Serum Copper and Zinc Levels in Thai Patients with Various Diseases†

SRIWATANA SONGCHITSOMBOON, D.Sc.*,
ARUNLUCK KOMINDR, M.D.***,
ORAWAN PUCHAIWATANANON, D.Sc.**,
SURAT KOMINDR, M.D.**,
SWAIRIN KULAPONGSE, M.Sc.*,
UMAPORN UDOMSUBPAYAKUL, M.Sc.*

Abstract

This study was conducted to evaluate the possible alteration of serum Cu and Zn levels in 118 medical inpatients (53 women and 65 men) in Ramathibodi Hospital. Patients were classified according to their main clinical diseases: pulmonary (n = 12), renal (14), infectious (30), malignant (9), cardiovascular (22), GI & hepatic (13) and hematological (18) diseases. Significantly increased serum Cu concentrations were found in patients with pulmonary, malignant, cardiovascular and infectious diseases; moreover, 75, 75, 50 and 37 per cent of these diseases, respectively, had serum levels greater than the normal mean+2SD (23.6 μmol/L). Besides, 5 per cent of patients (3 in renal, 1 in infectious and 2 in GI & hepatic diseases) had low serum Cu levels suggestive of Cu depletion. By contrast, significantly decreased serum Zn concentrations were found in patients with GI & hepatic, infectious, renal, cardiovascular and malignant diseases. Serum Zn levels below the normal mean-2SD (8.1 μmol/L) were presented in 46, 37, 29, 23 and 22 per cent of cases, respectively. It was found that serum Cu/Zn ratio in our patients not only with cancer but also with other diseases were statistically significant from the normal group. Hence, the use of serum Cu/Zn ratios as markers for the diagnosis of cancer or for staging tumors must be interpreted cautiously.

Key word : Copper, Zinc, Diseases

Trace elements are essential nutrients for normal growth and development. The biological role of copper and zinc, in different physiological and pathological conditions has been extensively investigated in recent years[1,2]. In various diseases, including malignant tumors and acute and chronic infections, serum copper (Cu) levels increase and/or serum zinc (Zn) levels decrease as a nonspecific reaction pattern during the active phase of the disease[3]. Elevated serum Cu was suggested as an

* Research Center,
** Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400,
*** Rajavithi General Hospital, Department of Medical Services, Ministry of Public Health, Bangkok 10400, Thailand.
† This study was supported by Ramathibodi Research Grant, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand.

accurate and minimally invasive index of lung diseases; e.g., bronchitis, asthma, and asbestosis[4]. On the contrary, a decrease in serum Zn levels were obtained in bronchial asthma patients[5,6]. Serum Zn was suggested to be a sensitive prognostic characteristic determining survival[7]. Furthermore, serum Cu, Zn and Cu/Zn ratio were described as helpful tools for the differential diagnosis of sarcoidosis from pulmonary tuberculosis and carcinoma[8], the Cu/Zn ratio especially might be a diagnostic test in lung cancer[9] In contrast, el-Ahmady OMR et al did not find any difference in this ratio between benign and malignant pulmonary diseases[10].

The objective of the present work was to evaluate the possible alteration in serum Cu and Zn levels and Cu/Zn ratio in medical inpatients in Ramathibodi Hospital.

MATERIAL AND METHOD

Subjects

From November 1994 to Febuary 1995, 118 patients (53 women and 65 men) admitted to the medical wards of Ramathibodi hospital, Bangkok, Thailand were recruited into the study. Physical examination, anthropometric assessments, dietary record, prescription of vitamin and mineral supplements were investigated by the nutritional support team. The mean (±SEM) ages were 52.4 ± 2.3 years in males and 54.1 ± 2.6 years in females, mean body mass indices (BMI) were 20.0 ± 0.5 and 22.3 ±1.9 kg/m^2, respectively.

Analytical method

Fasting blood was collected from each subject between 8.00-10.00 am. The samples were centrifuged (1200 g, 10 min) and serum was kept at -40°C until analysis. Extreme care was taken to avoid contamination from other sources. Serum Zn and Cu were analyzed by flame atomic absorption spectrophotometer (model 1100B; Perkin-Elmer)[11].

Statistical analysis

Results were presented as mean and standard error of mean (SEM), and were compared to normal values using Student's *t* test with p-value < 0.05 as statistical significance[12].

RESULT

The normal ranges of serum Cu and Zn levels were determined from 312 healthy adults aged 20-80 years (121 men; 191 women) living in Bangkok and surrounding districts. Serum Cu and Zn concentrations in this population were 18.0 ± 2.8 μmol/L (mean ± SD) and 12.7 ± 2.3 μmol/L[13], respectively.

Compared with the normal mean, significantly increased serum Cu concentrations were found in patients with pulmonary, malignant, cardiovascular and infectious diseases (Table 1). In these diseases the percentages of cases which had values 2SD above the normal mean were 75, 75, 50 and 37, respectively (Fig. 1A). By contrast, significantly decreased serum Zn concentrations were found in patients with gastrointestinal and hepatic, infectious, renal, cardiovascular, and malignant diseases (Table 1). The percentages of cases which had values 2SD below the normal mean were 46, 37, 29, 23, and 22, respectively (Fig. 1B). Increased Cu/Zn ratio found in every pathologic state studied was statistically significant from the normal group. Clinical signs of Cu and Zn deficiencies were not found in all of the patients.

Table 1. Means ± SEM of serum copper, zinc and copper/zinc ratio in patients with various diseases.

