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KETOANALOGUES AND ERYTHROPOIETIN MAY INFLUENCE PROGRESSION OF CHRONIC RENAL DISEASE IN PRE-DIALYSIS PATIENTS

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ABSTRACT: *Ketoacids (KA) and erythropoietin may influence the metabolic status of patients with chronic renal disease (CKD) in pre-dialysis stage treated with low-protein diets.*
We use three therapeutic protocols the first group low protein (LPD) with diet 0.6 gr/dl of protein with recombinant erythropoietin 6000 UI /week (40 UI/kg/week) and ketoacids (ketoanalogues 12 tab in day) the second group low protein diet 0.6 gr/dl and erythropoietin 6000 UI /week and third group only LPD.
The study involved 56 patients in the pre-dialytic stage of chronic renal disease with clearance of creatinine (ClCr) 20 - 35 ml/min with sign of renal anemia < 10 gr/dl. The patients were monitored at the beginning and after 6 months: groupe I had 18 patients, group II had 18 patients and group III had 20 patients.
In the finish of the study decrease in ClCr was significantly lower in group I (P < 0.01). At the same time a significant increase in serum albumin, body mass index (BMI), HDL –cholesterol, triglycerides, were found in group I (P < 0.05). The second and third groups have changes but no significantly.
As conclusion, co-administration of LPD, erythropoietin and KA constitute an effective alternative in conservative management of patients in pre-dyalisis stage, delaying in follow-up the period of progression of renal failure, correcting some metabolic parameters.
Key words:*Chronic renal disease, Ketoacids, Erythropoietin, Low protein diet.*

INTRODUCTION

Since the prevalence of chronic kidney disease (CKD) is rapidly increasing, every attempts should be done to slow the progression and to avoid the complications of CKD. Dietary protein restriction is an important strategy for delaying the progression of CKD, by reducing the accumulation of nitrogen catabolic substances, and by delaying the progress of CKD [1].

In early CKD stages the adoption of healthy diet might slow glomerular filtration rate (GFR) decline and decrease the prevalence of complete kidney failure [2].

The dietary protein can reduce albuminuria and will prevent uraemic symptoms. Until a means of preventing kidney disease or progression is found, safe methods of management such as dietary manipulation should be available for CKD patients [3].

Anemia is a frequent complication of chronic kidney disease.Richard Bright first observed this connection of anemia and renal failure in 1836. Miyake in 1977purified and identified erythropoietin. Eschbach (1985) did the first human use of EPO.

The introduction of erythropoietin (Epo) in clinical practice, more than two decades ago, altered completely the management of patients with chronic kidney disease (CKD). Some of the causes of anemia are failure of erythropoietin (EPO) production by diseased kidney and reduction in red cell survival.The successful correction of anemia of CKD has resulted in reduction of associated morbidity and improvement of

functionality, exercise, cognitive function and overall quality of life. [4] Moreover, significant reduction of cardiovascular morbidity and mortality has occurred. [5]

The purpose of this study is to determine whether low protein diet supplemented with KAAand treatment with erythropoietinare effective in preventing the progression of CKD.

PATIENTS AND METHODS

The study involved 60non-diabetic patients inpredialytic stages of CKD, randomized as regardsthe age, sex distribution, blood pressure control,etiology, serum creatinine, glomerular filtrationrate (GFR), body mass index (BMI) wereincluded in a randomized, prospective and parallel group study. The study was performedfrom September 2014 to September 2018 in patients ofCKD attending ambulatory of renal clinic oradmitted in Internal Service of the secondaryCare Center of Durres.

We use two therapeutic protocols: in the first group low protein (LPD) with diet 0.6 gr/dl of protein with recombinant erythropoietin (EPO) 6000-8000 UI/week, administered subcutaneously and the dose was adjusted in each patient to maintain hemoglobin levels in the 11 to 12 g/dL range and ketoacids (Ketoanalogues); in the second group low protein diet 0.6 gr/dl and erythropoietin 6000-8000 UI /week.

CKD were classified into 5 stages according to the GFR,estimated by Cockcroft-Gault formulaand presence of signs of kidney damage:

- stage 1: GFR > 90 ml/min and signs of kidney damage;
- stage 2: GFR = 60–89 ml/min and signs of kidney damage;
- stage 3: GFR = 30–59 ml/min;
- stage 4: GFR = 15–29 ml/min;
- stage 5: GFR < 15 ml/min [6, 7] (K/DOQI and KDIGO).

Were included in the study patients with CKD in stage 3 and 4 (15 ml/min/1.73 m^2 < GFR < 45 ml/min/1.73 m^2) receiving conservative treatment for CKD.
Were excluded from the study patients on dialysis, immunosupressed, pregnant women, those with malignancy.

