Assessment Of The Relation Between Trace Elements And Antioxidant Status In Children With Protein Energy Malnutrition

S El Hassan, N Abdelrazik, A Abd El-Aziz, R El-Iraqi

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Abstract

Background: Protein energy malnutrition represents one of the commonest nutritional deficiencies in developing countries. Marasmus is a severe form of protein energy malnutrition and is associated with oxidative hemolytic anemia. The oxidative hemolysis could be associated with reduced level of antioxidant enzymes (e.g. superoxide dismutase (SOD) and glutathione peroxidase (GPX) and some trace elements, which serve either cofactors for these enzymes or integral parts of them e.g. (zinc, copper, and selenium).

Objective: The current study was performed to evaluate the level of those antioxidant enzymes and some trace elements in different degree of marasmus and their correlation.

Patients and Methods: This study was carried out on thirty patients suffering from marasmus (14 patients with 1st degree marasmus and 16 patients with 2nd degree marasmus). They were selected from infants and children admitted to Mansoura university children 's hospital. Twelve healthy children of matched age and sex were included in the study as a control group. All patients and controls were subjected to estimation of the enzymatic activity of the RBCs SOD and whole blood GPX, and also the estimation of the serum levels of zinc , copper , selenium , lead , manganese , nickel, and chromium.

Results: Significant decrease of RBCs SOD, and whole blood GPX activity in the marasmic groups compared with the control group (902.45+80.87,25.87+3.39 for the 1st degree marasmus group, 662.14+135.57, 18.01+2.95 for the 2nd degree marasmus group and 1666.47+205.58, 56.04+11.58 for the control group, p=0.0005). Also,there is a significant decrease of the serum level of zinc, copper, and selenium in both groups of marasmus compared with the control group. Serum levels of nickel , manganese , and chromium show a significant increase in both groups of the marasmus compared with the control group.

Conclusion: 1.Decreased activities of antioxidant enzymes in marasmic children which make them liable to the possible toxic effect of the reactive oxygen species.2. Marasmic children have low serum levels of selenium , copper, and zinc in.3.There is an existing correlation between serum levels of micronutrients and blood activities of antioxidant enzymes which reflect the importance of these trace elements in the process of tissue protection against oxidative stress.5.High level of lead , chromium , and nickel in both control and diseased children may reflect environmental pollution.

INTRODUCTION

Protein energy malnutrition still represents a clinico-socio-economic problem in our children in Egypt. It is one of the most widespread deficiency diseases of infants and young children in developing countries ([1]).

Kwashiorkor and marasmus are clinical consequences of severe protein energy malnutrition. Kwashiorkor is characterized by hypoalbuminemia and edema while, marasmus is characterized by wasting and often associated with anemia ([2]).

An oxidative haemolysis has been suggested to be a possible mechanism for erythrocyte destruction leading to protein-energy malnutrition associated anemia ([3]). This hypothesis is supported by reduced levels of antioxidant enzymes and

their cofactors found in patients with protein energy malnutrition ([4,5]). Moreover, Free radicals have been implicated in the pathogenesis of edema in children with protein energy malnutrition ([6]).

Protein energy malnutrition often co-exists with micronutrients deficiencies ([7]) . These micronutrients are essential to human biologic functions and have important influences on immune responses ([8]).

The present work aims to evaluate the relation between the protective enzymes, superoxide dismutase and glutathione peroxidase and some trace elements in-patients with P.E.M, in an attempt to throw light on the possible role of these antioxidant enzymes and trace elements as protective agents and that their deficiencies are associated with the manifestations of P.E.M.

PATIENTS AND METHODS

PATIENTS

This study was carried out on 30 marasmic patients (17 males and 13 females) admitted to Mansoura University Children's Hospital between July 2000 and April 2001.Their age range from 6 months to 48 months(21.03+12.57) and weight from 4 - 12.5 Kgm (7.71+2.30) . These children were suffering from different degrees of marasmus, 14 patients were classified as 1st degree marasmus and 16 patients were classified as 2nd degree marasmus according to Elbehairy's classification ([9]), who graded marasmus into three degrees according to the extent of loss of body weight standard for age and the distribution of subcutaneous fat loss. Twelve healthy children of matched age and sex served as control group.All patients and control were of the same socio-economic levels.

Exclusion criteria: Clinical or laboratory evidence of underlying organic diseases which may interfere with the results, and antioxidant medication.

