Original Article

Serum Zinc and Copper levels in nephrotic syndrome patients

Asim Mumtaz[1], Muhammad Anees[2], Sundus Fatima[3], Rashid Ahmed[4], Muhammad Ibrahim[5]

ABSTRACT

Objective: To determine the serum zinc and copper levels in patients of nephrotic syndrome and healthy subjects.

Methodology: Forty patients of nephrotic syndrome, fulfilling the pentad criteria (proteinuria, hypoalbuminemia, hyperlipidemia, hyperlipiduria and edema) were included in this study. Proteinuria was more than 3.5g per 24 hour in adults and more than 1000 mg/m^2 in children. Ten healthy subjects were included as control. Patients on dialysis, pregnancy and with proteinuria of less than 3.5g per 24 hour were excluded from the study. Patients were selected from Nephrology outpatient department of Shalamar Hospital Lahore and Children hospital and Institute of child Health Lahore. The trace metals were measured on continuous source Atomic Absorption Spectrophotometer (ContrAA700) using flame mode for Zn and Cu.

Results: The levels of serum Zn and Cu were significantly lower (28.61±24.07, 47.62±34.1 µg/dl) as compared to controls (100.8±14.8, 112.3±10.6 µg/dl) respectively. Serum Zn level and 24 hour urinary protein had negative correlation with each other which was statistically significant (r= -0.442, p= 0.021). There was positive and significant correlation {(r= 0.712, p= 0.001), (r=0.612, p=0.002)} between serum albumin and serum Zn & serum Cu levels.

Conclusion: The results of the present study showed that there was high prevalence of Zn and Cu deficiency in patients suffering from nephrotic syndrome. Causes of hypozincemia and hypocuperemia were hypoalbuminemia and increased twenty four hour urinary protein losses. Other probable factors were decreased dietary intake and increased loss of trace metals in urine.

KEY WORDS: Nephrotic syndrome, Serum albumin, Zinc, Copper, Proteinuria.

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INTRODUCTION

The nephrotic syndrome (NS) is commonly described to encompass five clinical features: proteinuria, hypoalbuminemia, hyperlipidemia, hyperlipduria and edema.[1] Proteinuria is the cardinal feature of the syndrome, without which the diagnosis can not be made. Albumin excretion of 2.2g per 24 hours and protein excretion of 3.5g per 24 hours is usually accepted as the minimal level for nephrotic-range proteinuria in adults.[2] In children nephrotic range proteinuria is defined as proteinuria exceeding 1000mg/m^2 per day or spot urinary protein to creatinine ratio exceeding 2mg/mg.[3] Nephrotic syndrome can be primary (Minimal change nephrotic syndrome, Focal segmental

glomerulosclerosis, Membranous nephropathy) or secondary (Infections, Drugs, Malignancies).[4,5] Infection is one of the main complication of NS.[6]

Increased risk for infection is due to loss of immunoglobulin, complement and properdin, altered T-cell functions, immunosuppressive therapy and presence of edema. Common infections are Cellulitis, pneumonia and upper respiratory tract infection. NS is a wasting illness due to proteinuria and negative nitrogen balance which leads to 10 to 20% loss of lean body mass. To compensate this protein loss liver synthesizes more proteins including LDL, VLDL and lipoproteins leading to hyperlipedemia and lipiduria.

This thing leads to atherogenicity and cardiovascular complications. Urinary losses of binding proteins like vitamin D-binding proteins, thyroxine binding globulin (TBG), loss of binding proteins for Zn, Cu, Iron takes place in these patients which are usually not highlighted. The symptoms of the deficiency of these metals are confused with symptoms NS and are ignored. So this study was conducted to see the prevalence of Zn and Cu deficiency in patients with NS and factors affecting it.

METHODOLOGY

Forty patients of nephrotic syndrome, fulfilling the pentad criteria (proteinuria, hypoalbuminemia, hyperlipidemia, hyperlipduria and edema) were included in this study. Ten healthy subjects were included as control. Patients whose proteinuria was more than 3.5g per 24 hour in adults and more than 1000mg/m^2 in children were included in this study. Patients on dialysis, pregnancy and with proteinuria of less than 3.5g per 24 hour were excluded from the study. These patients were selected from Nephrology outpatient department of Shalamar Hospital Lahore and Children hospital and Institute of child Health Lahore.

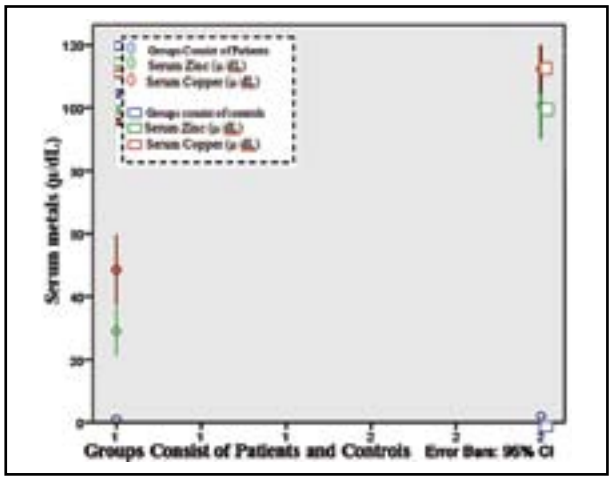

Fig.1: Serum zinc and copper levels in patient and control groups.

