of 0.2 g/kg was a associated with a 1.15 ml/min per/yr slower GFR decline that was 29% of mean GFR decline. The relative risk of renal failure or death was minimized and in the range 0.34 to 0.76 (mean 0.51). Also for the study in more severe renal insufficiency, a very low protein diet supplemented with a mixture of ketoacids and aminoacids, was demonstrated beneficial. The inadequacy of composition of the supplements and study design were acknowledged. In particular it was possible to understand that the reduction of GFR loss from the fifth months on was 1.1 ml/min per year lower than the mean (28% less), not different from the hypothesized benefit (30% reduction). The secondary analysis also disclosed a trend toward lower incidence of ESRD or death in the low protein diet group, as well as the reduction of protein excretion similar to that caused by low blood pressure. In fact the comparison of randomized studies showed that dietary protein restriction slowed the rise of protein excretion during follow-up. Similar effects were observed in comparison of the BP group. The study disclosed additive benefits of blood pressure control and low protein intake and also gave evidence of the safety of low protein intake although accurate supervision was needed. The study finally provided justification for prescribing a low protein diet providing 0.6 g/kg of protein/d and suggested dietitian-nephrologist interaction to prevent malnutrition (68).

Finally, it was more evident that a longer period of treatment was necessary. There were many pitfalls in that study. At the time of enrollment a prerequisite concerning progression was not fixed and 15% of the patients in the control group did not progress. In addition there was an excess of patients with polycystic kidney disease for whom the study "provides little evidence of a beneficial effect in moderate renal disease" . Furthermore the mean duration of the trial was 2.2 years although in many trials longer times were required to achieve a benefit. This was the case of fish oils in IgA nephropathy and of strict glycemic control in diabetes mellitus (69,70). Furthermore there was an unregulated use of ACEi. Finally it should be noticed that mean caloric intake was slightly below the recommended energy (35 kcal/kg/d or more).

A low protein diet reduces proteinuria as it was shown by Kaysen *et al.* (71) in 1986. An effect that has been confirmed in many trials and carries the possibility to reduce the risk of sclerosis.

Aparicio *et al.* (72) treated more than two hundred well motivated patients - mean GFR of 13 ml/min - with supplemented amino acid and ketoacid diets providing a protein intake 0.43 g/kg bw/d) for an average time of 29.8 months, without changes in body weight, BMI, serum albumin, and serum PTH. A significant improvement of plasma bicarbonate was observed over time. They were started on renal replacement therapy at GFR of 5.6±1.9 ml/min. The effect on acidosis was particularly important. Mortality rate after starting RRT was 2.4% in the first year and 6.8% in the second year. At five years the mortality was 25% and at 10 years of 50%.

Results of a 48 months randomized controlled trial of a low protein diet and of a moderate protein intake (respectively providing 0.73 and 0.90 g/kg/d of protein) in CKD patients with a GFR<30 ml/min were recently published by Cianciaruso *et al.* (73). The trial, had a follow-up of 30 months, was performed in order to assess the risk of malnutrition, the compliance to the dietary regimen, and patient outcomes. It randomized 423 patients, of whom 276 completed the trial. A low protein diet did not cause malnutrition, most patients were compliant with the diet, which did not impact patient outcomes. Body weight and creatinine excretion, strong clinical markers of

Table 2. Benefits of protein restriction in CKD

Reduces complications reducing the accumulation of waste products
Decreased protein intake
Decreases sodium intake
Decreases phosphate intake
Decrease intake of sulphur containing amino acids
Decrease intake of phenols
Decrease intake of oxalate
Reduces proteinuria
Reduces proteinuria even in patients treated with ACEi
Improves the control of hypertension
Reduces blood urea
Reduces accumulation of nitrogenous compounds
Corrects metabolic acidosis
Optimize serum levels of bicarbonate
Optimize serum level of potassium
Optimizes serum uric acid concentrations
Reduces phenols accumulation
Reduces phosphorus retentiom
Removes inhibition of calcitriol production
Controls PTH concentrations
Increases calcemic response to PTH
Improves osteomalacia and osteitis fibrosa
Delays onset or reduction of symptoms and signs of uremia
Nausea
Vomiting
Acidosis
Edema
Improves peripheral neuropathy
Improves insulin resistance
Improves red cell lipoid peroxidation
Improves the oxidative stress
Improves serum lipid profiles
Possible reduction in the level of an unidentified nephrotoxin derived from protein metabolism
Reduces progression in diabetic patients
Reinstates a renal reserve (XXX9)
Possible lowering of serums homocysteine concentrations
Reduces progression in nondiabetic patients
Forestalls dialysis
Reduce the need for erythropoietin to achieve target haemoglobin b concentrations
Achieves stability of body weight
Achieves stability of Body Mass Inmdex
Achieves constant creatinine generation
Does not cause hypoalbuminemia
Does not reduce serum transferrin concentration
Grants quality of life
Reduces the number of hospitalizations
Reduces the costs of therapy
Does not impair survival in subsequent dialytic treatment

