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EFFECTS OF DIETARY INTERVENTION ON LIPID PROFILE AND C-REACTIVE PROTEIN IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease (CVD). Both traditional risk factors, including dyslipidemia and nontraditional risk factors including inflammation may increase CVD risk. The aim of this study was to investigate the influence of conventional low-protein diet and diet supplemented with Ketosteril® on lipid profile and C-reactive protein in patients with CKD. Results of the study showed that hyperlipidemia following CKD was improved by both diets. Our findings suggest that changes in animal protein intake could play an important role for CRP levels. In conclusion, the low-protein diets may exert a beneficial effect on the development of CVD in patients with CKD.

INTRODUCTION

Mortality from cardiovascular disease among patients who are treated for end stage renal disease is 10 to 20 times higher than that of similarly aged individuals from the general population [Foley *et al.,* 1998]. In comparison with people without chronic kidney disease (CKD), a 1.5- to 3--fold increased risk for coronary heart disease (CHD) has been reported among the population with CKD, before the need for dialysis therapy [Culleton *et al.,* 1999; Go *et al.,* 2004]. Furthermore, several cross-sectional studies have identified a higher prevalence of traditional risk factors such as hypertension, higher LDL cholesterol level among patients with CKD compared with people with normal kidney function [Sarnak *et al.,* 2002]. An elevated level of C--reactive protein (CRP) has been recently recognized as and important nontraditional risk factor. Analyses of the Third National Health and Nutrition Examination Survey showed a higher prevalence of CRP and several other CHD risk factors among patients with *versus* without CKD [Muntner *et al.,* 2004]. Low protein diet treatment has been proved to slow chronic kidney disease progression. Diminishing in protein consumption may improve hormonal, metabolic and renal function parameters [Maroni *et al.,* 1997; Aparicio *et al.,* 2000]. However, the optimal level and composition of dietary protein is still under debate. In order to minimize the consequences of limiting protein supply, the supplementation with essential amino acids and amino acid ketoanalogues are often applied.

The aim of this study was to investigate the influence of conventional low-protein diet and diet supplemented with essential amino acids and ketoanalogues on lipid profile and C-reactive protein in patients with chronic kidney disease.

MATERIALS AND METHODS

Two groups of patients with conservatively treated chronic renal failure (I group – 12 patients aged 74.3±5.5 years, II group – 12 patients aged 65.2±17.1 years) were studied before and after 6 months of a low protein, low phosphorus diet. All the patients were on antihypertensive medications and drugs commonly used in the CKD and 11 patients before and during therapy were treated with stable doses of statins. Causes of CKD were chronic nephrosclerosis (n=7), glomerulonephritis (n=4), polycystic kidney disease (n=3), interstitial nephritis (n=1), and others (n=9). Exclusion criteria included diabetes mellitus, proteinuria greater than 2.0 g/day or renal transplantation. The recommended diet included protein 0.6 g/kg of ideal body mass with different level of animal protein: I group (KD) with less than half of the animal protein and oral administration of Ketosteril®, II group (UD) with at least half of the animal protein. An assessment of dietary intake from average of 3-day food records was performed before the dietary intervention and at the end of the study. Nutrient intake was calculated using Dieta 2 software (IŻŻ, Poland). In analysis of adherence to dietetic recommendations mean values in the range ± 10% were considered as correct [Ziemlański *et al.,* 1997]. Before the dietary intervention, fasting plasma lipid profiles (total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols), total proteins, albumin, C-reactive protein, creatinine and urea were measured using conventional methods. The same measurements were repeated at the end of the study. Weight and body composi-

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tion (by bioimpedance method) were also measured before and after dietary treatment. Calculations were performed using Statistica data analysis software system, version 6 (StatSoft, USA). The study was approved by the ethics committee of the Central Clinical Hospital of The Ministry of Internal Affairs and Administration, Warsaw, Poland.

