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Effect of personalized dietary intervention on nutritional, metabolic and vascular indices in patients with chronic kidney disease

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Abstract. – OBJECTIVE: Patients with chronic kidney disease (CKD) present a markedly increased cardiovascular (CV) morbidity and mortality since the early stages of the disease and a high prevalence of malnutrition, inflammation, and accelerated atherosclerosis. Personalized nutritional intervention, with of a low-protein diet (LPD), since the early stages of CKD should be able to achieve significant metabolic improvements. In our study we have verified the effects of a personalized dietary intervention in patients in the CKD stages 3/4 KDOQI on nutritional, metabolic and vascular indices.

PATIENTS AND METHODS: We have evaluated renal function, lipid profile, mineral metabolism, inflammatory indices, and acid-base balance of 16 patients with CKD (stages 3/4 KDOQI). Assessment of nutritional status, body composition, bone mineral density and muscle mass, using body mass index (BMI), handgrip strength, bioelectrical impedance analysis (BIA), and dual energy X-ray absorptiometry (DEXA) was performed. Vascular indices and endothelial dysfunction such as carotid intima-media thickness (cIMT) and the brachial artery flow-mediated dilation (baFMD) were also analyzed.

RESULTS: After dietary interventions, we observed a significant increase in plasma bicarbonate ($p = 0.004$) and vitamin D levels ($p = 0.03$) and a concomitant significant reduction of phosphorus concentration ($p = 0.001$) and C-reactive protein (CRP) ($p = 0.01$).

CONCLUSIONS: Nutritional intervention potentially plays a major role in reducing the progression of CKD and systemic complications of predialysis patients. A low-protein diet (LPD) ensuring vegetable protein intake and a reduced amount of specific micronutrients should be recommended to stage 3/4 CKD patients in order to ameliorate metabolic profile, renal outcome, and reduce cardiovascular risk factors.

Key Words:
Low protein diet, Chronic metabolic acidosis, Malnutrition, Inflammation, Mineral metabolism, Chronic kidney disease.

Introduction

Patients with chronic kidney disease (CKD) have increased morbidity and mortality for cardiovascular diseases (CVD)[1,2]. Although traditional risk factors are common among these patients, they can only in part explain the increased susceptibility to CVD. Patients during CKD present increased catabolic state especially in peripheral tissues, such as skeletal muscle. Malnutrition negatively impacts on patients' outcome by accelerating atherosclerosis and by increasing susceptibility to infections[3-6]. Low-protein diet (LPD) to maintain optimal nutritional status was suggested as a therapeutic measure in CKD by Beale in 1869[7] and by Giordano and Giovannetti[8,9] showing that LPD was able to amiliorate uremic symptoms, in order to delay the initiation of dialysis, positively influencing patients' quality of life and reducing midterm mortality. The effects of LPD on CKD progression remained uncertain[10-14].

LPD determines positive effects on secondary hyperparathyroidism, insulin resistance, hyperlipidemia, arterial hypertension, and acid-base balance[9]. Moreover the strict clinical monitoring during LPD administration may reduce the risk of developing negative effects on nutritional status. LPD should be pleasant, varied, not too restrictive, and tailored to patients' habits, because the modification of dietary habits entails a major change in lifestyle. Regarding protein intake, a threshold of with estimated Glomerular Filtration Rate (eGFR)

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for starting a LPD has not been defined yet. The common opinion among nephrologists and nutritionists is to start a LPD when eGFR is below 60 ml/min/1.73 m^2 (CKD stage 3). Indeed, a LPD is effective in reducing the levels of both phosphorus and parathyroid hormone[15-17]. However, the first aim of the nutritional intervention in CKD is the early and strict restriction of energy, salt, and saturated fat intake[9,15], because arterial hypertension, overweight, and obesity are highly prevalent from the initial stages of the disease and these conditions are associated with CKD progression. Indeed, it has been demonstrated that LPD improves lipid profile by reducing lipoprotein AI and the Apo-AI:Apo-B ratio[10,16-17].

In addition, a link exists between nutritional intervention, based on reduced salt and phosphorus intake, and cardiorenal protection[18-20]. Short-term studies have shown that dietary phosphate reduction effectively decreases phosphate-regulating hormone fibroblast growth factor (FGF)-23, which may directly cause left ventricular hypertrophy. Moreover, Yamamoto et al[21] have shown that higher serum phosphorus intake is associated with higher left ventricular mass.

