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CLINICAL RESEARCH

Influence of Diet Balanced with Essential Amino Acids / Keto Acid Analogs and High-Nutrient Blend on the Progression of Renal Failure in Patients in the Pre-Dialysis Stage of Chronic Kidney Disease Caused by Systemic Autoimmune Diseases

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Abstract

The aim of the study was to evaluate the effect of a low protein diet (LPD) balanced with essential amino acids (EAA) / keto acid analogs (KAA) and protein "SUPRO-XT 219D" in the composition of the high-energy nutrient blend (HENB) for slow down of renal failure in patients in the pre-dialysis stage of chronic kidney disease (CKD) induced by systemic autoimmune diseases (SAD).

Material and Methods: In this study, 46 patients (35 with systemic lupus erythematosus and 15 with various forms of systemic vasculitis) with CKD in stages 3-4 were randomized into three groups. Group 1 (18 patients: 10 with CKD stage 3 and 8 with CKD stage 4) was given LPD (0.6 g protein per kg of body weight per day comprising 0.3 g of vegetable protein and 0.3 g of animal protein) balanced with EAA/KAA (Diet #1); Group 2 (18 patients: 9 with CKD stage 3 and 9 with CKD stage 4) was given the same LPD, but with an increased vegetable protein content (purified soy protein SUPRO-XT 219D) up to 0.4 g/kg/day in the composition of HENB (Diet #2); Group 3, comparison group, (10 patients: 7 with CKD stage 3 and 3 with CKD stage 4) was given a free diet (Diet #3) based on the patient's personal preferences. Both options of LPD were offered to all the patients of Groups 1 and 2 regardless of their baseline nutritional status (NS). The duration of the observation was 24-48 months. The NS was evaluated based on the bioelectrical impedance analysis. The protein and calorie intake was calculated from the 3-day food diary.

Results: Among the 46 patients with CKD stages 3-4, NS impairment was detected in almost half the patients (45.7%). Both forms of LPD were well tolerated. The correction of the nutritive impairment was achieved in patients with baseline impaired NS; the remaining patients of Groups 1 and 2 demonstrated the safety of NS against LPD. At the same time, among Group 3 patients, during the progression of renal disorders, the NS rate was observed to increase by 1.5 times (from 40% to 60%). Slowing down the glomerular filtration rate (GFR) decline was observed in the patients treated with LPD for at least a year, which was more significant in the subgroup fed with the increased quota of vegetable protein SUPRO-XT 219D.

Conclusion: Early restriction (on pre-dialysis stage) of the protein intake (0.6 g/kg/day) supplemented with HENB and EAA/KAA revealed a positive effect on the NS of CKD patients and was found to be able to slow down the GFR decline.

Keywords: *systemic autoimmune diseases; chronic kidney disease; impairment of nutritional status; essential amino acids; keto acid analogs; SUPRO-XT 219D.*

Introduction

One of the major problems in nephrology is a warning for maximum decline in the end-stage of CKD with very limited possibilities to influence the expression of the disease.

The progression rate of renal failure in CKD patients depends on several factors, including the violation of NS, which significantly effects the survival and the rehabilitation level of the patients and has an important prognostic value [1-4]. Thus, according to Zakar G. [5], the mortality during the first year of dialysis was 15% among those patients whose serum albumin concentration at admission on hemodialysis was above 3.5 g/dl and 39% among those patients with a serum albumin concentration of less than 3.0 g/dl.

Over the recent years, a growing interest in the dietary treatment of patients in the pre-dialysis stages of CKD (PDS-

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CKD) has been observed. A few studies have shown that limiting the daily quota of protein to 0.6 g/kg/day with the addition of EAA/KAA prevented the accumulation of toxic products and reduced or postponed the development of terminal uremia [5-7]. However, the results of several multicenter studies with larger numbers of participants, including the MDRD (Modification of Diet in Renal Disease), do not provide a solid reason for such a clear conclusion [8-10]. The differences in the results can be explained by the complexity in the LPD organization, particularly large-scale ensuring of the sufficient quota of high biological value protein and caloric intake (at least 35 kcal/kg/day). With the energy deficit, there is an impairment of the EAA/KAA absorption in the gastrointestinal tract and the transformation of KAA in EAA [11,12].

The difficulties of prolonged LPD use, the mixed results of its effectiveness, spontaneous reduction of protein and calorie consumption due to the decreased appetite at the onset of the deterioration of the renal function, indicate the need for further clinical study regarding the influence of diet in renal failure.

The reasons for the high frequency of NS impairment in patients with systemic disease on PDS-CKD are still poorly studied.

We conducted our own study to assess the impact of LPD balanced with EAA/KAA and HENB based on SUPRO-XT 219D on the slowing of renal failure in patients with SAD on PDS-CKD.

