DIVALENT CATIONS LEVELS CHANGES IN NEPHROTIC SYNDROME

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DIVALENT CATIONS LEVELS CHANGES IN NEPHROTIC SYNDROME (Abstract):
Divalent cations (calcium, magnesium, zinc, cooper, manganese) play an important role in various biological processes. Different acute or chronic renal disorders in children or adults modify the urinary excretion of these cations and may influence their concentrations in organism. **Aim:** Evaluation of the changes of some divalent cations levels (Cu, Zn, Mg, Ca) in acute renal diseases. **Material and methods:** We measured plasma concentrations and urinary excretion of cations in pediatric patients with acute urinary infections. We also evaluated malondyaldehide (MDA) and total antioxidant capacity (TAC) plasma levels. **Results:** The obtained results show that serum levels of Ca, Cu, Zn are decreased in patients with acute urinary infections compared with a control group of healthy children, while urinary excretion of Cu and Zn there were higher in group study compared with control group. There are no significant differences of the serum magnesium concentration. Increased plasma MDA levels and decreased plasma TAC, Cu and Zn concentrations indicate an increased oxidative stress in patients with acute renal diseases. **Conclusions:** Our preliminary data show that trace elements should be measured routinely in children with renal disorders. **Key words:** ZINC, COPPER, MAGNESIUM, NEPHROTIC SYNDROME

Divalent cations (calcium, magnesium, zinc, copper, manganese) play multiple roles in all human tissues and systems. These cations can be found both intracellular and extracellular and there are complex systems for their transport through the cellular membrane, and also for their concentration regulation in the human body (1, 2). The activity of more than 300 enzymes is magnesium dependent, and a similar number of enzymes are dependent of zinc.

Copper (Cu) is an essential trace element that acts as a critical cofactor when is incorporated into specific copper-enzymes that catalyze electron transfer reactions required for cellular respiration, iron oxidation, neurotransmitter biosynthesis, antioxidant defense. Copper is both a pro-oxidant and antioxidant. Its antioxidant activity has been attributed to increased CuZnSOD activity.

Zinc (Zn) is an intracellular signaling molecule and it plays an important role in cell-mediated immune functions and oxidative stress. It is also an anti-inflammatory agent and an antioxidant (3).

The human body contains 2-3 g zinc,
most of which is bound to proteins. Over 300 enzymes have been shown to contain zinc, either directly involved in catalysis, as a cofactor, or for structural stabilization. Another large group of zinc containing proteins is transcription factors. Despite its important function, the body has limited zinc stores that are easily depleted and cannot compensate longer periods of zinc deficiency.

Zinc deficiency is a cause of immune dysfunction and infection. Previous human studies have shown that the activation of the acute phase response alters zinc metabolism.

The kidney plays a significant role in magnesium homeostasis. Proximal tubular magnesium reabsorption is proportional to sodium reabsorption, and a reduction in sodium reabsorption during long-term intravenous fluid therapy may result in magnesium deficiency.

Different acute or chronic renal disorders in children or adults modify the urinary excretion of these cations and may influence their concentrations in organism (4, 5). At present there are little data about how the therapy administrated in nephrotic syndrome influences the concentration of divalent cations. Kidney is the main elimination route for all divalent cations.

In this study we investigated the changes of some divalent cations levels (Cu, Zn, Mg, Ca) in pediatric patients with acute renal diseases.

**MATERIAL AND METHODS**

The study group was consisted of 18 children aged from 2 to 17 years, with acute nephropathies such as urinary tract infection and acute pyelonephritis, admitted in the nephrology clinic of Sf. Maria Children’s Hospital Iasi. We collected urine and blood samples and we measured the urine and plasma levels of magnesium, zinc and copper cations through atomic absorption method. We also measured the levels of serum MDA and TAC. Serum MDA levels were measured by thiobarbituric acid method and for TAC determination we used RANDOX kit. The same measurements were carried out as well for a control group consisted of 10 children aged from 2 to 15 years, with a normal health status.

**RESULTS**

Plasma levels of copper were decreased with 11% in children with renal disorders in comparison with control group, and plasma levels of zinc were decreased with 18% (p<0.01). Urinary levels of Cu and Zn there were significantly higher in group study compared with control group. There were found no significant modifications of the plasma or urinary magnesium concentrations between the study group and control group. MDA plasma levels (nmol/mL) were increased in patients with acute nephropathies compared with control group (2.12 ± 0.27 vs. 0.48 ± 0.15). Levels of serum TAC (mmol/L) were found significant decreased in study group in comparison with control group (1.16 ± 0.09 vs. 1.71 ± 0.14).

**DISCUSSION**

Our data are consistent with the literature data concerning clinical studies of divalent cation levels in renal diseases. There are few data about seric and urinary divalent cations changes related to renal diseases.

A study performed on 105 pediatric patients with nephrotic syndrome or nephritis-nephrosis which evaluated plasma zinc concentrations...
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concentration and quantitative urinary zinc excretion showed that the plasma level was decreased with 39% in patients with nephrotic syndrome compared with the control group. The rate of urinary zinc excretion was not different from that of the controls, with the exception of patients whose disease was in the polyuric phase of beginning remission where it was fivefold higher and those who had achieved a long-lasting remission of the disease (6).