All patients and controls were subjected to history taking with special concern to dietary history, clinical examination focusing on anthropometeric measurements, determination of enzymatic activities of RBCs SOD level, whole blood GPX level, and also determination of serum levels of zinc, copper, selenium, manganese, lead, chromium and nickel.

METHODS

(A) Antioxidants enzymes

The RBCs SOD and whole blood GPX activities were measured on the same day that blood was collected using the respective kits supplied by Randox Laboratories, United Kingdom.

Superoxide dismutuse

Kit No. SD 125. Assay principle: The SOD activity was measured using RBCs separated from whole blood. This method employs xanthine and xanthine oxidase to generate radicals, which react with 2-(4-iodsphenyle) ?3 (4-nitrophenyl tetrazolium) chloride (INT) to from a red formazan dye. The enzyme activity was then measured by the degree of inhibition of this reaction.

Glutathione peroxidase

Kits No RS 504. Assay principle: The GPX activity was measured using an appropriate whole blood. This method was based on that of Paglia and Valentine 1967 ([10]). Glutahtione peroxidase (GPX) catalyses the oxidation of glutathione (GSH) by cumene hydroperoxide. In the presence of glutathione reductase (GR) and NADPH. The oxidised glutathione (GSSG) is immediately converted to the reduced form with a concomitant oxidation of NADPH to NADP. The decrease in absorbance at 340 nm is measured.

(B) Trace elements

The separated plasma from 1st and 2nd degree marasmic patients were collected on the day of their hospital admission and was stored at - 80°C until measured by atomic absorption.

Precautions against contamination:

All laboratoryware used (glass and plastic) was cleansed by soaking in 10% nitric acid for 24 hours and rising thoroughly with deionized water. The same cleansing procedure was applied to polypropylene containers used for venous blood and urine sampling and for storing the serum and urine.

Sampling of blood:

Ten ml of venous blood was sampled for each subject. After allowing 30-60 minutes for spontaneous blood clotting, the serum was separated from the blood cells by centrifugation at 3000 rpm for 10 minutes at room temperature. The serum was decanted and centrifuged twice for 5 minutes at 3000 rpm to remove any blood cell remnants, decanted again, and

then stored at-20oC in stoperred metal free polypropylene containers until assay.

Principle of the test

By using atomic absorption spectrophotometry PERKIN ELMER 2380. Atomic absorption spectrophotometry has proved to be a useful technique with a high resolution. This technique has been used in the estimation of most metals in various biological materials since it is highly accurate, specific and reproducible.

Statistical analysis

Statistical analysis was performed using (SPSS) program version 8/97. The data were shown to be parametric by using Kolmogrov Smirnov test. The quantitative data were presented in the form of mean and standard deviation. Student T test was used for comparison between groups. Spearman rank correlation coefficient was used to study relation between variable in each group. Significance was considered when p value is less than 0.05.

RESULTS

Figure 1

Table 1: Demographic data of different groups

Groups	Number	Age (Month)	Weight (kg)	Height (cm)	H.C (CM)	MAC (cm)
Control	12	21.5 + 13.3	11.41 + 2.54	78.9 + 14.6	46.1 + 2.2	12.67 + 0.64
1st degree marasmus	14	19.53 + 13.48	8.5 + 2.63	75.61 + 12.14	44.69 + 2.71	10.71 + 1.26
2nd degree marasmus	16	22.06 + 12.5	7.03 + 1.77	75.81 + 11.19	44.31 + 2.46	10.4 + 1.12

Figure 2

Table 2: Mean + SD and intergroups comparison of SOD and GPX activity

	Control	1st degree marasmus	2nd degree marasmus
SOD (U/gm Hb)	1666.47+205.58	902.45+80.87 P=0.0005	662.14+135.57 P_1=0.0005 P_2=0.005
GPX (U/gm Hb)	56.04+11.58	25.87+3.39 P=0.0005	18.01+2.95 P_1=0.0005 P_2=0.005

P Control Vs 1st degree marasmus.
P_1 Control Vs 2nd degree marasmus.
P_2 1st degree marasmus Vs 2nd degree marasmus.

