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GROWTH HORMONE AND INSULIN-LIKE GROWTH FACTOR-1 AXIS RESPONSE TO LOW PROTEIN DIET IN CHRONIC KIDNEY DISEASE – A SHORT REPORT

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The aim of this study was to asses the influence of a conventional low-protein diet and diet supplemented with Ketosteril® on growth hormone and insulin-like growth factor-1 in patients with chronic kidney disease (CKD). Dietary intake of selected nutrients, anthropometric, hormonal and metabolic parameters were analysed before and after 6-month dietary treatment. We conclude that in CKD the response of the GH and IGF-I axis to a low protein diet can be determined by the quality of proteins and that animal protein seems to promote an increase in GH.

INTRODUCTION

Chronic kidney disease (CKD) affects endocrine regulations changing hormone metabolism and action. Under normal conditions, the growth hormone (GH) undergoes in kidney glomerular ultrafiltration, tubular reabsorption and lysosomal degradation. Its small amounts are excreted in the urine. Ultrafiltration of insulin like growth factor-1 (IGF-1) is very low due to its binding with proteins (IGFBPs) [Mak *et al.,* 2008]. In CKD both production and clearance of GH may be changed. Metabolic clearance of GH in CKD is diminished [Haffner *et al.,* 1994] while GH plasma levels are normal or increased [Mak *et al.,* 2008]. Diminished IGF-1 level in adults has been observed only in cachectic subjects. *In vitro* reduction in mRNA IGF-1 expression in CKD was observed in some but not all tissues and *in vivo* rate of IGF-1 synthesis has been reported to be normal even in adults with end stage renal disease [Mak *et al.,* 2008]. Despite of the GH level being normal or elevated in CKD, attenuation of GH action is observed, most often in children, contributing to severe growth retardation [Kaskel, 2003]. In adults with CKD, beneficial effects of GH therapy on urea kinetics, protein turnover and lean body mass have been demonstrated [Ikizler *et al.,* 1996; Garibotto *et al.,* 1997].

The aim of this study was to characterise the response of GH and IGF-1 to dietary treatment differing in the recommended source of protein.

MATERIALS AND METHODS

The experiment was carried out in two groups of patients with conservatively treated chronic kidney disease (group I – 12 patients aged 74.3±5.5 years, group II – 12 patients aged 65.2±17.1 years). Exclusion criteria included diabetes mellitus, proteinuria greater than 2.0 g/day or renal transplantation. Patients participated in a 6-month trial using a low protein, low phosphorus diet. Energy requirement of all subjects was calculated according to Harris and Benedict's formula and activity factor of 1.4. Dietary recommendations during the study were as follows: 30% of calories from fat, <7% of calories from saturated fat, <20% of calories from monounsaturated fat, <10% of calories from polyunsaturated fat, <200 mg cholesterol/day, about 52% of calories from carbohydrates, phosphorus 600-1000 mg/day, and protein 0.6 g/kg of ideal body mass. Different levels of animal protein were employed: group I with less than half of the total protein coming from animal protein and supplemented with oral administration of ketoanalogues of essential amino acids Ketosteril®, group II with at least half of the total protein brought by animal protein. Dietary intake (3-day food records), metabolic and hormonal parameters as well as weight and body composition were determined before and after the dietary treatment. Creatinine clearance (CCr) was estimated using the MDRD equation [Levey *et al.,* 1999]. Plasma levels of GH were measured using IRMA tests (Bio-Source Europe S.A., Belgium) and IGF-1 were measured by

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RIA kits (BioSource Europe S.A., Belgium). During daytime, GH upper limit is 5 ng/mL and the upper limits of age-related reference range for males are: 31-40 years 270 ng/mL, 41-50 years 318 ng/mL, 51-60 years 286 ng/mL, >60 years 245 ng/mL and for females are: 31-40 years 437 ng/mL, 41-50 years 406 ng/mL, 51-60 years 327 ng/mL, >60 years 320 ng/mL. Calculations of dietary intake were performed using Dieta 2 software (National Institute of Food and Nutrition, Poland) and Statistica data analysis software system, version 7.1 (StatSoft, Tulsa, USA). The experimental design was approved by the Ethical Committee of CSK MSWiA in Warsaw.

RESULTS AND DISCUSSION

Before treatment, dietary content of selected nutrients did not differ significantly between both groups except for the total fat intake, which was lower in group I. In all patients, the intake of animal protein per kilogram of body mass (kg bm) before treatment correlated positively with serum urea level (r=0.47, p=0.021), whereas consumption of vegetal protein/kg bm was inversely related to CCr and positively to serum creatinine concentration (r=-0.45, p=0.026; r=0.64, p=0.001 respectively). Additionally, CCr was negatively correlated with energy intake/kg bm (r=-0.518, p=0.009). After the treatment, the patients in group I consumed significantly more vegetal protein and less animal protein than the patients in group II (Table 1). Strong associations were observed between dietary nutrient intake before treatment and their changes during the dietary therapy. In group I changes in total carbohydrate as well as changes in energy, animal and vegetal protein per kg bm were negatively correlated to their consumption before the therapy (r=-0.792, p=0.002; r=-0.822, p=0.001; r=-0.889, p=0.000; r=-0.837, p=0.001 – respectively). Similarly, in group II alterations in energy, animal and vegetal protein per kg bw correlated negatively with their initial intake (r=-0.866, p=0.000; r=-0.768, p=0.004; r=-0.763, p=0.004, respectively). This indicates that patients who consumed these nutrients in excess before therapy, limited their content in the diet during the treatment, and persons with a very low intake increased it.

In group I BMI, body fat, fat free mass, CCr and urea serum concentration remained unchanged during dietary treatment. However, in group II after 6 months of the treatment a significant decrease of fat free mass together with an increase of fat mass occurred. In this group serum urea concentration was also significantly lower after the treatment.