Metabolic acidosis is present in the majority of patients with glomerular filtration rate (eGFR) below 20-25% of normal[22-24] and its degree generally ranges from mild to moderate. Experimental and clinical studies have shown that chronic metabolic acidosis, even when mild, determines several negative effects on organ function, including muscle wasting, bone disease, impaired growth, impaired insulin sensitivity, and progression of renal failure[22,24-26]. Metabolic acidosis directly stimulates bone resorption, inhibits bone formation and vitamin D production, and affects the stimulation of parathyroid hormone or alters its end-organ responsiveness. Therefore, acidosis can be a contributory factor in the development or exacerbation of bone metabolic and functional alterations[27-31].

Aim of the present study was to evaluate the effects of a personalized nutritional intervention in patients with CKD (stage 3/4, KDOQI) on nutritional and metabolic markers and on vascular indices.

Patients and Methods

The Clinical Research Ethics Committee of the University Hospital Policlinico Umberto I, Sapienza University of Rome, Italy, approved the study protocol.

Study Design

This is an interventional, single-center study performed over a period of 16 months (from July 2011 to November 2012). The clinical and laboratory parameters and instrumental data were evaluated at baseline (before administration of LPD) and subsequently at 3, 6, and 12 months. We performed a complete physical examination and complete nutritional assessment, including weight, height, body mass index (BMI) and body composition.

Inclusion Criteria

Patients aged > 18 years, CKD 3/4 stage, 60 ml/min ≤ eGFR ≥ 15 ml/min were enrolled.

Exclusion Criteria

Patients affected by neoplastic diseases, renal artery stenosis, liver disease, human immunodeficiency virus (HIV) and with polycystic kidney disease were excluded. Patients who had already followed a LPD were also excluded.

Diet

A trained renal dietician elaborated the personalized nutritional therapy for each patient. Diet was characterized by reduced protein intake and by an appropriate caloric intake, according to KDOQI guidelines[32], and by a controlled intake of calcium, phosphorus, sodium and potassium. Adherence to the diet during outpatient visits was verified every 3 months by the assessment of urinary nitrogen.

Laboratory Measurements

Blood was drawn in the morning after an overnight fasting of at least 12 h. In all patients, the levels of fasting plasma glucose, total serum cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatine phosphokinase (CPK), creatinine, nitrogen in the blood, serum calcium, phosphate, albumin, prealbumin, serum electrolytes, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were measured using standard automated techniques. Vitamin D (as 1,25-dihydroxyvitamin D (1,25(OH) 2D3) was measured using radioimmunoassay. PTH was measured using a two-site assay that measures "intact" hormone (iPTH). Arterial blood gas (ABG) analysis was performed using a blood gas analyzer (Nova Phox Plus C). Thyroid function test was done using chemiluminescent assays for thyroid stimulating hormone

(TSH), triiodothyronine (T3), and thyroxine (T4). Urinary protein and nitrogen were assessed with collection of 24-h urine.

Vascular Assessment

Flow-Mediated Dilation Brachial Artery (baFMD)

According to the method described by Celermajer et al[33] the endothelium-dependent vasodilation (FMD) of the brachial artery was assessed using high-resolution ultrasound. Patients were studied by a single investigator and Toshiba Aplio XV (Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 5- to 12-MHz linear transducer with a 0.01-mm resolution. This was used for the ultrasonographic study of FMD, following a standardized vascular protocol. The brachial artery was imaged above the antecubital fossa in the longitudinal plane. A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall was selected for continuous 2D gray-scale imaging. To create a flow stimulus in the brachial artery, a sphygmomanometric cuff was initially placed on the forearm. Typically, the cuff was inflated to at least 50 mmHg above the SBP to occlude the arterial inflow for a standardized length of time. The release of the occluding cuff resulted in reactive hand hyperemia and an associated increase in blood flow through the brachial artery, which induced shear stress on the arterial wall and provided a stimulus for endothelium-dependent dilatation. Brachial artery diameter following reactive hyperemia was recorded for 5 min after tourniquet release. Flow-mediated dilation was typically expressed as the change in poststimulus diameter as a percentage of the baseline diameter[31].

FMD = [(diameter post-hyperemia − basal diameter) / basal diameter] × 100. The values of FMD were considered normal if they were greater than 10%.

Carotid Intima-Media Thickness Assessment (cIMT)

At 0, 3, 6, 9, and 12 months, right (R) and left (L) carotid ultrasound was blindly performed by an experienced sonographer who was unaware of the characteristics of the subjects under examination. Participants were studied with the high-resolution B-mode ultrasound machine Toshiba Aplio XV (Toshiba Aplio xV, Toshiba American Medical Systems, Inc., Tustin, CA, USA) equipped with a 5- to 12-MHz linear transducer with a 0.01-mm resolution, following a standardized vascular protocol. Three different longitudinal views (anterior oblique, lateral, and posterior oblique) and a transverse view were obtained. cIMT was measured at three points on the far walls of both left and right distal common carotid arteries, carotid bulb, and the proximal portion of the internal carotid arteries. Images were captured in end diastole triggered by electrocardiographic recording. The mean IMT was computed as the average cIMT on both sides. The value of cIMT was considered normal when between 0.55 and 1 mm[34].