Figure 3

Table 3: Mean+SD and intergroup comparison of Zinc, Copper, Selenium, Manganese, Lead, Chromium, and Nickel

	Control	1st degree marasmus	2nd degree marasmus
Zinc (mg/L)	0.680 + 0.206	0.1722 + 0.0747 P=0.0005	0.1393 + 0.0232 P_1=0.0005 P_2=0.40
Copper (mg/l)	1.209 + 0.318	0.182 + 0.0837 P=0.0005	0.0827 + 0.0397 P_1=0.0005 P_2=0.0005
Selenium (ug/L)	65.4 + 10.7	48 + 7.4 P=0.001	41 + 9.7 P_1=0.001 P_2=0.005
Manganese (ug/L)	9.75 + 3.93	15.714 + 3.72 P=0.0005	22.50 + 4.14 P_1=0.0005 P_2=0.005
Lead (ug/L)	135 + 90.33	168.07 + 95.6 P=0.41	104.92 + 37.33 P_1=0.35 P_2=0.059
Chromium (ug/L)	9.308 + 1.943	22.57 + 7.26 P=0.0005	47.43 + 10.69 P_1=0.0005 P_2=0.0005
Nickel (ug/L)	26.65 + 18.35	102.63 + 16.35 P=0.005	138.80 + 27.08 P_1=0.0005 P_2=0.05

P 1st degree marasmus Vs control.
P_1 2nd degree marasmus Vs control.
P_2 2nd degree marasmus Vs 1st degree marasmus.

Figure 4

Table 4: Sperman rank correlation coefficient between blood levels of (SOD& GPX) and serum levels of trace elements in control group.

	SOD		GPX	
	R	P	R	P
Zn	-0.66	0.018	-0.65	0.02
Cu	0.14	0.66	-0.14	0.66
Se	0.03	0.92	-0.20	0.52
Mn	-0.12	0.72	-0.40	0.19
Pb	-0.44	0.19	-0.71	0.018
Cr	0.53	0.076	-0.30	0.33
Ni	-0.12	0.72	-0.58	0.048

Figure 5

Table 5: Spearman rank correlation coefficient between blood levels of (SOD& GPX) and serum levels of trace elements in 1st degree marasmus.

	SOD		GPX	
	R	P	R	P
Zn	- 0.03	0.91	0.07	0.79
Cu	- 0.25	0.37	-0.49	0.09
Se	0.55	0.01	0.28	0.32
Mn	- 0.38	0.16	- 0.06	0.82
Pb	0.49	0.09	0.20	0.54
Cr	- 0.25	0.37	- 0.17	0.55
Ni	- 0.05	0.85	-0.19	0.51

Figure 6

Table 6: Spearman rank correlation coefficient between serum levels of trace elements and (SOD & GPX) blood levels in 2nd degree marasmus.

	SOD		GPX	
	R	P	R	P
Zn	0.14	0.61	- 0.30	0.24
Cu	-0.24	0.38	- 0.21	0.42
Se	0.70	0.004	-0.02	0.92
Mn	- 0.08	0.78	0.55	0.03
Pb	0.18	0.53	-0.14	0.61
Cr	- 0.07	0.79	-0.56	0.02
Ni	-0.26	0.33	0.06	0.82

DISCUSSION

Many studies have proved the deleterious effects of R.O.S on body tissues ([11]). Antioxidants either exogenous as some micronutrients or endogenous as antioxidant enzymes serve as a defense system against such toxic effects. In the present work, we examined the status of both antioxidant enzyme activities and some relevant trace elements and their possible relationship in selected groups of children with 1st degree and 2nd degree marasmus as well as normal healthy children.

The diseased children with either 1st or 2nd degree marasmus showed significant decrease of SOD activity compared with control subjects. Our results are in agreement with Golden and Ramadath,1987 ([3]). However, Ashour et al., 1999 ([6]) reported an increase of the antioxidant enzymatic activities in 40% of the marasmic children, whereas Sive et al ., 1993 ([4]) found no changes. Inter groups comparison revealed significant reduction of SOD activity in 2nd degree marasmus compared with 1st degree, which may be related to the severity of the disease.

Mean whole blood GPX activity in the present study showed significant decrease in marasmic children compared with control group. These results are in agreement with that reported by Ashour et al., 1999([6]), Golden and Ramdath 1987 ([3]) , and Sive et al., 1993([4]) . Inter groups comparison showed significant decrease of GPX in 2nd degree marasmus compared with 1st degree, which may be related also to the severity of the disease. Decreased activities of both SOD & GPX in marasmic children may be due to deficiency of certain trace elements. Cu and Zn are an integral part of Cu-Zn SOD containing enzyme ([12]) and Se which is an integral part of Se-GPX containing enzyme([13]) .The present work showed reduced serum levels of these trace elements in marasmic children which may explain the obtained reduction in these metalloenzymes in marasmic cases. Another contributing factor is low energy intake and hypoproteinemia in marasmus ([14]), which may reduce enzyme synthesis.

