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EVALUATION OF SERUM CANAVANINE AND CREATININE LEVELS IN PATIENTS WITH CHRONICAL KIDNEY DISEASE BEFORE DIALYSIS AND AFTER DIALYSIS

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ABSTRACT **Background:** Canavanine an amino acid arginine analogue is present in legumes and when ingested by animals creatinine is produced when it is metabolized; this amino acid is associated with the actívation or exacerbation of chronic kidney disease (CKD); therefore the aim of the present study was to know canavanine and creatinine levels in blood samples from patients with CKD immediately before dialysis and after dialysis.

Material and methods: Serum canavanine levels were evaluated in 57 blood samples of patients with CKD to determine the levels of canavanine using the Rosenthal technic and creatinine with an autoanalyzer "Dimension RxL" of Siemens.

Results. The values obtained before dialysis for creatinine were from 3.0 to 14 mg/dl and canavanine from 10.0 to 21 mg/dl and after dialysis creatinine values were from 0.9 to 7.5 mg/dl decreasing an average of 64% and the values for canavanine they were of 9.5 to 19 mg/dl.

Conclusions: Our data indicate that the values of serum canavanine do not change after dialysis; therefore it is necessary to modify the composition of dialysis solution or to change the composition of semipermeable membrane so that the canavanine levels decrease in blood of patients with CKD and serum creatinine levels do not continue to increase.

KEYWORDS : dialysis, Canavanine, chronic kidney disease, creatinine

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem. CKD have always been a problem because the disease is more frequent every day and their treatment is difficult until reaching the dialysis application; which implies a heavy financial cost for health institutions. Usually when the diagnosis is done, the disease is in advanced state because the symptoms are diverse and non specific. Chronic Kidney disease is a pathophysiological process of progressive and irreversible nature that frequently leads to the terminal phase in which the patient requires renal replacement therapy (RRT); these can be : dialysis or transplantation to survive. Dialysis is a process that achieves the extracorporeal removal of waste products such as creatinine , urea and free water from the blood when the kidneys are in a state of kidney failure. Toxic substances such as homocysteine, canavanine, guanidine, B2 microglobulin have been identified [1]. CKD in critically ill patients is associated with the activation of protein catabolism and a negative nitrogen balance. Renal replacement therapy (RRT) aggravates this problem by eliminating a substantial amount of amino acids [2,]. As a result, patients with CKD are at increased risk of developing protein energy wasting, which can increase the likelihood of in-hospital death and complications .

In the urine of uremic patients a low molecular weight substance was isolated, which is toxic to cells grown in culture and when injected into laboratory animals It causes twitching, hemolysis of red cells and gastroenteritis; also interferes with the absorption of potassium in erythrocytes ; this substance appears to be the guanidine-succinic acid and it is produced from L-canavanine. Canavanine is a non-protein amino acid, analogue of arginine that exhibits antimetabolic activity in lowers animals up to higher animals ; its toxic properties are due to its structure similar to arginine interfering with its metabolism; inhibits the synthesis of proteins, also interfering the synthesis of RNA and DNA and alters the synthesis of immunoglobulins.[3]. The toxic effect of canavanine occurs when there is a high content of the amino acid in the tissues of the different organs and its ingestion is for a long time, therefore it accumulates in the organism observing a high content of the amino acid in the blood and into the cells. Canavanine is a substrate for the arginase enzyme and when metabolized produces urea and canaline [4].

In a previous study done in leukocytes of patients with CKD, high levels of canavanine were found in comparison with the levels of healthy subjects [5] and then was evaluated the canavanine in blood serum of patients with CKD also finding high values of canavanine; in addition it was observed that canavanine levels increase before the creatinine levels [6]. When reviewing the literature, it was observed that the transamidinase enzyme metabolizes canavanine with glycine producing guanidinoacetic acid and creatinine (compounds that are also produced from arginine and glycine) therefore increases the production of creatinine in such a way that canavanine accumulates first in blood due to the consumption of vegetables and seeds that contain canavanine and for this cause is present exacerbation or activation of disease; therefore the aim of our study was to evaluate the canavanine levels in blood of patients with CKD before and after dialysis to observe if their levels decrease as well as creatinine.

MATERIAL AND METHODS

Creatinine and canavanine levels were evaluated in 57 blood samples from patients with CKD and aged 7 to 18 years and both sexes on pre-dialysis and post-dialysis. Creatinine levels were evaluated with an autoanalyzer "Dimension RxL" of Siemens [7]; and canavanine was evaluated using Rosenthal technic [8].

RESULTS

The values obtained in patients with CKD before the dialysis were: canavanine 10 to 21 mg/dl, and creatinine 3 a 14 mg/dl; after dialysis levels of creatinine were from 0.9 to 7.5 mg/dl decreasing an average of 64% and the values for canavanine they were from 9.5 to 19 mg/dl. Canavanine values are about the same before and after dialysis in all patients (100%), table 1.