Anthropometric Assessments

Body weight was determined to the nearest 0.1 kg using a calibrated digital scale. Body mass index was calculated from patient's weight and height (weight (kg) / [height (m)]^2.

Bioelectrical Impedance Analysis (BIA)

A noninvasive method to monitor body fluid variation is the bioelectrical impedance analysis (BIA, Akern, Florence, Italy). In particular, multifrequency bioelectrical impedance analysis (MF-BIA) measures total body water and compartmental volumes by passing a series of different electrical currents and electrical frequencies through the body. Bioimpedance analysis was performed using an impedance plethysmograph that emits an 800-μA, 50-kHz alternating current. Measurements were taken with subjects being in a supine position for 5 minutes, according to the manufacturer's guidelines. The analysis of the entire body involves the placement of two electrohydraulic injectors at the back of the hands and feet at the distal ends of metacarpals and metatarsals, and two measuring electrodes were placed on the dorsal surfaces of the wrists and ankles. Then, we proceed recording the impedance, resistance, reactance, and phase angles and the subsequent transformation into estimates of lean body mass, cell mass, and body water.

Handgrip Strength

The handgrip strenght is the assessment of muscle mass function by means of the hand dynamometry. It is based on the determination of the strength of the finger flexor muscles performed with the use of a dynamometer. The handgrip strength is evaluated in the upright position, with the dominant arm held away from the body and, at the request of the examiner, exerts

the maximum force of contraction of the hand. The test is repeated 3 times, with a minimum interval of 5 minutes between each test.

Dual-energy X-ray Absorptiometry

Body fat, lean body mass and bone mineral density (BMD) were measured by Dual-Energy-X-Ray Absorptiometry (DEXA) (Hologic 4500 RDR), with coefficient of variation of < 1% for bone density and < 1.5% for fat mass[35].

Statistical Analysis

Data management and analysis were performed using IBM® SPSS® Statistics 17 for Windows® software (SPSS Inc., Chicago, IL, USA). The normality of variables was tested using the Shapiro-Wilk method for normal distributions. Categorical variables were expressed as number (percentage). All variable are expressed as mean ± standard deviation. Friedman Analysis of Variance or Repeated Measures ANOVA were used to test the equality of means. A probability value of $p < 0.05$ was considered statistically significant.

Results

Patients' Characteristics

Sixteen consecutive patients (10 female and 6 male subjects, mean age of 47.8 ± 8.4 years) with CKD (stages 3/4, 60 ml/min ≤ eGFR ≥ 15 ml/min, according to the KDOQI guidelines) were enrolled. The eGFR was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) formula[43]. Fifteen patients were suffering from hypertension with good control of blood pressure and 4 patients were affected by diabetes mellitus with good control of blood glucose levels. Ten patients were taking ACE inhibitors, 9 patients were taking angiotensin receptor blockers and 4 of them taking double blockade. Therapy was not changed during the follow-up period.

The characteristics of the personalized nutritional therapy are summarized in Table I.

The anthropometric, biochemical and instrumental parameters of the patients enrolled are shown in Table II. There were no significant differences in serum glucose, sodium, potassium, calcium, hemoglobin, and urinary proteins during the entire follow-up. Out of the 16 patients enrolled, 14 patients completed the follow-up at 12 months, and 2 patients completed the follow-up at 6 months and 9 months (1 patient because of pregnancy and 1 patient because of an acute coronary syndrome). The biochemical, metabolic, inflammatory and instrumental parameters analyzed during the follow-up are shown in Table III.

In particular, urinary nitrogen remained stable in all patients indicating a good compliance to the LPD. The blood urea nitrogen and proteinuria sig-

Table I. Personalized nutritional therapy.

Energy	27.78 ± 3 Kcal/Kg /day
Protein	0.7 ± 0.1 g/Kg Ideal Body Weight/day; 50% high biological value including protein-free food products
Phosphorus	≤ 1000 mg/day
Potassium	Individualized according to patient's potassium levels
Sodium	2-5 g/day
Calcium*	Supplementation 500 mg/day with calcium carbonate

*According to patient's needs.

Table II. Patients' characteristics at baseline.