Material and Methods

In this study, 46 patients (35 with systemic lupus erythematosus and 15 with various forms of systemic vasculitis) with CKD in stages 3-4 were randomized into three groups (Table 1). Group 1 (18 patients: 10 with CKD stage 3 and 8 with CKD stage 4) was given LPD (0.6 g protein per kg of body weight per day comprising 0.3 g of vegetable protein and 0.3 g of animal protein) balanced with EAA/KAA (Diet #1); Group 2 (18 patients: 9 with CKD stage 3 and 9 with CKD stage 4) was given the same LPD, but with an increased vegetable protein content (purified soy protein SUPRO-XT 219D) up to 0.4 g/kg/day in the composition of HENB (Diet #2). EAA and KAA (Ketosteril; Fresenius Kabi, Germany; daily dose 0.1 g/kg) was additionally administered to the LPD in the patients of Groups 1 and 2. Group 3, comparison group, (10 patients: 7 with CKD stage 3 and 3 with CKD stage 4) was given a free diet (Diet #3; 1.1-1.3 g protein per kg of body weight per day) based on the patient's personal preferences.

Table 1.

Distribution of patients according to CKD stage

Groups	CKD stage 3 (eGFR: 59-30 ml/ min/1.73 m²)	CKD stage 4 (eGFR:2 9-15 ml/ min/1.73 m²)
	Number of patients	
Group I, n=18; Diet #1	10	8
Group 2, n=18; Diet #2	9	9
Group 3, n=10; Diet #3 (free diet)	6	4
Total	25	21

The mean daily caloric content of the LPD in Group 1 was 33 kcal/kg. Nutrient blend "Peptoproten Nephro" (ProtenPharma, Russia) was used as a dry powder for the cocktail (17g of highly purified soy protein, including protein hydrolysate 4 g per 100 g powder) or bars (12 g of soy protein, including protein hydrolysate 2 g per 50 g bar). The composition also includes slowly absorbed carbohydrates (maltodextrin) and vegetable fats (soybean, palm), vitamins B and E, folic acid, nicotinamide, calcium pantothenate, L-carnitine and dietary fiber. The total caloric content of the nutrient blend was 405 kcal (1693 kJ) per 100 g.

The groups were equal in terms of severity of the blood pressure and proteinuria. Antihypertensive therapy included fosinopril 5-10 mg/day and loop diuretics.

Recurrent nephritis was found to occur in the patients surveyed. To study NS, bioelectrical impedance analysis and laboratory tests (an absolute lymphocyte count, albumin and transferrin levels) were used. The protein and calorie intake was calculated from the 3-day food diary, where the patient recorded, in detail, his daily diet by indicating the protein and calorie content.

Statistical analysis of the study results performed using the SPSS 10 software package for Windows. Frequencies of individual values, mean, standard deviation of the mean, Student's *t*-test, confidence level, and the level of significance *p* were calculated. The Mann-Whitney (U Test) was used to compare the differences between the two independent groups (for nonparametric data). The value of p less than 0.05 was considered significant.

In the calculation of renal survival, the decrease in eGFR<15ml/min/1.73m² or the commencement of renal replacement therapy was considered the endpoints.

Result and Discussion

The NS impairment was detected in almost half the patients (21/45.7%) (Table 2). However, nutritive impairment was detected only at CKD stage 4 in patients with chronic glomerulonephritis, but it appeared at CKD stage 3 in all the patient groups with SAD and increased with the progression of renal failure to CKD stage 4 [12].

Table 2.

Nutritional status impairment in patients with CKD stages 3-4

Groups	CKD stage 3 (eGFR: 59-30 ml/ min/1.73 m²)	CKD stage 4 (eGFR: 29-15 ml/ min/1.73 m²)
	Number of patients	
Group I, n=18	40% (4/10)	62.5% (5/8)
Group 2, n=18	33.3% (3/9)	55.5% (5/9)
Group 3, n=10	33.3% (2/6)	50% (2/4)
Total, n=46	36% (9/25)	57.1% (12/21)

Previously, we demonstrated the influence of a low-calorie diet, the severity of renal failure, high proteinuria, and the duration of corticosteroid therapy in SAD on the reduced BMI, which is the integral index of nutritive impairment in CKD patients [12].

In the present study, Diets #1 and #2 were administered to all the Group 1 and 2 patients, respectively (regardless of NS and without its prior correction). We had to contend with two major issues. Could LPD supplemented with EAA/KA (Ketosteril;

Fresenius Kabi, Germany; daily dose 0.1 g/kg) adjust and prevent NS impairment in patients with SAD, and slow down the progression of CKD? Is it possible to increase the beneficial effects of LPD through a partial replacement of animal protein on HENB comprising soy isolate (SUPRO-XT 219D)?