As regards zinc, in control group the present study showed low zinc level compared with the standard value (0.7-12 mg/L) reported by Iyengar and Woittiez 1988([15]) . These results are in agreement with that of Hansen and Lehman, 1969 ([16]) who found reduced plasma zinc level to 65% of the expected value in normal children without any apparent manifestations of malnutrition and Hegazi, 2002 ([17]) who reported low serum zinc level in our apparently healthy children compared with the children of developed countries. Zinc deficiency in apparently healthy infants may be due to,

abnormally low zinc content in human milk. Moreover, in artificially fed infants, the bioavailability of zinc in cow's milk is even lower than human milk ([18]) . Another contributing factor is low content of zinc in the soil of the area around the Mediterranean Sea ([19]) . Finally phytate which is present in most foods of plant origin can hinder zinc absorption ([20]) .

The results of this study revealed significant decrease in serum zinc level in both groups of patients compared with control group. However, there is no significant difference between 2nd and 1st degree marasmus, which may indicate that zinc deficiency occurs in early stage of the disease. These results are in agreement with that reported by El-Sherbini 1984 ([21]) and Ibrahim 1990([22]) . A number of factors may be responsible for this low level of serum zinc in marasmic children including deficient intake, malabsorption, which is a common feature in marasmus, and unsupported parentral nutrition ([23]) .

The present work revealed significant negative correlation between serum level of zinc and both SOD & GPX activities in control group. It seems that zinc deficiency (an exogenous antioxidant) may lead to an increase of both antioxidant enzymes as a compensatory mechanism for protection against ROS.

As regards copper, our study revealed significant decrease in serum level of copper in marasmic children compared with control group which are in agreement with that reported by Ashour et al., 1999 ([6]) and Ibrahim 1990 ([22]) . Also, serum copper level is significantly lower in 2nd degree marasmus compared with the 1st degree that may be related to the severity of the disease. The low level of serum copper in marasmic children may be due to reduction in ceruloplasmin in marasmic children, which, is attributed to its excessive loss or destruction or inability to synthesis leading to lack of copper transport to the liver ([16]) . Another contributing factor that may lead to copper deficiency in marasmic cases is repeated bouts of acute and chronic diarrhoea and malabsorption which are common with marasmus ([24]) .

As regards selenium, the present study revealed significant decrease of serum level of selenium in both groups of marasmus compared with control group. Inter group comparison showed significant reduction in 2nd degree marasmus compared with 1st degree marasmus that may be related also to the severity of the disease. Our results are in agreement with that reported by Ashour et al., 1999 ([6]) who found significant reduction of serum level of selenium in marasmic children. Deficiency of selenium in marasmus may be due to restricted protein intake, unsupported parentral nutrition. Also, malabosrption which is a common association in children with P.E.M ([23]) may be a contributing factor.

In the present study, there was a significantly positive correlation between the serum level of selenium and SOD blood activity in both 1st and 2nd degree marasmus. However, no correlation was detected between the blood activity of GPX and the serum level of selenium, which is an integral constituent of the former. Also, no significant correlation was detected between serum zinc and both SOD and GPX activity in marasmic children It seems that the relation is not a simple one and other factors are essential partners. In marasmus, there are multi-nutrient deficiencies including calories, vitamins, and minerals. It is worth mentioning that some minerals affect the metabolization of others and also some vitamins cannot be probably metabolized if certain vitamins or minerals are not present in sufficient quantities.

As regards manganese, in control subjects the present work revealed increase in serum level of manganese more than the standard value (0.54-1.76m g/L) as reported by Iyengar and Woittiez, 1988 ([15]). Also, this study showed significant increase of serum level of manganese in both groups of marasmic children compared with control subjects. Our results are in agreement with study performed in Benha , Egypt, by Rizk, 1993([25]) . Inter groups comparison showed significant increase in serum level of manganese in 2nd degree marasmus compared with the 1st degree that may be related to the severity of the disease. Higher level of manganese in control group may be due to, high amounts of manganese in cow's milk([26]) which, is commonly used by many mothers in our rural areas. Another contributing factor is higher amount of Mn retained by the body in early infancy ([27]). In marasmic cases further increase of serum level of manganese may be due to, decrease Mn excretion in bile. Malnourished dehydrated infants and subjects receiving high carbohydrate diet showed decreased bile secretion ([28]). Again impaired renal function in chronic malnutrition may lead to further accumulation of Mn in marasmic cases ([26]). There is a significant positive correlation between serum level of Mn and GPX activity in 2nd degree marasmus. Manganese is a constituent of metallo-enzymes, which are important for many metabolic pathways such as pyruvate carboxylase for

carbohydrate metabolism, farnesyl pyrophosphate synthetase for lipid metabolism and arginase for protein metabolism ($_{29}$).