	Population
Male n (%)	6 (37.5%)
Age (year)	47.8 ± 8.4
Body mass index (kg/m^2)	29.9 ± 7.4
Hb (g/dL)	11.6 ± 3.2
Serum Creatinine (mg/dL)	2.2 ± 0.4
Blood urea nitrogen (mg/dL)	97.3 ± 39.4
eGFR (mL/min/1.73 m^2)	33.0 ± 5.8
Serum Uric Acid (mg/dL)	6.1 ± 1.6
Homocysteine (µmol/L)	28.9 ± 16.3
Calcium (mg/dL)	9.6 ± 0.8
Phosphorus (mg/dL)	4.1 ± 0.4
iPTH (ng/L)	58.3 ± 32.7
1.25(OH)2D3 (ng/mL)	23.6 ± 13.2
ESR (mm/h)	17.1 ± 9.8
CRP (mg/dL)	0.2 ± 0.2
Proteinuria (g/24h)	0.60 ± 0.70
pH	7.39 ± 0.04
HCO_3^- (mmol/L)	21.1 ± 3.3
BE (mmol/L)	-3.4 ± 3.2
cIMT (mm)	0.88 ± 0.22
RRI	0.68 ± 0.12
FMD (%)	16.7 ± 7.7

Data are show as mean ± standard deviation or number (%). *Abbreviations*: Hb: Hemoglobin; eGFR: estimated Glomerular Filtration Rate; iPTH: intact Parathyroid Hormone; 1,25(OH)2D3: 1,25-dihydroxyvitamin D; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein; BE: Base Excess; cIMT: carotid Intima Media Thickness; RRI: Renal Resistive Index; FMD: Flow Mediated Dilation.

Table III. Biochemical, metabolic, inflammatory, and instrumental parameters during the follow-up.

	T0 (Baseline)	T1 (3 months)	T2 (6 months)	T3 (9 months)	T4 (12 months)	
Serum Creatinine (mg/dL)	2.20 ± 0.38	2.14 ± 0.47	2.07 ± 0.38	2.18 ± 0.58	2.21 ± 0.68	$p = 0.645$
Blood Urea Nitrogen (mg/dL)	97.30 ± 39.44	66.20 ± 25.41	63.40 ± 17.53	63.30 ± 18.20	66.10 ± 23.77	$p = 0.008$
eGFR (mL/min/1.73m^2)	32.95 ± 5.82	36.13 ± 9.09	36.25 ± 7.98	35.25 ± 9.62	35.72 ± 11.14	$p = 0.394$
Serum Uric Acid (mg/dL)	6.08 ± 1.57	6.58 ± 1.18	6.08 ± 0.98	6.02 ± 1.41	6.21 ± 1.50	$p = 0.174$
Homocysteine (µmol/L)	28.89 ± 16.30	23.03 ± 9.93	18.28 ± 5.27	16.09 ± 3.65	14.98 ± 5.26	$p = 0.377$
Serum Calcium (mg/dL)	9.57 ± 0.83	9.38 ± 0.91	9.45 ± 0.56	9.36 ± 0.81	9.28 ± 0.82	$p = 0.411$
Serum Phosphorus (mg/dL)	4.20 ± 0.38	3.98 ± 0.33	3.87 ± 0.45	3.88 ± 0.38	3.55 ± 0.30	$p = 0.001$
iPTH (ng/L)	58.34 ± 32.72	70.98 ± 26.46	77.82 ± 38.48	70.74 ± 21.40	78.42 ± 32.58	$p = 0.453$
1.25(OH)2D3 (ng/mL)	23.64 ± 13.20	22.60 ± 11.08	20.76 ± 12.41	27.64 ± 9.93	30.23 ± 11.06	$p = 0.032$
CRP (mg/dL)	0.18 ± 0.17	0.13 ± 0.09	0.07 ± 0.10	0.16 ± 0.28	0.12 ± 0.21	$p = 0.013$
Proteinuria (g/24h)	1.17 ± 1.74	0.87 ± 1.37	0.67 ± 0.95	0.53 ± 0.51	0.46 ± 0.58	$p = 0.046$
*p*H	7.39 ± 0.04	7.41 ± 0.04	7.40 ± 0.02	7.40 ± 0.04	7.39 ± 0.03	$p = 0.493$
HCO_3^- (mmol/L)	21.08 ± 3.30	23.76 ± 2.90	23.75 ± 1.28	24.26 ± 1.93	22.99 ± 2.60	$p = 0.004$
BE (mmol/L)	-3.36 ± 3.19	-0.61 ± 2.97	-0.73 ± 1.29	-0.55 ± 2.10	-1.77 ± 2.47	$p = 0.002$
cIMT (mm)	0.88 ± 0.20	0.91 ± 0.22	0.88 ± 0.22	0.90 ± 0.21	0.94 ± 0.23	$p = 0.562$
RRI	0.68 ± 0.12	0.70 ± 0.11	0.65 ± 0.12	0.69 ± 0.11	0.68 ± 0.11	$p = 0.763$
FMD (%)	16.73 ± 7.70	14.63 ± 7.11	17.41 ± 5.31	16.08 ± 5.05	17.32 ± 5.53	$p = 0.764$