RESULTS AND DISCUSSION

Before the treatment dietary content of the nutrients studied did not differ significantly between both groups except for total fat and fatty acids intakes, which were lower in the KD. After the treatment, KD consumed significantly more vegetal protein and fiber as well as less animal protein and monounsaturated fatty acids (MUFA) than the UD. In both groups total protein and saturated fatty acids (SFA) consumption exceeded the prescribed level. Moreover, in the KD animal protein intake was higher than the upper level of recommendation and in the UD energy, fiber as well as carbohydrate intakes were lower than recommended (Table 1). Despite the fact that compliance with diet was not complete, positive changes in dietary habits were observed. Strong associations were observed between dietary nutrients intake before treatment and their changes during diet therapy. In the KD changes in total carbohydrate, fiber and cholesterol intakes were inversely related with their initial intake (r=-0.792, p=0.002; r=-0.728, p=0.007; r=-0.701, p=0.011, respectively). Moreover, changes in energy, animal and vegetal protein per kg body weight as well as energy percent from SFA and MUFA were negatively related with their initial consumption (r=-0.822, p=0.001; r=-0.889, p=0.000; r=-0.837, p=0.001; r=-0.746, p=0.005, respectively). Similarly in the second group alterations in energy, animal and vegetal protein per kg body weight as well as energy percent from MUFA correlated negatively with their initial intake (r=-0.866, p=0.000; r=-0.768, p=0.004; r=-0.763, p=0.004; r=-0.773, p=0.003, respectively). Patients who consumed excess of these nutrients before therapy, limited their content in the diet during treatment, and persons with low intake increased it.

Before the treatment, none of the investigated parameters differ significantly between groups (Table 2). In all patients HDL cholesterol serum concentration correlated positively with creatinine clearance (r=0.477, p=0.029) and negatively with serum creatinine (r=-0.681, p=0.043). Such relations were also reported by others in 1.795 patients with chronic renal insufficiency enrolled in the baseline period of Modification of Diet in Renal Disease (MDRD) Study. After adjustment for age, gender and the presence of diabetes, glomerular filtration rate was positively associated with HDL cholesterol, but not associated with total or LDL cholesterol [Sarnak *et al.,* 2002].

After therapy again no significant differences in the parameters examined were noted between both groups. Body mass index, body fat and fat free mass were not affected by treatment in the KD. In the UD body mass index remained also unchanged, however body fat mass increased and fat free mass decreased. In this group, a decrease in serum urea concentration after therapy was observed as well.

Treatment significantly lowered serum total and LDL cholesterol concentrations in both groups. In KD alterations in total cholesterol concentration correlated negatively with its baseline value (r=-0.661, p=0.037), indicating the strongest effect of treatment in the patients with most severe hypercholesterolemia. The reasons of amelioration of lipid profile in both groups could be partly the same and partly different. In both groups this could be due to the decrease in animal protein intake. Substitution of animal for plant protein could be beneficial in KD since in this group indirect relations were observed between changes in serum total

TABLE 1. Recommended dietary intake of selected nutrients and actual dietary intake at the beginning and after 6 months of dietary treatment (mean values and standard deviations).

Nutrient	I group			II group		
	Recommended	At the beginning	After 6 months	Recommended	At the beginning	After 6 months
Energy (kcal/day)	1865 ± 318	1467 ± 677	1771 ± 414	1999 ± 277	1745 ± 715	1720 ± 418
Total protein (g/day)	41.1 ± 4.2	57.4 ± 18.1	50.1 ± 8.9	42.1 ± 5.1	64.7 ± 20.6$^{\#}$	49.8 ± 8.8$^{\#}$
Animal protein (g/day)	< 20.5 ± 2.1	34.7 ± 13.8$^{\#}$	23.7 ± 6.4*$^{\#}$	> 21.1 ± 2.6	43.6 ± 17.5$^{\#}$	32.0 ± 8.1*$^{\#}$
Vegetal protein (g/day)	> 20.5 ± 2.1	22.7 ± 9.7	26.4 ± 5.5*	< 21.1 ± 2.6	21.1 ± 8.2	18.7 ± 5.6*
Total fat (g/day)	62.2 ± 10.6	38.9 ± 23.2*$^{\#}$	58.5 ± 24.5$^{\#}$	66.6 ± 9.2	73.6 ± 35.5*	71.6 ± 21.2
SFA (g/day)	< 14.5 ± 2.5	18.2 ± 10.6*	23.4 ± 13.1	< 15.5 ± 2.2	32.0 ± 14.3*	25.4 ± 9.8
MUFA (g/day)	≤ 41.4 ± 7.1	12.9 ± 8.7*$^{\#}$	20.4 ± 11.0*$^{\#}$	≤ 44.4 ± 6.2	26.7 ± 15.4*	26.0 ± 8.0*
PUFA (g/day)	≤ 20.7 ± 3.5	4.6 ± 2.4*$^{\#}$	9.7 ± 3.9$^{\#}$	≤ 22.2 ± 3.1	9.1 ± 4.9*	15.0 ± 10.1
Cholesterol (mg/day)	< 200.0	223.2 ± 127.2	180.3 ± 69.4	< 200.0 ± 0.0	295.4 ± 164.2	200.8 ± 66.6
Fibre (g/day)	20.0 ± 30.0	20.3 ± 13.6	22.7 ± 3.9*	20.0 ± 30.0	15.4 ± 7.0	16.4 ± 4.0*
Total carbohydrate (g/day)	285.3 ± 52.4	239.5 ± 134.2	281.4 ± 55.1	307.7 ± 44.0	217.4 ± 105.4	234.1 ± 65.1

