

## Measurement of Serum Trace Elements (Zinc, Copper, Magnesium and Iron) Concentrations in Pediatric Patients with Otitis Media with Effusion in Iraq

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### Abstract

Otitis media with effusion (OME) is a common disease especially among young children (before school age) and it is one of the common causes of acquired hearing loss in childhood. Pediatric patients with OME are usually undernourished. The purpose of this study is to determine whether the serum levels of trace elements (zinc, copper, magnesium, iron) have a role in the development of OME in children. This study carried out on 55 children and subdivided them into two groups. Group 1 (patient group) consist of 30 children suffering from OME and group 2 (control group) included 25 apparently healthy children. Serum levels of zinc, copper, magnesium and iron were measured for both groups. Comparison the results between the two groups showed that group 1(patients) had significantly lower serum zinc, copper, and iron levels than group2 (P <0.05).

Meanwhile the differences between the two groups in terms of serum values of magnesium were not statistically significant (p>0.05). This study postulated that serum levels of zinc, copper, and iron may have a role in the development of OME in children. While, serum magnesium may not have effect on the development of OME in children.

**Keyword:** Pediatrics, Otitis media, Trace elements.

### قياس تراكيز العناصر النادرة في مصل الدم (الزنك، النحاس، المغنسيوم والحديد) عند المرضى الاطفال المصابين بالتهاب الاذن الوسطى الانصبابي في العراق نجوان قيصر فخري<sup>\*,1</sup>

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### الخلاصة

التهاب الاذن الوسطى الانصبابي هو احد الامراض الشائعة خاصة عند الاطفال ( قبل سن المدرسة) وهو احد الاسباب المؤدية الى ضعف السمع المكتسب في مرحلة الطفولة. وحيث ان الاطفال المصابين بالتهاب الاذن الوسطى الانصبابي هم عادة يعانون من سوء التغذية. لهذا اصبح الغرض من هذه الدراسة هو لتحديد فيما اذا كان مستويات العناصر النادرة (زنك، نحاس، مغنسيوم، حديد) في مصل الدم لها دور في حدوث التهاب الاذن الوسطى الانصبابي لدى الاطفال. هذه الدراسة اجريت على 55 طفل وتم تقسيمهم الى مجموعتين. المجموعة الاولى (مجموعة المرضى) وتشمل 30 طفل يعانون من التهاب الاذن الوسطى الانصبابي و المجموعة الثانية (الكونترول) وتشمل 25 من الاطفال الاصحاء. تم قياس مستويات الزنك، النحاس، المغنسيوم والحديد في مصل الدم للاطفال في كلتا المجموعتين. بعد مقارنة النتائج بين المجموعتين تبين ان في المجموعة الاولى كانت مستويات الزنك، النحاس والحديد في مصل الدم اقل بصورة ملحوظة مقارنة مع المجموعة الثانية. في حين لم يكن الاختلاف ملحوظ في مستويات المغنسيوم في مصل الدم عند المجموعتين. هذه الدراسة افترضت ان مستويات الزنك، النحاس والحديد في مصل الدم ممكن ان يكون لها دور في طبيعة حدوث التهاب الاذن الوسطى الانصبابي عند الاطفال. بينما مستوى المغنسيوم في مصل الدم ربما لا يلعب دور في حدوث هذا المرض عند الاطفال.

الكلمات المفتاحية: العناصر النادرة، التهاب الاذن الوسطى، طب الاطفال.

### Introduction

Otitis media with effusion (OME) is the most common ear disease in children; it is characterized by the accumulation of fluid in the middle ear space behind an intact tympanic membrane without symptoms of acute inflammation. It may lead to complications such as hearing loss, speech and language delay or poor balance<sup>(1,2)</sup>. Approximately 90% of children experience OME at some time before school age, with peak incidence in 6 months to 4 years<sup>(3)</sup>.