Data are presented as mean ± standard deviation. Friedman Analysis of Variance or Repeated Measures ANOVA were used to test the equalityof means. *Abbreviations*: eGFR: estimated Glomerular Filtration Rate; iPTH: intact Parathyroid Hormone; 1,25(OH)2D3: 1,25-dihydroxyvitamin D; CRP: C-Reactive Protein; BE: Base Excess; cIMT: carotid Intima Media Thickness; RRI: Renal Resistive Index; FMD: Flow Mediated Dilation.

nificantly decreased in all patients and eGFR remained stable (Table III). Serum albumin (g/dL) and total proteins (g/dL) levels remained stable during the follow-up (baseline: 4.5 ± 0.4; 12 months: 4.7 ± 0.5; p = n.s.) (baseline: 7.4 ± 0.43, 12 months: 7.3 ± 0.37; p = n.s.; respectively). We also observed a reduction, although not statistically significant, in total cholesterol (mg/dL) (baseline 176.3 ± 37.5; 12 months 159.3 ± 26.2; p = n.s.) and in HDL cholesterol (mg/dL) (baseline 47.2 ± 18.5; 12 months 52.9 ± 26.6; p = n.s.), and triglycerides levels (mg/dL) did not differ in all patients before and after dietary intervention (baseline 126.6 ± 43.8; 12 months 100.2 ± 36.7; p = n.s.). Regarding the blood gas parameters, we did not observe pH changes, although a statistically significant increase in serum bicarbonate levels was shown (Table III). Serum calcium levels remained stable during the follow-up and iPTH values increased at 12 months, although not significantly (Table III).

Phosphorus concentrations significantly reduced, whereas 1,25(OH)2D3 significantly increased. Moreover at the end of the follow-up, CRP levels were significantly reduced (Table III).

The anthropometric parameters were stable throughout the entire follow-up [BMI (kg/m^2): baseline 29.9 ± 7.4; 12 months 28.4 ± 4.8; p = n.s.). Moreover, cIMT and brachial artery FMD remained stable during the 12-months follow-up (Table III). No significant changes in muscle strength and body composition were observed during the entire follow-up (data not shown).

Discussion

Patients with CKD present an increased catabolic and inflammatory state with loss of proteins from muscles and other tissues, presenting a high risk of developing malnutrition and atherosclerosis and a high risk for CV morbidity and mortality since the early stages of the disease. In this light, a tailored nutritional intervention could represent a reliable strategy to reduce these risks[36-39].

Our dietary intervention provided a low concentration of salt, phosphorus, and acid-inducing dietary proteins, preferring base-inducing proteins by fruits and vegetables intake. A significant increase in the concentration of serum bicarbonate levels and vitamin D and a significant reduction of the concentration of serum phosphorus and inflammatory markers such as ESR and CRP were shown. As indicated in our results, body composition analysis revealed a non-significant reduction of fat mass but maintenance of lean mass, even in overweight subjects in whom

we obtained a reduction of BMI values. We also observed a slight but not significant improvement in muscle strength, indicating a maintenance/increase in functional muscle mass, and an improvement in metabolic parameters with a reduction of total and LDL cholesterol, triglycerides, and an increase in HDL cholesterol, although not statistically significant. In addition, there was no reduction in serum albumin and total serum proteins, and renal function remained stable with a significant reduction of urinary protein excretion during the follow-up. cIMT and brachial artery FMD, early markers of atherosclerosis and endothelial dysfunction, remained stable for the duration of the follow-up, indicating a slowdown of accelerated atherosclerosis, which is a common feature in patients with CKD[5].