Statistically significant differences (Student's t test) between groups at given time points *p<0.05. Statistically significant differences (paried test) within groups in comparison to starting values $^{\#}$p<0.05. Abbreviations: SFA - saturated fatty acids; MUFA- monounsaturated fatty acids; PUFA - polyunsaturated fatty acids

TABLE 2. Patient data (mean values and standard deviations) before and after 6 months of dietary treatment.

Parameters	I group		II group	
	At the beginning	After 6 months	At the beginning	After 6 months
BMI (kg/m^2)	26.4 ± 4.1	26.8 ± 4.0	27.0 ± 3.0	27.3 ± 2.8
Weight (kg)	72.1 ± 2.8	73.1 ± 12.2	75.4 ± 8.7	76.3 ± 9.8
Fat mass (kg)	23.00 ± 8.47	23.7 ± 8.7	21.7 ± 7.5$^{\#}$	24.3 ± 7.5$^{\#}$
Fat mass (%)	31.5 ± 8.4	31.9 ± 8.6	28.6 ± 8.4$^{\#}$	31.6 ± 8.0$^{\#}$
Fat free mass (kg)	49.1 ± 9.3	49.5 ± 9.0	53.3 ± 7.9$^{\#}$	52.0 ± 7.8$^{\#}$
Fat free mass (%)	68.5 ± 8.4	68.1 ± 8.6	71.0 ± 8.7$^{\#}$	68.4 ± 8.1$^{\#}$
CrCl (mL/min/1.73m^2)	24.7 ± 8.8	26.6 ± 14.8	32.6 ± 12.0	33.4 ± 13.5
Creatinine (μmol/L)	250.0 ± 101.4	272.1 ± 144.2	230.9 ± 103.7	239.7 ± 121.1
Urea (mmol/L)	16.2 ± 5.7	15.8 ± 7.2	16.8 ± 9.1$^{\#}$	14.6 ± 7.4$^{\#}$
Total cholesterol (mmol/L)	4.7 ± 1.5$^{\#}$	4.1 ± 1.0$^{\#}$	5.2 ± 1.2$^{\#}$	4.5 ± 1.0$^{\#}$
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.2
LDL cholesterol (mmol/L)	2.6 ± 1.3$^{\#}$	2.1 ± 0.9$^{\#}$	3.3 ± 1.0$^{\#}$	2.7 ± 1.0$^{\#}$
Triacylglycerols (mmol/L)	1.6 ± 0.6	1.6 ± 0.6	1.5 ± 0.7	1.4 ± 0.4
C-reactive protein (mg/dl)	3.1 ± 2.6	4.5 ± 4.0	2.6 ± 2.5	2.4 ± 2.2

Statistically significant differences (Student's t test) between groups at given time points *p<0.05. Statistically significant differences (paried test) within groups in comparison to starting values #p<0.05. Abbreviations: BMI - body mass index; CrCl – calculated creatinine clearance

cholesterol concentration and changes in vegetal protein intake (r=-0.659, p=0.038) as well as changes in carbohydrates intake (r=-0.691, p=0.027), which depends, to a considerable degree, on vegetal food consumption. Also in KD fibre intake was significantly higher in comparison to the values seen before the treatment (Table 2). Supplementation of amino acid ketoanalogs might also be partly responsible for lipid lowering effect. Such effect was also stated by Teplan *et al.* [2003].