Pathogenesis of OME is not well understood, but a low-grade infection, especially with species similar to acute otitis media, eustachian tube dysfunction, inflammatory response following acute otitis media and complex interactions of biochemical, immunologic and inflammatory mediators in middle ear and adenoid hypertrophy have all been implicated<sup>(1, 4, 5)</sup>. The oxidative stress and the deficiency of antioxidants may be one of the factors leading to the pathogenesis of OME<sup>(6, 7)</sup>.

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In OME (which is considering as inflammatory disease in the middle ear) Oxygen radicals are blamed in the pathogenesis of inflammation. Infections are one of the reasons of increased reactive oxygen species production<sup>(8)</sup>. Excessive production of reactive oxygen species which is known as oxidative stress may lead to increase the duration of middle ear inflammation by disturbing the immune function of leucocytes through damaging to the membrane lipids. Also DNA damage by free radicals decreases production of certain critical factors by leucocytes and lowered their proliferation capacity<sup>(6)</sup>. Moreover, oxidative stress and free radicals causes damage to the cellular DNA and proteins to the cilia in the middle ear (change the structure of cilia) leading to slow down the cilia activity and inhibit cellular regeneration<sup>(9)</sup>.

Under normal physiological conditions enzymatic and non enzymatic antioxidant defenses protect aerobic organisms against the action of free radicals<sup>(7)</sup>. One of the most important enzymatic antioxidants is superoxide dismutase (SOD)<sup>(10)</sup>. The cytoplasmic copper/zinc-SOD, one of three forms of SOD, contains copper and zinc as cofactors and is believed to have a predominant role in the first step of antioxidant defense<sup>(7)</sup>. Ceruloplasmin, the copper-containing protein of extracellular fluids, has been shown to have important antioxidant properties towards peroxidising lipids<sup>(8)</sup>. This suggests that the risk of middle ear infection may potentially affect by factors (dietary or otherwise) which impair copper or zinc status<sup>(2)</sup>.

Magnesium has an indirect antioxidant effect. it act as a cofactor on enzymatic reactions which have a role on energy production, thus activity of glutathione reductase (antioxidants) may decrease due to dietary deficiency of magnesium leading to free-radicals induced protein oxidation and lesion to tissues<sup>(11, 12)</sup>.

Bacterial infections are considered as one of the etiological factors in OME<sup>(6)</sup>. Iron is an integral component of enzyme myeloperoxidase (MPO) activity which is used by neutrophil for killing process of bacteria by production of highly toxic reactive oxygen species intermediates (hydroxyl radicals)<sup>(13)</sup>.

Poor iron status are associated with decreased neutrophil function and impaired their bactericidal activity, thymic atrophy with reduction of T-lymphocytes numbers, defective proliferation of T helper (Th)-1 and Th-2 lymphocytes, reduction in the activity of natural killer cell, reduction in the interleukin-2 levels produced by lymphocytes and decreased in the macrophage migration inhibition factors production<sup>(13)</sup>.

In developing countries, studies on middle-ear diseases and their influence with micronutrient

status may provide valuable information on the knowledge of the pathogenesis of middle-ear infection, prevention and treatment. Our hypothesis is that low serum values of trace elements (Zinc, Copper, Magnesium and Iron) may be a contributory factor in the development of OME in children.

## Patients and Methods

This study was carried out at ear-nose – throat (ENT) department in Al Yarmook teaching hospital. The study consists of 55 children 29 male and 26 female with age range between 3 -6 years (with a mean age of  $4.6 \pm 1.06$ ). They were divided into two groups:

**1-Group 1**(patients group): consisted of 30 patients diagnosed to have OME.

**2-Group 2**(control group): included 25 healthy children without any complaint in the ear-nose-throat region. No Infection or any other systemic diseases.

Patients group were diagnosed to have OME by using otoscope, otomicroscopic and tympanometric evaluation by specialized physician.