malnutrition, remained constant. Furthermore albumin and transferrin, sensitive markers of visceral protein, remained also stable under both diets. Only 3 out 423 patients (0.7%) met predefined criteria of malnutrition. The risk of reaching dialysis and the risk of mortality were low and were not affected by the diets under study. There was a low loss (3.4%) to follow-up. The mortality rate was 3.8%. Low protein diet did not affect survival on dialysis. It should be noticed however that patients did not adhere strictly to prescribed protein. To a prescription of 0.55 g/kg/d corresponded a real intake of 0.73 g/Kg and to a prescribed intake of 0.80 g/kg/d corresponded a true intake of 0.9 g/kg, however a difference of 0.17g/kg d between the two diets was always present. The study is relevant for the continuous strict monitoring of dietary management over a long-period, a monitoring which is missed by recent papers of the MDRD study which were followed-up only for nine months after completion of the study.

7. THE BENEFITS OF LOW PROTEIN DIETS IN CKD

Table 2 is a synopsis of various benefits of dietary protein restriction in CKD patients receiving adequate energy inputs. There is evidence that a low protein restriction can slow the rate of progression of renal disease and the time until end-stage renal failure. A low protein intake ameliorates uremic symptoms and prevents osteodystrophy, hypertension, and metabolic acidosis because of the lower intake of phosphate, sodium, potassium and acid. Although still debated, evidence has been accumulated indicating that low-protein alimentation can also slow progression of renal disease. It was possible to hypothesize a) either the reduction of proteinuria which occurs independently of reduction achieved through ACE inhibitors, b) or an improved control of blood pressure, and c) a possible reduction of a nephrotoxin originating from protein metabolism (74).

Proteinuria, which causes progression of renal disease, is reduced within 1 week by a low protein diet (71) and is observed. The reduction was in the range 24-37%, whereas in 202 patients Walser reported a 27% reduction (75). A linear correlation between decrease in protein and reduction of proteinuria has also been described. In study A of Klahr *et al.* (55) there was an association between reduction in urine protein and subsequent GFR decline. Dietary proteins reduced the rate of rise of urine protein excretion during follow-up. An initial reduction in proteinuria of 1 g/day caused a lower decline in GFR of nearly 1 ml/year. Also in the study of Aparicio (72) low protein intake was reduced with a nearly 50% reduction of proteinuria. Suppression of proteinuria was also achieved in patients under angiotensin-converting enzyme inhibitors (76).

Low protein diets do not cause malnutrition. It is known from 1966 (Table 1) that a low protein diet providing 25 g/kg/d resulted in a positive nitrogen balance in 85% of the patients who adhered to the prescription (25). In addition in 1973 Coburn and Kopple have demonstrated that a protein intake of 0.6 g/kg/d results in a neutral nitrogen balance (77).

We now know that body weight, creatinine production, albumin, transferrin are constant in patients given low protein diets. This is also true in patients treated with low protein diet supplemented with ketoacids (74).

Should protein intake be restricted in predialysis patients? (78). The authors stressed that he experience tells that protein restriction ameliorates uremic signs and symptoms including peripheral neuropathy (79). It also improves insulin resistance (80), red cell lipid peroxidation (81), osteodystrophy because of reduced phosphorus intake (82). The low protein diet reduced blood urea and well as blood concentration of other waste products.

Dialysis can be postponed of nearly 1 years when GFR is of 10 ml/min in non-diabetic and 15 ml/min in diabetic patients. The low protein diet is not associated with

higher rates of death, hospitalization or sign of malnutrition since they provide appropriate intakes of energy and protein and other nutrients. In addition a low protein diet reduces proteinuria and ameliorates acidosis. The cost for low protein diet is modest (78).

The benefits of dietary protein restriction in CKD include the reduction of the breakdown of protein and aminoacids, and also of albuminuria, gravity of hyperphosphatemia, acidosis and azotemia and may even cause an increase in serum albumin (83). Furthermore it reinstates renal reserve in CKD (84). In addition since homocysteine concentration in serum correlates with protein content, a low protein diet probably reduces homocysteine levels.

The amelioration of acidosis deserves some specific comments. Metabolic acidosis, which has been considered as a uremic toxin (85), causes defect in growth hormone, IGF-1, insulin, glucocorticoids, thyroid hormone, parathyroid hormone and vitamin D, which in adults are associated with loss of bone mass in adults. In CKD many abnormalities in bone and muscle metabolism can be linked to acidosis and may be corrected with sodium bicarbonate administration. Acidosis impacts on albumin synthesis, nitrogen balance, the ability to adapt to a low protein intake, increases amino acid and protein degradation, and much more on insulin resistance, which stimulates muscle degradation by proteolytic mechanisms (86,87). In particular we do know that acidosis decreases GH secretion, IGF-1 response, suppresses insulin mediate glucose metabolism, decreases T_3 and T_4 and increases TSH as well as the production of glucocorticoids, decreases sensitivity of PTH secretion to changes in plasma calcium, suppresses activation to $1,25(OH)_2$ cholecalciferol (86). In CKD Papadoyannakis *et al.* have improved nitrogen balance with bicarbonate administration (88), Garibotto *et al.* showed that proteolysis was proportional to acidosis and blood cortisol (89). Williams *et al.* (90) improved urea production and nitrogen balance by bicarbonate administration. In addition in patients with metabolic acidosis a reduction in albumin synthesis occurs (91). Thus two serious adverse effects of CKD, namely bone disease and loss of protein stores can be prevented and cured by achieving optimal bicarbonate concentrations (91). In a recent study of Cianciaruso *et al.* (92) in patients of a tertiary care unit at a eGFR of 9.8±1.3 ml/min had a serum bicarbonate of 24.1±3.3 mol/L. At the end of the study when their GFR >6.0 ml/min serum bicarbonate averaged23.3±3.8 mEq/L. The same investigators in compliant patients CKD grade 4-5, observed that serum bicarbonate did not fall below 23.1±3.4 with a protein intake of 0.72 and below 22.1±4.0 mEq/L with a protein intake of 0.92 g/Kg (93).