As regards lead, the present study revealed high level of lead in the serum of both patients and control compared with the standard level (1m g/L) reported by Iyengar and Woittiez 1988($_{15}$). Also, this study showed no significant difference between both patients and control or between both groups of marasmus. Our results are in agreement with that reported by Rizk, 1993 ($_{25}$) who attributed increased serum level of lead in both patients and control to heavy environmental pollution. High level of serum lead in both control and patients may be due to; absorption of higher amounts of ingested lead in infants and young children than adults ($_{30}$). Another contributing factor, is zinc deficiency, which increases lead absorption ($_{30}$). Again protein deficiency may be a factor since protein hinders lead absorption ($_{31}$). Finally, children have a bad habits like ingestion of paints chips, nail biting, finger suckling and hand to mouth activities are contributing factors ($_{32}$).

The present work showed a negative significant correlation between the blood activity of GPX and the serum lead in the control group. This may reflect a toxic effect of lead on the enzymatic activity of that enzyme.

As regards chromium, the present study showed higher serum level of Cr in control group than the standard value (0.12- 2.1m g/L) reported by Iyengar and Woittiez 1988 ($_{15}$). Also, this work revealed significant increase in both groups of marasmus compared with control group and significant increase of serum chromium in 2nd degree marasmus compared with the 1st degree that may be related to the severity of the disease. Our results are in agreement with previous study reported by Rizk, 1993($_{25}$). This high level of chromium in control group may be due to environmental pollution as chromium originates from various industrial processes that pollute the ground water, air and food ($_{33}$). In marasmic children further increase serum level of chromium may be due to impaired renal function in chronic malnutrition and decreased urinary excretion of Cr ($_{34}$).

The present work showed significant negative correlation between GPX blood level and serum level of Cr in 2nd degree marasmus, which may be, due to toxic effects of Cr late in the marasmic cases.

As regards nickel, the present work revealed highly increase of serum level of nickel in control children compared with the standard value (2.6-7.5 m g/L) reported by Iyengar & woittiez 1988($_{15}$). In marasmic children the results of the present work showed significant increase of serum level of nickel compared with control group. Inter groups comparison showed significant increase in 2nd degree marasmus compared with the 1st degree that may be related to the severity of the disease. Our results are in agreement with that reported by Rizk, 1993($_{25}$) High level of nickel in both control and diseased children may be related to environmental pollution since, nickel is released from many industrial activities like incineration of waste and tobacco smoke ($_{35}$) . Also, addition of nickel in agricultural soil ($_{33}$) may be a contributing factor. In marasmic cases further increase of serum level of Cr may be attributed to impaired renal function in chronic malnutrition leading to reduced urinary excretion of Cr which, is mainly excreted in urine ($_{34}$) .

The present study revealed significant negative correlation between blood level of GPX enzyme and serum level of nickel in control group, which may be attributed to toxic effects of nickel.

From the previous finding, antioxidant supplementation should be considered as a part of treatment of marasmic children, zinc supplementation in marasmic children should be considered and further studies of zinc deficiency in apparently normal children are recommended. Also the problem of environmental pollution with heavy metals in different age groups and different localities needs further studies to evaluate accurately the magnitude of the problem and its management.

In summary, in marasmus, there are altered trace elements statuses together with decreased activity of antioxidant enzymes, which predispose the marasmic children to the possible risk of R.O.S.

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92 Lyon France.

Author Information

Samir Mohammed Abou El Hassan
Professor and chairman of Pediatrics department, Mansoura Faculty of Medicine

Nabil Mahmoud Abdelrazik
Assistant Professor, Mansoura Faculty of Medicine

Abd El-Aziz Fotouh Abd El-Aziz
Associate professor of Biochemistry, Mansoura Faculty of Medicine

Reda Ragab El-Iraqi
Resident of pediatrics, Ministry of Health