Venous blood samples of all children were taken. Serum zinc, copper, magnesium and iron measurements were obtained calorimetrically using commercial diagnostic kits<sup>(14- 17)</sup>. The reference ranges for the trace elements measured are listed in table 1.

**Table (1): The reference range for the trace elements measured.**

Trace element	Reference ranges
Zinc (umol/l)	10.7-17.6
Copper (umol/l)	4.72-23.6
Magnesium (mmol/l)	0.8-1.0
Iron (umol/l)	6.6-26

## Results

The serum trace elements values of both patient group (group 1) and control groups (group 2) are shown in table 2.

Comparison between two groups showed that group 1(patients) had significantly lower serum zinc levels than group 2 (control)  $P < 0.05$ . (Serum levels of zinc in group 1 and group 2 were  $8.7303 \pm 1.5503$  and  $16.8039 \pm 2.4528$ (umol/l) respectively) Also patients group had significantly lower serum copper values as comparing with control group ( $P < 0.05$ ) (Serum copper levels were  $14.2097 \pm 4.3439$  in group 1 and  $18.1874 \pm 3.01628$  (umol/l) in group 2). As shown in table 2 and figure 1. According to the results in table 2 although the serum magnesium levels in group 1 was lower than in group 2 ( $0.8349 \pm 0.08903$  and  $0.8645 \pm 0.09598$  (mmol/l)) respectively there was no significant difference between the group's  $p > 0.05$  (figure 1).

The Serum iron levels of patients and control groups were  $16.9850 \pm 3.0323$  and  $19.4356 \pm 3.1020$  (umol/l) respectively. The patient

group had significantly lower serum iron as comparing with control group ( $P < 0.05$ ) (table 2 and figure1).

**Table ( 2): Serum levels of Zinc, Copper, Magnesium and Iron in groups**

Trace element	Group 1 N= 30	Group 2 N= 25	<i>p</i> value
Zinc ( $\mu\text{mol/l}$ )	8.7303 $\pm$ 1.5503	16.8039 $\pm$ 2.4528	0.000
Copper ( $\mu\text{mol/l}$ )	14.2097 $\pm$ 4.3439	18.1874 $\pm$ 3.0162	0.000
Magnesium ( $\text{mmol/l}$ )	0.8349 $\pm$ 0.08903	0.8645 $\pm$ 0.09598	0.241
Iron ( $\mu\text{mol/l}$ )	16.9850 $\pm$ 3.0323	19.4356 $\pm$ 3.1020	0.005

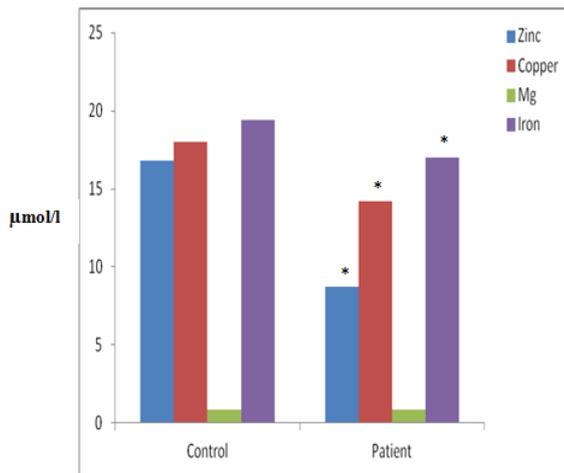
Group 1 (patients group).

Group 2 (control).

Data were expressed as mean  $\pm$  standard deviation (SD).

N= number of children.

The statistical significant differences in the concentrations of trace elements determined in group 1 and group 2 were investigated using student t-test)



\*  $P \leq 0.05$

**Figure (1): Serum concentrations (mean serum concentrations) of trace elements in control group and patients group of children.**

## Discussion

Ear disease consider as one of the major health problem particularly in developing countries<sup>(2)</sup>. A close interaction among nutrition, infection, and health has been recognized since many decades. Adequate intake of micronutrients is essential for the proper function of the immune system<sup>(18)</sup>. Nutritional factors may play a contributory role in the middle ear diseases<sup>(2, 8)</sup>.