Low-protein intake alone, although relevant, represents only one part of the nutritional treatment in CKD. Indeed, a dietetic intervention with reduced energy, saturated fats, salt, proteins, and specific micronutrients (phosphorus, sodium, potassium, etc.) should be strongly recommended to improve metabolic derangements, renal outcome, and cardiovascular risk[40-42]. Factors that should be taken into consideration, as recommended by the National Kidney Foundation–KDOQI or Care of Australians With Renal Disease guidelines[32,43,44], include the following: (1) level of calcium and phosphorus control, (2) presence of atherosclerotic vascular disease, (3) protein intake, (4) degree of muscle wasting, (5) presence of comorbidities, and (6) stage of renal failure[22,41,42]. Moreover, the disturbances of mineral metabolism and increased serum phosphate levels are associated with cardiovascular events and mortality representing independent risk factors for mortality in patients with CKD. Metabolic acidosis develops in patients with CKD secondary to reduced renal mass and inability of the remaining nephrons to excrete the daily acid load through ammoniagenesis and to preserve and produce bases. Metabolic acidosis determines an increase of muscle protein catabolism, insulin resistance and reduction of protein synthesis[43-44]. Protein restriction ensures a reduction of endogenous production of fixed acids and studies showed that base-inducing fruits and vegetables reduce kidney injury and improve metabolic acidosis in patients with reduced GFR (45,46). Further studies should determine if patients with CKD should be prescribed with alkaline diets as part of their nutritional and metabolic management[47-50].

Normalization of serum bicarbonate concentrations in all patients is advisable, but bases administration is not without possible side effetcs and might be associated with volume overload, congestive heart failure, exacerbation of preexisting hypertension, associated with the development of vascular calcifications[22,24,30]. Indeed, normalization of serum bicarbonate concentrations might promote metastatic calcification by decreasing the solubility of calcium phosphate.

The personalized nutritional intervention, aimed at providing adequate intake of essential aminoacids with proteins of high biological value, has to ensure an adequate caloric intake (30-35 kcal/kg/d) in order to prevent the development of malnutrition and to correct the presence of metabolic acidosis[45]. Moreover, proteins type more than total protein amount might importantly affect nephropathy progression[10]. The use of protein-free food products may help in reducing protein, phosphorus, and sodium intake while supplying an adequate energy intake[48]. In our study, dieteray intervention was tailored taking into account the degree of renal dysfunction (eGFR), BMI, and food intakes of each patient, thus differentiating the degree of protein restriction and energy intake to achieve greater compliance and, consequently, a greater effectiveness of the nutritional treatment prescribed[49,50]. In our patients the urinary nitrogen remained stable during the entire follow-up, indicating a good compliance of patients to the LPD.

We enrolled a limited number of patients, not including a control group, to observe the improvements obtained by a personalized nutritional intervention. Our data may reflect the small sample size and, therefore, larger randomized controlled trials are needed to confirm our findings. Also, our study is based on associations with surrogate end points. The generated hypothesis needs further prospective follow-up studies with stronger end points to show causality.

Conclusions

In CKD, a LPD has minimal effects on the decline of eGFR but it may be able to delay the start of renal replacement therapy. The main pathophysiological rationale for nutritional intervention in CKD is to prevent the onset and to reduce the worsening of metabolic derangements and to possible modify the cardiorenal risk factors associated with CKD[12,24]. Although a high-

degree scientific evidence is still lacking, the initiation of a nutritional intervention is recommended from the early stages of CKD, with the progressive implementation of a LPD and increasing vegetables protein intake to reduce serum phosphorus, uremic toxins and to improve the metabolic acidosis[49]. The protein-free food products represent a very important tool for the implementation of a LPD to ensure adequate energy supply, reducing the production of nitrogenous waste products[46,48,50]. Because obesity might be an important factor in increasing the prevalence of CKD, nutritional strategies targeting obesity might also reduce CKD progression[11,51]. The results obtained in the present work highlight the positive effects of a tailored dietary intervention in CKD on several nutritional, metabolic and atherosclerosis markers[52].

Conflict of Interest

The authors report no conflicts of interest.