The patients comprised of individuals of any age group and belonged to low and middle income groups. Written consent was taken from the patients and parents of patients for inclusion in the study. Sample for trace metals was collected in 2%nitric acid treated tubes. The trace metals were measured on the principle of absorption of primary radiation by the analyte atom in their ground state. The measured absorbance signal constitutes a measure of concentration of respective element in the analyzed sample (Instrument CONTRA 700). The Zn and Cu were measured on continuous source Atomic Absorption Spectrophotometer (ContrAA700) using flame mode.

Statistical Analysis: The continuous variables were expressed as mean ± S.D, whereas categorical variables were expressed in frequencies and percentages. Graph was also used to display the data. Pearson correlation coefficient was applied to find relationship among variables. SPSS version 16.0 was used to analyse the data. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age ± SD of patients and controls included in the study were 13.82 ± 13.65 years (range 1-60 years) and 25.30 ± 3.020 years (range 23-32 years) respectively. There were 19 (47.5%) males and 21 (52.5%) females in patient group. Mean level of 24 hour urinary protein was 5.09 g in adults and 2.88 g in children. Lab data of the patients is shown in Table-I. Serum trace metals of patients were significantly lower (Zn= 28.61±24.07, Cu= 47.62±34.1 µg/dl) as compared to controls (Zn= 100.8± 14.8, Cu= 112.3±10.6 µg/dl) as shown in Fig.1. Serum Zn level and 24 hour urinary protein had negative correlation which was statistically significant (r= -0.442, p= 0.021). Positive

Table–I: Demographic & Laboratory data.

S. No	*Parameter*	*Mean ± SD*
1	Body Mass Index(kg/m2)	19.77 ± 3.95
2	Body Surface Area(m2)	1.09 ± 0.43
3	Duration of disease(Months)	8.80 ± 12.20
4	Serum Albumin(gm/dl)	2.63 ± 1.11
5	Urea(mg/dl)	48.55 ±41.00
6	Creatinine (mg/dl)	1.37 ± 1.44
7	Cholesterol(mg/dl)	344.6 ± 118.6
8	Triglyceride(mg/dl)	348.21 ± 249
9	Serum Zinc (mcg/dl)	100.8 ± 14.8
10	Copper (mcg/dl)	112.3 ± 10.6

and significant correlation was observed between serum albumin and serum Zn & serum Cu level (r= 0.712 p= 0.001, r=0.612, p= 0.002). Serum Zn and serum Cu had positive correlation with each other which was statistically significant (r=0.735, p=0.004). Serum Zn level had negative correlation with BMI which was significant (p=0.004)

DISCUSSION

Zn and Cu are one of the essential trace metals and are members of one of the major subgroups of the micronutrients that have attained prominence in human nutrition and health. The total body content of Zn in a 70-kg man is about 2.5g and recommended dietary intake for women is 9 mg/day for men is 14 mg/day. Recommended dietary intake of Cu for adults is 0.9 mg/day. The biological role of trace metals, especially serum Zn and Cu, in different physiologic and pathologic conditions has been extensively investigated in recent years.[7]

In this study serum Zn and Cu level were statistically significantly reduced as compared to control subjects. Similar observations were made by Stec J et al[8] and Dwivedi J et al[1] as shown in Table-II. They performed study including 50 nephrotic syndrome patient and 50 controls subjects. They reported statistically significant (p<0.001) decreased levels of serum Zn and Cu in patients with nephrotic syndrome as compared to control group. But different observation have been reported by Joshi A et al[9] and Teitikar T et al[10], that serum Zn levels were on the lower side of normal but the difference was not statistically significant and serum Cu level showed no significant change in nephrotic syndrome group.

In this study serum Zn level had negative correlation with 24 hour urinary protein which was statistically significant (r = -0.442, p=0.021). It means that as proteinuria increases serum Zn level also decreases. Most probably this is due to loss of metals binding proteins in the urine.[11] Cogan MG et al[12] observed that there is increased urinary excretion of high density lipoproteins and of transport proteins for iron, copper and Zn in patients with nephritic syndrome. Not only the transport proteins are lost in urine but even there is increased excretion of trace metals. Many studies have shown increased urinary losses of Zn. Freeman et al[13] reported a linear correlation between proteinuria and zincuria in nephrotic syndrome patients. Filtered protein from the glomerulus is reabsorbed in the proximal tubules, excessive catabolism of protein in the tubules leads to defective proximal tubular reabsorption.[14] Due to disturbed tubular function, reabsorption of filtered aminoacids and trace metals can't take place. According to Shah KN et al[15], urinary losses of Zn occurs even in the absences of proteinuria which means that alteration in renal tubular secretion or reabsorption may contribute to increased Zn losses.