Diets #1 and #2 were satisfactorily tolerated, as documented in the three-day food records. Satisfactory tolerance of diet explained the treatment compliance. Thus, the majority of patients were taking Diets #1 and #2 for long periods (over 1.5 years). In this case, the intake Diets #1 and #2 in patients with anorexia resulted in its significant decrease. Anorexia was decreased, primarily, in patients with a partial replacement of animal protein on highly purified soy protein in the diet. As a result, after three months' treatment of employing these diets, normalization of the main indicators of the NS was achieved in those patients with initial NS impairment. The effectiveness of the diets was observed in both women and men. Normalization of body weight and other NS parameters occurred more quickly in patients treated with Diet #2 and the change in the nutritive indicators at the end of three months was more significant than with Diet #1 (Table 3).

Table 3.

Dynamics *of changes in NS* parameters *in patients with CKD stages and initial NS impairment on LPD (n=17)*

Parameter	Diet #1 (n=9)		Diet #2 (n=8)	
	Baseline	After 3 months	Baseline	After 3 months
BMI (kg/m^2)	17.9±0.35 (18.9-15.0)	19.5±0.33 1.6 (23-18.4)	17.6±0.21 (17.9-15.1)	20.0±0.29* 2.4 (21.5-18.9)
Muscle mass (%)	28.9±0.3 (27.6-30.0)	36.4±0.62* (38.0-32.0)	28.5±0.5 (27.8-29.9)	37.1±0.85** (39.1-31.1)
Serum albumin (g/l)	32.0±1.2 (35-30)	38.0±0.9* (41-35)	29±1.1 (32-28)	37.0±0.8* (38-35)
Serum transferrin (mg/dl)	169.7±2.03 (175-164)	190.3±2.3* (195-186)	163.5±2.95 (169-158)	196.4±3.38* (200-190)
Lymphocytes (abs. number)	1689.3±21.3 (1750-1618)	1895.3±26.2* (1956-1830)	1433.5±115.9 (1655-1218)	1931.3±38.4** (200-1830)

**P <0.05, **P<0.01 vs baseline*

During the same period of observation, the increased nutritive impairment and the deterioration of health, despite a free diet without protein restriction, were observed in 10 patients of the control group, including four patients with NS impairments of an initial degree. As the progression of renal disease increased the frequency of NS impairment increased by 1.5 times (from 40% to 60%) in patients with CKD stage 4.

To assess the effect of LPD on the progression of chronic renal failure, we compared the GFR curve decline in patients treated with Diets #1 and #2 with that of the patients of the comparison group on a regular diet (Table 4, Fig.1). By the end of one year of observation, the GFR curve decline was close to the estimated index (4 ml/min/year) in 10 patients of the control group. Two of the three patients of the control group received hemodialysis at the end of 1.5 years. In patients treated with LPDs, for at least a year, the GFR curve decline compared with the estimated GFR was about 0.75 ml/min/year in patients treated with Diet #1 and 0.8 ml/min/year on Diet #2.

Based on these calculations, one can assume that a 4-year use of Diets #1 and #2 in patients with CKD stage 4 and an initial GRF of 26 ml/min will lead to an increase in the pre-dialysis period by 11 months and 12 months, respectively.

Table 4.

Effect of LPD on the progression of chronic renal failure in patients with CKD stage 4

Diet options/ N of patients	eGFR (59-30 ml/min/1.73 m^2)			
	Period of observation (years)			
	Screening	0.5	1.0	1.5
Diet #1 (n=18)	26.4±0.21	24.8±0.41 Δ1.6	23.1±0.17 Δ3.3	21.6±0.19 Δ5.0
Diet #2 (n=18)	26.5±0.33	24.9±0.32 Δ1.6	23.3±0.27 Δ3.2	22.0±0.23 Δ4.5
Diet #3 (n=10)	26.8±0.22	24.7±0.29 Δ2.1	22.8±0.35 Δ4.0	20.6±0.25 Δ6.2 P<0.05

Δ - *GFR curve decline*

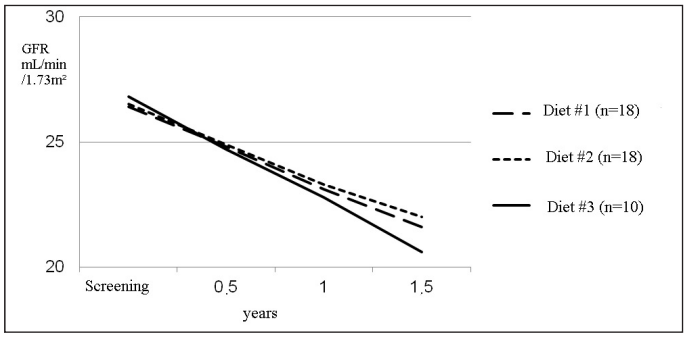

Figure 1.