In the UD, the improvement in lipid profile could be ascribed mainly to a decrease in animal protein consumption. The mean HDL cholesterol concentration was not affected by treatment, but its increase was observed in 4 patients from the KD group and 6 from the UD group. In the UD changes in serum HDL cholesterol were negatively correlated with changes in animal protein intake (r=-0.651, p=0.030). Protein of animal origin has been proved to be more cholesterolemic and atherogenic than plant protein. Animals fed soy protein excrete more neutral and acidic steroids, and have increased activity of hepatic HMG CoA reductase and cholesterol 7 alpha-hydroxylase than those given animal protein. Animal protein may exert its hypercholesterolemic effect by mechanisms which include increased absorption of cholesterol and decreasing its turnover [Kritchevsky *et al.,* 1990]. Additionally in the UD changes in serum total cholesterol and LDL cholesterol were inversely related with changes in energy percent from polyunsaturated fatty acids (r=-0.790, p=0.007 and r=-0.752, p=0.008, respectively) clearly showing the antiatherogenic effect of PUFA consumption.

Interdependence between renal status and lipid metabolism could be deduced from positive correlations between creatinine clearance and HDL cholesterol serum concentration observed in both groups after the treatment (KD – r=0.787, p=0.001; UD – r=0.638, p=0.035). Changes in dietary cholesterol were directly related to changes in C-reactive protein level (r=0.690, p=0.027).

On the other hand, direct relation between initial creatinine level and changes in serum HDL concentration (r=0.835, p=0.005) seen in group KD could indicate the most pronounced effect of the diet in patients with most severe impairment of renal function.

Several relations observed in our study could indicate the impact of nutritional status on the efficacy of therapy. In the KD body fat mass percent before treatment was inversely related with changes in creatinine and urea serum concentrations, and directly related with changes in creatinine clearance (r=-0,578, p=0.049; r=-0.783, p=0.003; r=0.691, p=0.013, respectively). In the UD fat mass percent and BMI were directly related to serum C-reactive protein level (r=0.619, p=0.042; r=0.613, p=0.045, respectively). In the MDRD Study in patients with earlier stages of kidney disease, CRP level was related directly to measures of body fat and CVD risk factors. GFR level does not appear to influence CRP level in the earlier stages of chronic kidney disease [Menon *et al.,* 2003]. However in predialysis patients with terminal CRF (glomerular filtration rate 7 ± 1 mL/min) CRP level was significantly higher than healthy controls. Malnourished patients with CRF had higher CRP levels than well nourished [Stenvinkel *et al.,* 1999]. Beneficial effect of decreasing protein intake on inflammation appears from direct relation found between animal protein intake and CRP level (r=0.601, p=0.049) as well as between changes in animal protein intake and changes in CRP level in UD (r=0.634, p=0.030). In this group also changes in CRP concentrations were inversely related to their baseline concentrations (r=-0.684, p=0.029). Only in UD there was observed a significant decrease in serum urea concentration in spite that in both groups any significant differences in dietary total protein intake were noted. This could be caused by the fact that KD additionally had supplementation of Ketosteril®.

Treatment with vegan diet (0.3 g/kg/day) supplemented with essential amino acids and ketoanalogues significantly lowered serum urea and CRP levels [Bergesio *et al.,* 2005]. This might indicate that the decrease of serum urea concentration and possibly reduction of other protein breakdown products may account for decreased acute-phase response.

CONCLUSIONS

Results of the study showed that hyperlipidemia following CKD was improved by both diets. Our findings suggest that changes in animal protein intake could play an important role for CRP levels. In conclusion, the low-protein diets may exert a beneficial effect on the development of cardiovascular disease in patients with CKD.

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WPŁYW TERAPII DIETETYCZNEJ NA PROFIL LIPIDOWY I STĘŻENIE BIAŁKA C-REAKTYWNEGO U PACJENTÓW Z PRZEWLEKŁĄ CHOROBĄ NEREK

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U pacjentów z przewlekłą chorobą nerek (CKD) występuje zwiększone ryzyko chorób serca i układu krążenia, które jest związane z częstszym występowaniem zarówno tradycyjnych jak i nietradycyjnych czynników ryzyka takich, jak np. dyslipidemia czy stany zapalne. Celem pracy było zbadanie wpływu standardowej diety niskobiałkowej oraz diety suplementowanej preparatem Ketosteril® na profil lipidowy i stężenie we krwi białka C-reaktywnego (CRP) u pacjentów z CKD. Stwierdzono, że oba typy terapii dietetycznej miały pozytywny wpływ na profil lipidowy. Zaobserwowano ponadto, że zmiany podaży białka zwierzęcego mogą mieć istotny wpływ na stężenie CRP we krwi. Terapia dietetyczna u pacjentów z CKD może zatem odgrywać ważną rolę w prewencji i leczeniu chorób serca i układu krążenia.