8. DEFERRING RENAL REPLACEMENT THERAPY

In USA, Medicare criteria allow dialysis treatment when GFR is < of 10 ml/min in nondiabetic patients when GFR is < of 15 ml/min in diabetic patients. Having this in mind a study was therefore performed to explore the possibility of deferring initiation of dialysis with a supplemented very low protein diet providing 0.3 g/kg. Ideal Body weight. A total of 23 patients (GFR of 7.4±1.9 ml/min had renal survival to dialysis was 353 days (12 patients had survival times > 2 years), when their GFR averaged 4.5±1.8 ml/min. Acidosis and hypercholesterolemia were both predictive of shorter renal survival time, BUN and GFR were not. Signs of malnutrition did not develop. Rate of progression averaged 1.07±0.32 ml/min per yr (94).

Recently Cianciaruso *et al.* (93) studied prospectively a group of patients with eGFR <11 ml/min/1.73 m^2 receiving 0.6 g/kg of protein having fixed a minimum eGFR of 6.1 ml/min for receiving dialytic therapy. Median time to dialysis start was 11.8 months. A total of eight patients ended the study without starting dialysis after 21.8 months. There was an excellent control of systolic and diastolic blood pressure, absence of signs of malnutrition, left ventricular hypertrophy did not progress, a normal left ventricular mass was seen, 80% of them had hemoglobin level > 11g/dl. The study shows the possibility to safely postpone initiation of dialysis without affecting quality of life and with a lower economic impact (93). These findings are in agreement with recent findings in CKD patients with a GFR < 15 ml/min. Some 37% of them after 2 years of follow-up did not reach the outcomes of dialysis or death.

A diet providing 0.55 g/kg bw (Diet A) was evaluated for 18 months for several markers of uremic toxicity against a diet providing 0.8 g/kg bw protein (Diet B) in a randomized controlled trial in patients with CKD4-5, having eGFR of 18 ±7 ml/min/1.73 m^2 (92.) Both diets provided a minimum energy intake not below 30 cal/kg bw/d. Diet A diet provided 0.72 g/kg of protein whereas Diet B provided a protein intake of 0.92 g/kg, the difference was of 0.2 g/Kg bw/d. Both diets did not cause malnutrition and kept PTH serum levels constant. No difference was seen for blood pressure under both regimens. Diet A was associated with a better control of blood urea, a lower urinary sodium excretion (30 mmol/day), and a reduced need for of phosphate binders, bicarbonate supplements, allopurinol and diuretics. Furthermore Diet A kept plasma stable, thus pointing to a better metabolic control in comparison with Diet B. Some 27% of the patients were compliant with Diet A, 53% with diet B.

In a prospective randomized multi center study excluding diabetic patients (95) a supplemented very low protein diet was compared to maintenance hemodialysis, in patients with a GFR of 6.1±1.1 ml/min. In patients receiving the diet proved metabolically safe as indicated by stability of albumins, hemoglobin and bicarbonate. Patients entered in dialysis with a mean GFR of 4.3±1.1 ml/min. The control group was started on dialysis. One year later 50% of the patients on hemodialysis and 58% of patients on diet died (p not significant). Such approach turned very beneficial in economical terms (96).

9. CONCLUSION

Fifth years after the introduction of dietary management of renal failure (15-17) hundreds of studies, including 17 prospective randomized trials (50-66),

discussed in 5 meta-analyses (45-49) have shown the feasibility, the safety and the efficacy of low protein diets made of natural foods and very low protein diets made of amino acids and/or ketoacids. The diet does not impair survival on subsequent dialytic treatment and grants the maintenance of nitrogen balance by impacting not only on symptomatology and biochemistries at a low cost. The controversy on the usefulness of low protein diet and of the amino acids and of their nitrogen free analogues in chronic renal failure is settled (97,98) and patients may be kept in safe conditions even months after Medicare allows the starting of dialysis.

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Key Words: Low protein diets, Very Low Protein Diets, Essential Amino Acids, Ketoacids, High Biological Value Proteins, Caloric Intake, CKD, Review

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