The changes of GFR, serum total proteins serum albumin,phosphor, HCO_3blood gas,BMI,were evaluated after six months treatment.
The values were expressed as mean ± SD.
The results were expressed as mean (± SD). Statistical significance between pre- and post-treatment values in each group was calculated using Student's paired t-test. Statistical significance between groups was calculated using unpaired t-test. P-values <0.05 were considered statistically significant.

RESULTS

Sixty patients (31 males and 29 females) mean aged 41 years (range 25-68 years) were included in the study (Table 1). The two study groups, did not significantly differ for gender distribution (six males and four females in each group), age (52 ± 15 years vs. 57 ± 17 years, respectively).
None of the patient in either group required dialysis, and till the end of study all patients were alive.

Table 1. Patients' demographics data

Demographic variable	Total number of patients NR=60
N	Mean
Sex (M/F)	31/29
Age (years)	36.3±10.7 (27-63)
Weight (kg)	64.2±6.7

	(54-96)
Height (cm)	152.7±7.4 (150-182)

After 12 months, BMI,seric level of sodium, potassium,serum total proteins and serum albumin did not changesignificantly in both groups compared with thebaseline values,while GFR, seric level of creatinine wereincreased significantly in the group II.

Also, sericlevels of phosphor were decreased significantlyin the group II after 12months of treatment withKAA. Bicarbonates in blood wereameliorated inpatients of thegroup II, compared with thebaseline values(Table 2).

Table 2. Comparison of biochemical parameters before and after treatment

	After 12 months of treatment		
	Group I (29)	**Group II (31)**	**P**
GFR (ml/min/1.73 m^2)	25.9±9.3	22.8±8.4	P<0.05
Serum creatinine (mg/dl)	2.17±2.1	2.48±2.7	P<0.01
BMI (kg/m^2)	24.2±3.8	23.9±3.6	NS
EPO dose (UI/kg/week)	55.3±8.2	55.3±8.2	NS
Hemoglobin level (g/dl)	11.6±0.4	11.7±0.3	NS
Albuminemia (g/dl)	2.8±0.7	3±0.3	NS
HCO_3	21.2	18	P<0.01
Proteinuria (24 hour g/dl)	2.8±0.7	2.7±0.6	NS
Seric level of sodium (mmol/l)	141±2.6	142.6±2.3	NS
Seric level of potassium (mmol/l)	4.3±0.2	4.2±0.9	NS

DISCUSSION

KAA therapy combined with protein restricted diets should play a principal role in the treatment of patients with CKD, improving symptoms, maintains a good nutritional state, limits proteinuria and delaying the time until renal replacement therapy.

Our study demonstrates that in patients with advanced CKD, a combined LPD, KAA and EPO has a favorable effect on renal function.

In the conditions of our country with poor outcomes, conservative management is very important to prevent CKD and to prevent progression of CKD to end-stage renal disease (ESRD). Consequently, CKD patients accumulate salt, phosphates, uric acid and many nitrogen-containing metabolic products, and secondary problems of metabolic acidosis, bone disease and insulin resistance become prominent [8]. These problems can be avoided with dietary planning. Protein-restricted diets do not produce malnutrition and with these diets even patients with advanced CKD maintain body weight, serum albumin and normal electrolyte values [8].

Hence, newer treatment modalities are being searched, which can halt nephron damage, delay the development of ESRD, and cost-effective. KAA might be useful in the treatment of uremia [8].Ketoacids reduce protein degradation and urinary protein excretion, producing a reduction of plasma urea, urea synthesis and urea excretion and an improvement in nitrogen balance in CKD patients [9].These might be the probable mechanisms for beneficial effects of KAA and erythropoietin in our study.

In concordance with study of Di Iorio [10], also in our study results a reduce of phosphate burden from KAA may decrease proteinuria and slow the progression of renal disease in CKD patients.In our study KAA are showed to be beneficial in stages 3 and 4 of CKD, with an improvement in clinical features as well as biochemical parameters. So, the KAA therapy in predialysis CKD patients can be consider an essential part of therapy [11].A limitation of our study is the small number of patients.These results need to be followed by more studies.

CONCLUSION

We conclude that the co-administration of LPD, erythopoietin and KA constitutes an effective alternative in conservative management of patients in pre-dyalisis stage, delaying in follow-up period progression of renal failure corrected of metabolic parameters.

Ketoanalogues are safe, well tolerated, and efficacious in retarding the progression of renal failure and preserving the nutritional status of CKD patients, but cost may still be a limiting factor.

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