Effect of LPD on the progression of chronic renal failure

A significant reduction in hyperphosphatemia was observed in all the 36 patients taking KAA, which contain calcium salts (without phosphorus) that promote the binding of the phosphate in the intestine and its removal from the organism. Decreasing the severity of hyperphosphatemia in patients with CKD stages 3-4 becomes very important. As is known, hyperphosphatemia causes increased secretion of the parathyroid hormone with hypercalcemia and the development of secondary hyperparathyroidism [1,13,14]. The decrease in hyperphosphatemia was more significant among the Group 2 patients; therefore, replacing animal protein with highly purified soy protein having low phosphate content can more effectively control the hyperphosphatemia and prevent the development of secondary hyperparathyroidism. At the same time, the hyperphosphatemia was increasing in all the 10 patients of the comparison group, who did not limit the protein in their diet and were not given Ketosteril (Table 5).

Table 5.

Effect of LPD on hyperphosphatemia and hyperazotemia in patients with CKD (n = 36)

Parameter	Control	Diet #1 (n=18)		Diet #2 (n=18)	
		Baseline	After 12 months	Baseline	After 12 months
Serum phosphorus (mg/dl)	2.5-5.5	6.8±0.55 (5.8-7.8)	5.0±0.29** (4.5-5.8)	6.9±0.42 (5.7-7.9)	4.7±0.23** (4.0-5.2)
Serum urea nitrogen (mg/dl)	10-12	67.4±5.11 (35-30)	53.8±4.04* (45-60)	69.7±3.12 (65-74)	48.2±2.03** (55-75)

**P <0.05, **P<0.01 vs* baseline

Our data are consistent with the results of Mitch W. et al., who noted the possibility of achieving reutilization of the urea nitrogen for the synthesis of EAA from the KAA with a reduction of azotemia on the intake of LPD and KAA [15].

The results of this study indicate that the LPD balanced with the EAA/KAA and highly purified soy protein over prolonged use (at least 12 months) caused a reduction in the levels of total cholesterol and LDL cholesterol, triglycerides, and HDL cholesterol increasing in the plasma, in 36 patients (18 patients of Group1 and 18 patients of Group 2) with dyslipidemia.

According to some data [1,7], the LPD balanced with EAA/KAA and highly purified soy protein caused other metabolic effects such as a reduction of urinary albumin excretion, a reduction in the concentration of oxalic acid, free radicals, and an increase in the testosterone levels and vitamin D_3 in the plasma. All these effects slowed the progression of atherosclerosis and reduced the manifestations of renal osteodystrophy, according to bone biopsy [1,14].

Conclusion

Thus, NS impairment is one of the most frequent complications in CKD patients with SAD, which reaches 36% at stage 3 and 57% at stage 4. Among those patients with chronic glomerulonephritis, the NS impairment was detected only at stage 4 in 28.3% of cases [12,16]. The high risk of NS impairment in patients with SAD is caused by the factors of the disease activity and the duration of the corticosteroid treatment.

The primary prevention of malnutrition in patients with CKD at stages 3-4 traditionally includes the restriction of dietary protein intake with the addition of EAA/KA intake. The LPD balanced with the EAA/KA prevents the accumulation of toxic products, reduces or postpones the appearance of uremic dyspepsia, while a diet without protein restriction, exacerbating dyspepsia, is capable of inducing the NS impairment [1, 7, 13].

The results of our study indicate that the intake of vegetable protein of high biological value (SUPRO-XT 219D) is a prospective way for nephroprotection in PDS-CKD. The ratio of dietary animal protein to highly purified soy protein (SUPRO-XT 219D) may depend upon the patients' food tastes and habits. According to our data, it was appropriate to increase the content of highly purified soy protein up to 0.3 g/kg/d in patients committed to using mostly vegetable protein, as well as in anorexic patients. Soy protein increases the hyperperfusion and hyperfiltration in the remnant nephrons less than animal protein (meat, fish, milk, etc) [12]. According to our data, the LPD (0.6 g protein per kg of body weight per day) with partial replacement of animal protein on HENB with the addition of EAA/KAA allows the slowing down of the GFR decline by 0.8±0.03 ml/min/1.73 m² and ensures the prevention of malnutrition in patients with CKD caused by SAD. This LPD version is recommended for patients with CKD stage 4 and digestive disorders caused by uremia; these dietary recommendations must be applied in patients with SAD, starting with CKD stage 3, if the disease is actively persistent.

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