Another study that investigated the effect of proteinuria on urinary zinc and copper excretion in children with nephrotic syndrome (NS) revealed that clearance, fractional excretion, and urinary excretion of zinc and copper were significantly higher in children with relapse of NS than in children with remission of NS or in healthy children. The authors found a linear correlation between proteinuria and urinary zinc and copper excretion in relapse of NS. The results of the study suggested that zinc and copper deficiency in NS may be related also to increased urinary zinc and copper losses (7). Since about two thirds of the plasma zinc is bound to albumin, an unchanged zinc-albumin ratio would reflect an equal zinc and albumin loss.

Some authors evaluated copper, zinc, calcium and magnesium concentrations in plasma, erythrocytes and urine in patients with chronic renal failure. They revealed significant plasma hypozincemia and hypozincuria in uremic patients (though the erythrocytes zinc concentration was significantly higher than in controls), increased erythrocytes copper levels, significant hypocalcemia in erythrocytes and plasma, magnesium levels being increased (8).

The causes of Zn deficiency in kidney disease are not clear. Decreased dietary Zn intake and intestinal absorption, increased endogenous Zn loss, and increased urinary Zn excretion (as in the nephrotic syndrome) all may contribute to altered Zn metabolism (9).

The benefit of the administration of Zn doses requires further evaluation under controlled conditions. Some researchers showed that in children (1-16 years) with steroid-sensitive nephrotic syndrome, zinc administration (10 mg/day) reduced by 20% the frequency of relapses. The patients which received zinc developed a significantly higher likelihood of sustained remission (10).

Another study performed on 14 children with nephrotic syndrome showed that the mean blood zinc level was significantly lower than that of 113 control children. The blood albumin/zinc ratio was also lower in nephrotic children than in healthy children. There was no correlation between blood albumin and blood zinc levels. The authors suggested that abnormally low zinc levels are partly due to deficient zinc uptake and may explain some of the disorders described in children with persistent nephrotic syndrome (11).

The comparison of the status of zinc and copper in chronic hemodialysed patients with and without diabetes showed that the alteration in the distribution of zinc in patients with chronic kidney disease is independently of the presence of diabetes and also the status of copper seems not to be influenced by chronic kidney disease, but only by the metabolic derangements associated with diabetes (12).

Oxidative stress has been proposed as one of the possible mechanism involved in the nephrotic syndrome. Peroxidation of lipid membranes raises the concentration of their byproducts malonyldialdehyde (MDA) and
the consequent lowering of antioxidants (13). Total antioxidant capacity (TAC) is involved in antioxidant protection in nephrotic syndrome (14). In the kidney, oxygen radical production has been detected in vascular cells, juxta glomerular cells, tubular cells, podocytes, mesangial cells and isolated glomeruli. Free radicals have a negative influence on renal tissue in nephrotic syndrome.

There are studies that investigated oxidant and antioxidant status of copper, zinc and homocysteine (HCY) in nephrotic syndrome patients and the effect of antioxidants, mineral and B-complex vitamins on oxidant and antioxidant status. Results showed a significant statistically decreased level of serum TAC, Cu, Zn, plasma Vit C while serum malonyldialdehyde and homocysteine level were increased in nephrotic syndrome patients compared with control. The level of serum homocysteine and MDA were significantly decreased and activity of serum TAC, Cu, Zn was significantly increased after 3 months with Zincovit (15).

Data suggest that it can appear a relative deficit of oxidant/antioxidant balance in nephrotic syndrome, which could predispose to increased oxidative stress.

In many diseases, zinc deficiency may complicate the clinical features; affect adversely immunological status, increases oxidative stress and increase the generation of inflammatory cytokine. It is therefore important that the status of zinc to be evaluated. Alterations in zinc metabolism in some disease conditions must be studied taking into account the links between homeostatic perturbation and cellular biology, for to characterize zinc distribution and for elucidate the regulatory processes and the factors to which they respond (16).

Copper deficiency has been documented in conditions predisposing to excessive copper losses. Urinary losses of ceruloplasmin-bound copper likely play a significant role in predisposing patients with nephrotic syndrome to copper deficiency (17). Renal patients undergoing continuous ambulatory peritoneal dialysis may also experience excessive losses of ceruloplasmin-bound copper via dialysis exchanges.

Copper imbalances in humans not only impair normal function of ceruloplasmin, superoxide dismutase or of other copper-dependent proteins, but can also lead to disease states (18).

Hypomagnesemia is occasionally observed in chronic renal failure due to an obligatory renal magnesium loss. It is also seen during the diuretic phase of acute renal failure, in post-obstructive diuresis and after renal transplantation. Patients on continuous ambulatory peritoneal dialysis develop hypomagnesaemia when low magnesium dialysis fluid is used.

**CONCLUSIONS**

Our data show that in acute urinary diseases occur some cationic imbalances which may influence the clinical manifestations and development of the renal disease and these imbalances should be corrected.

Oxidative stress may be one of the possible mechanisms involved in the nephrotic syndrome.

We consider that the decrease of plasma zinc concentration may be involved in the immune dysfunction associated with nephrotic syndrome.

The knowledge of bivalent cations imbalances may open new ways in the treatment of nephrotic syndrome and in the reduction of some side effects of drugs usually used in treatment.
REFERENCES