Serum albumin is most abundant protein in plasma, which serves as a carrier for a variety of nutrients and metabolites.[16] Metal binding capacity of albumin has been acknowledged for a long time. Albumin bound to a variety of essential and toxic metal ions including Cu, Zn, Ca and Ni by its metal binding sites with clear specification for different metal ions. In our study a positive correlation was found between serum Zn & Cu levels and serum albumin level (r value of 0.712, p= 0.001 and r = 0.612, p = 0.002 respectively). It means as serum albumin level decreases the serum Zn and Cu level also decreases. Another thing which has been observed for the first time is that serum Zn and serum Cu has positive correlation with each other which was statistically significant (r=0.735, p= 0.004). In this study, as patients were suffering from NS, so all of them were having hypoalbuminemia (2.14±0.54 gm/dl) as compared to control subjects (4.60± 0.41

Table-II: Comparison of results of different studies of trace metals on nephrotic syndrome.

Year	*Author*	*No. of subjects*	*Serum Zinc*	*Urinary Zinc*	*Serum Copper*	*Urinary Copper*
2010	Present study	40	Decreased	Not measured	Decreased	Not measured
2009	Dwivedi J	50	Decreased	Not measured	Decreased	Not measured
2008	Shah K N	1	Decreased	Not measured	Not measured	Not measured
1994	Pedraza-Chaverri J (Rats)	-	Decreased	Increased	Decreased	Increased
1993	Joshi A	50	Normal	Not measured	Normal	Not measured
1993	Teitiker T	16	Decreased	Not measured	Normal	Not measured
1990	Stec J	-	Decreased	Increased	Decreased	Increased
1990	Perrone L	32	Decreased	Increased	Not measured	Not measured
1984	Brown E A	6	Not measured	Not measured	Decreased	Increased
1978	Lindeman R.D	5	Not measured	Not measured	Normal	Increased
1975	Freeman RM (Rats)	9	Decreased	Increased	Not measured	Not measured

gm/dl) which is the reason for hypozincemia and hypocuperemia in these patients.

Similar observation was made by Boyett et al[17] that hypozincemia is associated with hypoalbuminemia not only in NS but even in other disease states for example cirrhosis of liver. Parsad AS et al[18] also suggested that hypoalbuminemia was a likely explanation of hypozincemia in aminonucleoside-induced nephrosis, as plasma Zn is largely protein bounded. Cartwright GE et al[19] observed hypocupremia in 13 out of 16 patients with hypoalbuminemic and nephrotic syndrome however the state was present in all patients. As we know that approximately 80% of plasma Zn is complexed with albumin, while the remainder bound to other plasma proteins such as α2 macronglobulin and amino acids (histidine and cystine). 90% copper is bound to ceruloplasmin (major source of Cu binding protein) and 10% to albumin. Ito S et al[20], suggested that in nephrotic syndrome the hypocuperemia was the consequence of the loss of ceruloplasmin in the urine.

Low concentration of plasma Zn levels in patients of NS may possibly be because of restricted food intake. In Pakistan, health system is very week and there is late referral of kidney patients to nephrologists[21] because of non availability & less number of nephrologists. Most of the patients before referring to nephrologist are being treated by non renal physicians who restrict protein intake (major source of Zn) right from the start of the proteinuria. Even there is common myth among people that if they have any kidney disease, protein intake should be restricted in the diet, which is the rich source of Zn intake. This diet according to the food analysis tables provides only 10.7 mg of Zn while the advisable optimal daily requirement of Zn for human is 15mg. Similar observation was made by Sen S et al.[22] According to him, rich sources of Zn like meat, fish, cheese, chicken, nuts and almond were restricted in patients suffering from kidney disease. It is therefore obvious that dietary restriction plays an important role in Zn deficiency in our patients. Loss of appetite, impaired absorption by gastrointestinal tract due to gut wall edema and increased excretion by fecal rout may also contribute to this deficiency.

CONCLUSION

The result of the present study showed that there is high prevalence of Zn and copper deficiency in patients suffering from nephrotic syndrome. Causes of Hypozincemia and hypocuperemia were hypoalbuminemia and increased twenty four hour urinary protein losses. Other probable factors were decreased dietary intake and increased loss of trace metals in urine.

Limitations of this study: Large sample size and multi centric study is required for making recommendations.

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Authors Contribution:

Dr. Muhammad Anees: Overall designing, coordination and writing the article.
Dr. Asim Mumtaz: Designing the methodology to draw sample and running the instrumental procedure at the pathology Lab. Of University of Health Sciences, Lahore.
Sundas Fatima: Collection of all the data and sample.
Dr. Rashid Ahmad: Did related review literature.
Muhammad Ibrahim: Did the whole statistical analysis.