References

1) Kuznik A, Mardekian J, Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of National Health and Nutritional Examination Survey Data, 2001-2010. BMC Nephrol 2013; 14: 132.
2) Verhave JC, Troyanov S, Mongeau F, Fradette L, Bouchard J, Awadalla P, Madore F. Prevalence, Awareness, and Management of CKD and Cardiovascular Risk Factors in Publicly Funded Health Care. Clin J Am Soc Nephrol 2014; 9: 713-719.
3) Zyga S, Christopoulou G, Malliarou M. Malnutrition-inflammation-atherosclerosis syndrome in patients with end-stage renal disease. J Ren Care 2011; 37: 12-15.
4) Yilmaz MI, Carrero JJ, Axelsson J, Lindholm B, Stenvinkel P. Low-grade inflammation in chronic kidney disease patients before the start of renal replacement therapy: sources and consequences. Clin Nephrol 2007; 68: 1-9.
5) Akdag I, Yilmaz Y, Kahvecioglu S, Bolca N, Ercan I, Ersoy A, Gullulu M. Clinical value of the malnutrition-inflammation-atherosclerosis syndrome for long-term prediction of cardiovascular mortality in patients with end-stage renal disease: a 5-year prospective study. Nephron Clin Pract 2008; 108: 99-105.
6) Pecoits-Filho R, Lindholm B, Stenvinkel P. The malnutrition, inflammation, and atherosclerosis (MIA) syndrome--the heart of the matter. Nephrol Dial Transplant 2002; 17: 28-31.
7) Beale LS. Kidney Diseases, Urinary Deposits and Calculous Disorders, Their Nature and Treatment. Philadelphia: Lindsay and Blakiston, 1869.
8) Giordano C. Protein restriction in chronic renal failure. Kidney Int 1982; 22: 401-408.
9) Thilly N. Low-protein diet in chronic kidney disease: from questions of effectiveness to those of feasibility. Nephrol Dial Transplant 2013; 28: 2203-2205.
10) Bellizzi V. Low-protein diet or nutritional therapy in chronic kidney disease? Blood Purif 2013; 36: 41-46.
11) Paes-Barreto JG, Silva MI, Qureshi AR, Bregman R, Cervante VF, Carrero JJ, Avesani CM. Can renal nutrition education improve adherence to a low-protein diet in patients with stages 3 to 5 chronic kidney disease? J Ren Nutr 2013; 23: 164-171.
12) Goraya N, Wesson DE. Dietary management of chronic kidney disease: protein restriction and beyond. Curr Opin Nephrol Hypertens 2012; 21: 635-640.
13) Levey A. Effects of dietary protein restriction on the progression of moderate renal disease in the Modification of Diet in Renal Disease Study. J Am Soc Nephrol 1996;7:2616-2626.
14) Levey AS, Greene T, Beck GJ, Caggiula AW, Kusek JW, Hunsicker LG, Klahr S. Dietary protein restriction and the progression of chronic renal disease: what have all of the results of the MDRD study shown? Modification of Diet in Renal Disease Study group. J Am Soc Nephrol 1999; 10: 2426-2439.
15) Cianciaruso B, Pota A, Pisani A, Torraca S, Annecchini R, Lombardi P, Capuano A, Nazzaro P, Bellizzi V, Sabbatini M. Metabolic effects of two low protein diaets in chronic kidney disease stage 4-5--a randomized controlled trial. Nephrol Dial Transplant 2007; 23: 636-644.
16) Kaysen GA, Odabaei G. Dietary protein restriction and preservation of kidney function in chronic kidney disease. Blood Purif 2013; 35: 22-25.
17) Newsome B, Ix JH, Tighiouart H, Sarnak MJ, Levey AS, Beck GJ, Block G. Effect of protein restriction on serum and urine phosphate in the modification of diet in renal disease (MDRD) study. Am J Kidney Dis 2013; 6: 1045-1046.
18) Zoccali C, Ruggenenti P, Perna A, Leonardis D, Tripepi R, Tripepi G, Mallamaci F, Remuzzi G, REIN Study Group. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. J Am Soc Nephrol 2011; 22: 1923-1930.
19) Kanda E, Ai M, Kuriyama R, Yoshida M, Shiigai T. Dietary acid intake and kidney disease progression in the elderly. Am J Nephrol 2014; 39: 145-152.
20) Kuwahara M, Bannai K, Segawa H, Miyamoto K, Yamato H. Cardiac remodelling associated with protein increase and lipid accumulation in early-

stage chronic kidney disease in rats. Biochim Biophys Acta 2014; 1842: 1433-1443.

21) Yamamoto KT, Robinson-Cohen C, de Oliveira MC, Kostina A, Nettleton JA, Ix JH, Nguyen H, Eng J, Lima JA, Siscovick DS, Weiss NS, Kestenbaum B. Dietary phosphorus is associated with left ventricular mass. Kidney Int 2013; 83: 707-714.

22) Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis 2009; 54: 270-277.

23) Kraut JA, Nagami GT. Chapter 29 – Metabolic Acidosis of Chronic Kidney Disease. Textbook of Nephro-Endocrinology, 2009; pp. 457-481.

24) Kraut JA, Kurtz I. Metabolic acidosis of CKD: diagnosis, clinical characteristics, and treatment. Am J Kidney Dis 2005; 45: 978-993.

25) Krieger NS, Culbertson CD, Kyker-Snowman K, Bushinsky DA. Metabolic acidosis increases fibroblast growth factor 23 in neonatal mouse bone. Am J Physiol Renal Physiol 2012; 303: 431-436.

26) May RC, Kelly RA, Mitch WE. Mechanisms for defects in muscle protein metabolism in rats with chronic uremia. Influence of metabolic acidosis. J Clin Invest 1987; 79: 1099-1103.

27) Cochran M, Wilkinson R. Effect of correction of metabolic acidosis on bone mineralisation rates in patients with renal osteomalacia. Nephron 1975; 15: 98-110.