Zinc is an essential trace element. It plays structural, regulatory, and catalytic roles in the body. Dietary zinc deficiency impairs immune function and resistance to infection by suppressing lymphocytes and neutrophils activity, decreased

phagocytosis by macrophages, decreased functions of natural killer cell, and decreased antibody responses among other<sup>(19)</sup>. Some studies have found that children with vitamin A, Zinc and Iron deficiency were more susceptible to upper respiratory and ear infections<sup>(20, 21, 22)</sup>.

In a previous study in Bangladeshi children, zinc supplementation significantly reduced the incidence of suppurative otitis media in those children<sup>(2)</sup>. Our results showed that patients in group 1 (OME) had significantly lower serum zinc values than those of group 2 (healthy control).

Copper has a specific regulatory role in the development and expression of the immune reactions. It has been demonstrated that copper deficiency reduced numbers and functions of neutrophil, decrease function and proliferation of T- lymphocytes and reduced macrophages activity<sup>(18)</sup>. Also copper attends to important catalytic functions in a number of enzymes such as Cu,Zn superoxide dismutase (SOD), cytochrome oxidase, and ceruloplasmine. Thus impairing copper or zinc status (due to dietary or otherwise factors) markedly reduced tissue Cu, Zn-SOD (which consider as enzymatic antioxidant defenses important in ear disease) and cause peroxidative damage and mitochondrial dysfunction<sup>(12)</sup>.

In a comprehensive review of literatures, no human research specifically examining the relation between copper status and middle ear diseases was identified. In our results, we found that group 1 children had significantly lower serum copper levels than those of group 2.

Magnesium has a relationship with the immune system both in innate and acquired immune response<sup>(23)</sup>. In human, antibody production and susceptibility to infections have been associated with lack of magnesium<sup>(23)</sup>. Also magnesium has indirect antioxidant effect, and a dietary magnesium deficiency may reduce glutathion reductase activity (antioxidant defense) leading to radical-induced protein oxidation<sup>(11, 12)</sup>. Previous study showed that the levels of magnesium and iron were significantly depressed in children suffering from the exudative otitis media comparing with the control group<sup>(24)</sup>. In our study there were no differences in the level of Mg between patients and healthy children.

Iron deficiency is the most widespread nutritional deficiency worldwide, especially in children living in poor resource countries<sup>(13)</sup>. Iron is essential for normal development of immune system and studies indicated that individuals with iron deficiency showed impairment of cell-mediated immunity, in addition phagocyte microbicidal function, natural killer cell activity and mucosal immunity are reduced leading to increase susceptibility to infections<sup>(13, 25)</sup>.

In a previous study by Margareta B. et al children with frequent middle ear infections

seemed to account for most of the differences in the serum levels of Iron and Zinc between the patients and controls <sup>(26)</sup>. Other study by Golz A et al concluded that the children with iron-deficiency anemia have higher prevalence of episodes of acute otitis media in comparison to healthy <sup>(27)</sup>. These findings are in accordance with our results, we found that serum levels of iron in patients group were significantly lower than those in control group children.

The antioxidant and micronutrient status of the patients group may be a significant factor in predisposition to OME. We found that serum levels of Zinc, copper, and iron in group 1 (OME) were significantly lower than group 2(control). However, there were not statistically significant differences between both groups regarding serum magnesium levels. We speculated that deficiency of serum Zinc, copper, and iron have a role in pathogenesis of OME in children.

## Conclusion

This study postulated that deficiency of serum Zinc, copper, and iron levels may have a role in pathogenesis of OME in children. Further clinical studies needed to elucidate the effect of other micronutrient and vitamins status in pathogenesis of OME in children.

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