Table 1. Values of canavanine and creatinine obtained in blood samples of patients with CKD before dialysis and after dialysis

n	PREDIALYSIS		POSTDIALYSIS	
	creatinine mg/dl	canavanine mg/dl	creatinine mg/dl	canavanine mg/dl
1	2.8	12	1.4	10.5
4	4.4	13	2.1	12
3	5.8	12	2.5	12
5	6.2	12	2.4	12
2	6.5	12.5	1.6	12.5
2	6.9	13	3.7	12
3	7.3	15	2.5	14.5
3	7.5	13	1.5	12
2	7.8	16	3.2	14
1	8.2	13	0.9	12
8	8.5	12.5	3.7	12.5
2	9.2	10	3.1	9.5
9	10.2	13	3.5	12.5
4	11.6	15	4.3	13

4	13	14	3.4	13
1	14	13.5	7.5	1.35
3	14	21	3.2	19

DISCUSSION

The kidneys perform several functions in the body. 1) they filter the blood and eliminate waste products of the metabolism as well as endogenous and exogenous substances, 2) maintain the electrolyte balance, 3) regulate the acid-base balance, 4) secrete hormones such as erythropoietin and renin and 5) modify substances such as vitamin D for the regulation of phosphorus and calcium. As renal function decreases, the hydroelectrolytic balance is disturbed, which translates into salt retention and decreases the ability to excrete water in the urine.

The options of RRT for patients with CKD are renal transplantation, hemodialysis and peritoneal dialysis with its different modalities. Hypotension is the most frequent complication of dialysis occurring in 20-50% of dialysis sessions . Muscle cramps are the second most frequent complication, in addition to other symptoms known as dialysis imbalance syndrome. Dialysis solutions traditionally contain glucose in various concentrations; therefore there may be hyperglycemia, hyperinsulinemia and obesity that are cardiovascular risk factors. CKD represents one of the most costly diseases worldwide and the number continues to increase by about 21000 new cases every year in North America [9]. In 2008 , there were 1.75 million patients worldwide who regularly received RRT in the form of dialysis and there is an increasing need for RRT due to the growing number of cases with CKD leading to end-stage renal disease .

The amount of serum canavanine found after dialysis should be taken into account for treatment of critically ill patient with CKD. The toxicity of canavanine amino acid is due to the fact that it is incorporated in the proteins instead of the arginine and is metabolized by the enzyme arginase producing canaline and urea; furthermore it is also incorporated into the nucleus and cytoplasm of the cells of the different organs and tissues of human body; therefore the canavanine is being released continuously into the bloodstream due to cellular metabolism, therefore it is necessary to suppress the intake of foods containing canavanine because their blood levels continue increasing up to leading to end-stage renal disease. When alfalfa seeds were administered to monkeys, they developed hemolytic anemia. In rats with a diet based on canavanine, some organs were affected and decreased the number of leukocytes and erythrocytes; in addition decreases the synthesis speed of some enzymes [10]. The toxic effect of canavanine occurs when there is a high content of canavanine in the blood and also when its ingestion is for a long time. Thus, in monkeys feed alfalfa, the disease appeared after 7 months and when the alfalfa intake was suppressed, the symptoms of the disease disappeared [11] . In rats the administration of canavanine its toxic effect is very severe; the amino acid is incorporated in the tissues of the organs such as the spleen, heart, lungs, salivary glands and brain. It also produces damage in the renal glomeruli in normal mice [12]. When canavanine is administered in rats, high concentrations of guanidinoacetic acid are eliminated in the urine. This compound comes from transamidination of glycine with canavanine and is toxic in cells cultures and also interferes with the absorption of potassium in erythrocytes.

The degradation products of canavanine are: O-ureidohomoserine which is an analogous to citrulline and canavanine-succinic acid which is an analogue of arginine-succinic acid [13]. This causes the urea cycle to be altered and furthermore the creatinine production to be greater due to the fact that creatinine is synthetized from the transamidination reaction of glycine with canavanine. For this fact, blood levels of creatinine are increased in patients with CKD; and creatinine continues to increase because it is being produced from canavanine which is not removed with dialysis [14].

It is very possible that the accumulation of canavanine in organs and tissues of patients with CKD is the cause of the progression of kidney failure until its terminal state: furthermore it has been observed that the highest incidence of patients with CKD worldwide occurs in some countries of Central America which is possibly due to the sword beans a tropical leguminous that is consumed as a substitute for mashed potatoes, seeds also are used as a coffee substitute. Sword beans have high protein content, but also containing protease inhibitors and canavanine 4.1% [15].

Our data indicate that serum canavanine is not removed with dialysis; therefore we think that it is necessary modify the dialysis solution and another possibility is to change the composition of semipermeable membrane so that canavanine can be removed from the patients blood and in this way also the frequency of application of dialysis. An alternative method for extracorporeal separation of blood components such as plasma can be apheresis for patients with serum creatinine concentration above 6 mg/dl and has been observed that renal function remained stable for at least one month [16,17] and on the other hand it is necessary to eliminate from the diet the consumption of all food containing canavanine so that this amino acid do is not accumulate in the blood; in order to stop the progression of the disease, delay or apply the dialysis less frequently and in this way can be offered a better quality of life to the patients.

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