GH level before the treatment was in the range of 0.31 to 8.87 ng/mL, whereas after the treatment it ranged from 0.47 to 8.46 ng/mL, in 2 cases exceeding normal values. In all patients both before and after the treatment GH serum concentration correlated negatively with age (r=-0.57, p<0.006 and r=-0.53, p=0.010). Before the treatment it was also negatively related with body mass (r=-0.53, p=0.012), and intake of total protein (r=-0.45, p=0.035). The response to the treatment depended on the diet (Table 2). A significant increase in GH level was observed only in group II (p=0.020). GH concentration in this group significantly exceeded the level observed in group I (p=0.008). After the treatment, GH concentration correlated negatively with vegetal protein intake (r=-0.42; p=0.030).

Values of IGF-1 concentration ranged from 103.8 to 387.9 ng/mL before the treatment and from 79.14 to 395.0 ng/mL after the therapy. After dietary treatment 2 patients had IGF-1 levels below normal values and 3 persons above them. In all patients before the treatment the mean serum IGF-1 concentration was inversely correlated to CCr (r=-0.47, p=0.021) and directly related to the intake of starch (r=0.54, p=0.016), vegetal protein and energy per kg bm (r=0.46, p=0.048; r=0.50, p=0.031, respectively). After the treatment, in 17 cases IGF-1 level was in the normal range, in 3 cases below and in 3 above the limits. The treatment did not evoke any consistent responses. An increase, a decrease or a lack of change were seen, thus statistically significant changes in IGF-1 level was not observed (Table 2). In group I, IGF-1 after the therapy was directly related to serum creatinine concentration (r=0.72, p=0.008) and negatively to CCr (r=-0.59, p=0.042). In group II, at the end of the treatment IGF-1 correlated positively with BMI (r=0.63, p=0.029), and intake of animal protein/kg bm (r=0.60, p=0.040). In this group changes in IGF-1 were inversely related to its initial level (r=-0.90, p=0.013).

Growth hormone level in our study was negatively correlated with patient's age, indicating preservation of relation existing in healthy people [Giordano *et al.,* 2008]. Both GH and IGF-1 serum levels showed considerable individual variation,

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

Nutrient	I group		II group	
	At the beginning	After 6 months	At the beginning	After 6 months
Energy (kcal/day)	1467±677	1771±414	1745±715	1720±418
Total protein (g/day)	57.4±18.1	50.1±8.9	64.7±20.6#	49.8±8.8#
Animal protein (g/day)	34.7±13.8#	23.7±6.4*#	43.6±17.5#	32.0±8.1*#
Vegetal protein (g/day)	22.7±9.7	26.4±5.5*	21.1±8.2	18.7±5.6*
Total fat (g/day)	38.9±23.2*#	58.5±24.5#	73.6±35.5*	71.6±21.2
Total carbohydrate (g/day)	239.5±134.2	281.4±55.1	217.4±105.4	234.1±65.1
Fibre (g/day)	20.3±13.6	22.7±3.9*	15.4±7.0	16.4±4.0*

Statistically significant differences (Student's t-test) between groups at given time points (*p<0.05). Statistically significant differences (paired test) within groups in comparison to starting values (#p<0.05).

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/1.73 m^2)	24.5±9.0	26.0±14.9	28.5±14.0	29.2±16.0
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#
GH (ng/mL)	2.07±1.38	1.28±1.10*	2.00±2.66#	2.93±2.41*#
IGF-1 (ng/mL)	211.33±88.05	168.65±70.36	186.67±70.36	195.22±79.70
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 (paired test) within groups in comparison to starting values (#$p<0.05$). Abbreviations: BMI – body mass index; CrCl – calculated creatinine clearance.

but they remained almost entirely within normal limits. Both before and after the therapy, GH level was inversely related to protein consumption. Under physiological conditions GH secretion has been shown to be stimulated by protein intake [Muller *et al*., 1999]. Since in CKD the rate of disappearance of GH from circulation has been shown to be reduced [Haffner *et al.*, 1994], our results may reflect deleterious effects of excessive protein consumption on GH secretion in CKD and/or resistance to GH, a well-recognized complication of CKD [Haffner *et al*., 1994]. To our knowledge there are no reports dealing with the effects of protein intake on GH-IGF I axis in CKD. However, the negative effects of excessive protein intake on the growth of children with CKD have been reported [Zadik et al., 1998]. On the other hand, GH response to dietary treatment was in our study more pronounced in a group consuming more animal protein than in the group receiving predominantly vegetal protein supplemented with Ketosteril. This might indicate that under conditions of a decreased protein intake in CKD, the stimulating effect of full quality, protein rich in essential amino acids on GH secretion is seen.

In contrast to GH, in our study IGF-I serum concentration was directly correlated with protein and energy consumption, likewise under normal conditions [Thissen *et al*., 1994]. This dichotomy between the effects of nutrition on GH and IGF-I observed in our study is difficult to explain, taking into consideration that synthesis of circulating IGF-I originating from liver is under GH control. However, serum IGF-I concentration reflects both the rate of biosynthesis and metabolic clearance, largely dependent on IGF-I binding protein profile [Thissen *et al*., 1994]. Thus, it may be speculated that this complex regulation is responsible for the observed relations. On the other hand, IGF-I concentration was directly correlated with serum urea and creatinine concentration and inversely with creatinine clearance, thus indicating a connection between the increase in IGF-I level and renal deterioration.

CONCLUSIONS

In conclusion, we could state that in CKD the response of the GH and IGF-I axis to low protein diet may depend on protein quality and that animal protein seems to promote an increase in GH.

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