28) Krieger NS, Frick KK, Bushinsky DA. Mechanism of acid-induced bone resorption. Curr Opin Nephrol Hypertens 2004; 13: 423-436.

29) Jara A, Felsenfeld AJ, Bover J, Kleeman CR. Chronic metabolic acidosis in azotemic rats on a high-phosphate diet halts the progression of renal disease. Kidney Int 2000; 58: 1023-1032.

30) Yonova D. Vascular calcification and metabolic acidosis in end stage renal disease. Hippokratia 2009; 13: 139-140.

31) Disthabanchong S, Radinahamed P, Stitchantrakul W, Hongeng S, Rajatanavin R. Chronic metabolic acidosis alters osteoblast differentiation from human mesenchymal stem cells. Kidney Int 2007; 71: 201-209

32) Levey AS. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007; 53: 766-772.

33) Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R; International Brachial Artery Reactivity Task Force. Guidelines for the ultrasound assessment of endothelial-dependent flow mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39: 257-265.

34) Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. Circulation 2006; 113: 396-398.

35) Greco EA, Fornari R, Rossi F, Santiemma V, Prossomariti G, Annoscia C, Aversa A, Brama M, Marini M, Donini LM, Spera G, Lenzi A, Lubrarno C, Migliaccio S. Is obesity protective for osteoporosis? Evaluation of bone mineral density in individuals with high body mass index. Int J Clin Pract 2010; 64: 817-820.

36) Ikizler TA. Role of nutrition for cardiovascular risk reduction in chronic kidney disease patients. Adv Chronic Kidney Dis 2004; 11: 162-171.

37) Caglar K, Hakim RM, Ikizler TA. Approaches to the reversal of malnutrition, inflammation, and atherosclerosis in end-stage renal disease. Nutr Rev 2002; 60: 378-387.

38) Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, Terwee P, Teta D, Wang AY, Wanner C. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int 2013; 86: 1096-1107

39) Ikizler TA. A Patient with CKD and Poor Nutritional Status. Clin J Am Soc Nephrol 2013; 8: 2174-2182.

40) Filipowicz R, Beddhu S. Optimal nutrition for predialysis chronic kidney disease. Adv Chronic Kidney Dis 2013; 20: 175-180.

41) Ebner N, Springer J, Kalantar-Zadeh K, Lainscak M, Doehner W, Anker SD, von Haehling S. Mechanism and novel therapeutic approaches to wasting in chronic disease. Maturitas 2013; 75: 199-206.

42) Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr 2013; 97: 1163-1177.

43) National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. Am J Kidney Dis 2000; 35: 1-140.

44) Elder G, Faull R, Branley P, Hawley C; The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. Caring for Australasians with Renal Impairment (CARI). Nephrology 2006; 11 Suppl 1: S230-261.

45) Schwalfenberg GK. The alkaline diet: is there evidence that an alkaline pH diet benefits health? J Environ Public Health 2012; 2012: 727630.

46) Eustace JA, Astor B, Muntner PM, Ikizler TA, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int 2004; 65: 1031-1040.

47) Menon V1, Tighiouart H, Vaughn NS, Beck GJ, Kusek JW, Collins AJ, Greene T, Sarnak MJ. Serum bicarbonate and long-term outcomes in CKD. Am J Kidney Dis 2010; 56: 907-914.

48) D'Alessandro C, Rossi A, Innocenti M, Ricchiuti G, Bozzoli L, Sbragia G, Meola M, Cupisti A. Dietary protein restriction for renal patients: don't forget protein-free foods. Ren Nutr 2013; 23: 367-371.

49) Giordano M, Ciarambino T, Castellino P, Paolisso G. Light and shadows of dietary protein restriction in elderly with chronic kidney disease. Nutrition 2013; 29: 1090-1093.

50) Paes-Barreto JG, Silva MI, Qureshi AR, Bregman R, Cervante VF, Carrero JJ, Avesani CM. Can renal nutrition education improve adherence to a low-protein diet in patients with stages 3 to 5 chronic kidney disease? J Ren Nutr 2013; 23: 164-171.

51) Liu M, Li XC, Lu L, Cao Y, Sun RR, Chen S, Zhang PY. Cardiovascular disease and its relationship with chronic kidney disease. Eur Rev Med Pharmacol Sci 2014; 18: 2918-2926.

52) Al Suleimani YM, Al Za'abi M, Ramkumar A, Al Mahruqi AS, Tageldin MH, Nemmar A, Ali BH. Influence of treatment with gum acacia on renal vascular responses in a rat model of chronic kidney disease. Eur Rev Med Pharmacol Sci 2015; 19: 498-506.