Disease	n	Copper μmol/L	Zinc μmol/L	Copper/Zinc
Control (normal range)	312	18.0 ± 0.3 (12.4-23.6)	12.7 ± 0.2 (8.1-17.3)	1.46 ± 0.02
Pulmonary	12	26.2 ± 1.4 [a]	11.6 ± 0.7	2.32 ± 0.57 [a]
Renal	14	18.5 ± 2.2	9.3 ± 0.6 [a]	2.05 ± 0.95 [d]
Infectious	30	21.8 ± 1.1 [b]	9.4 ± 0.6 [a]	2.66 ± 1.17 [a]
Malignant	9	25.6 ± 2.7 [d]	9.4 ± 1.2 [a]	3.04 ± 1.30 [c]
Cardiovascular	22	24.4 ± 1.6 [b]	10.4 ± 0.7 [b]	2.50 ± 0.98 [a]
GI & hepatic	13	18.2 ± 1.4	9.1 ± 1.1 [c]	2.31 ± 1.09 [d]
Hematologic	18	19.8 ± 1.2	11.5 ± 0.9	1.89 ± 0.77 [d]

Significant difference from healthy controls: [a] $p < 0.001$, [b] $p < 0.005$, [c] $p < 0.01$, [d] $p < 0.05$

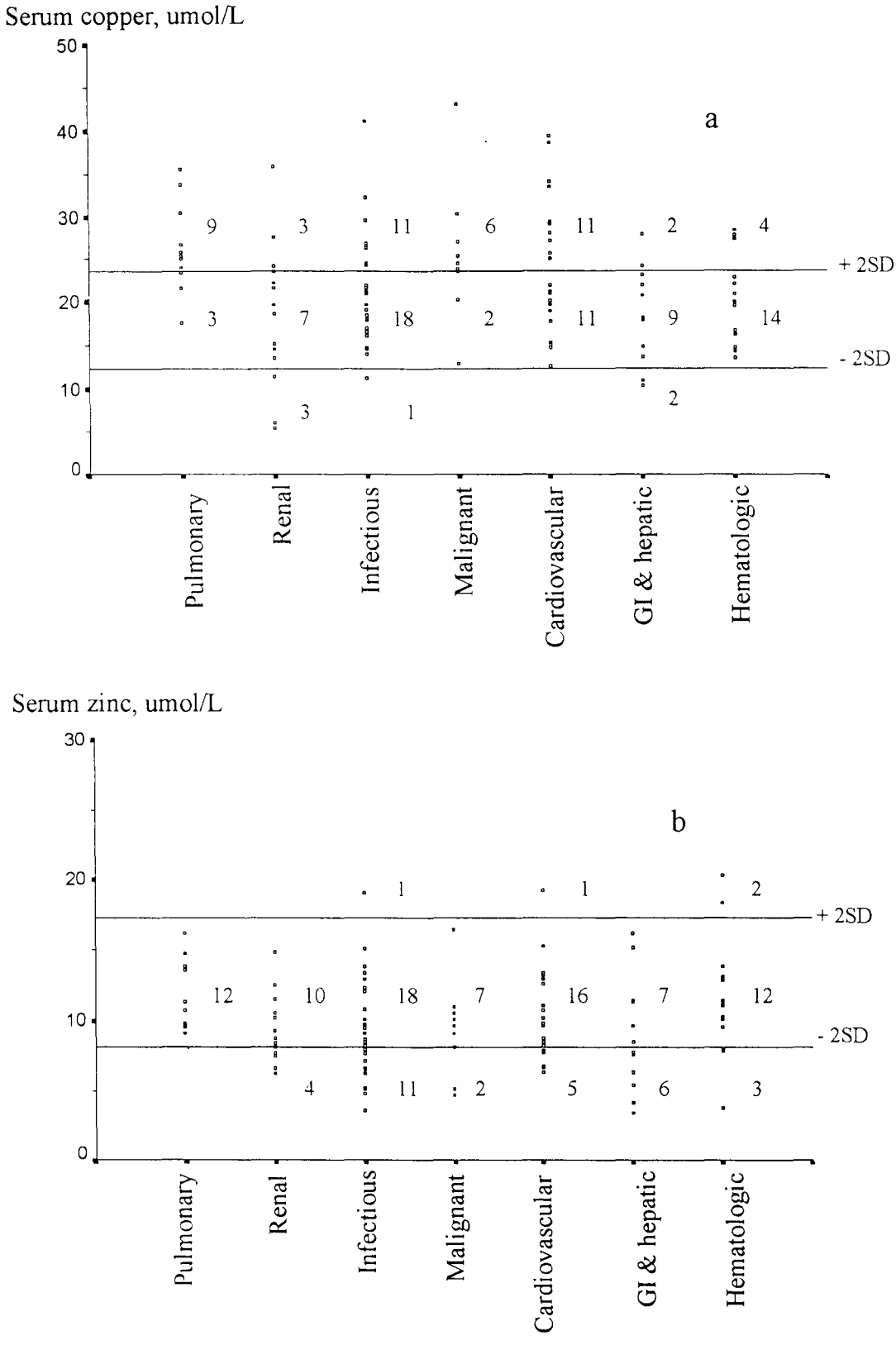

Fig. 1. Serum levels of A) copper and B) zinc in patients with various diseases. Number of patients are indicated.

DISCUSSION

Assessment of trace element status is difficult in most clinical situations. In such cases, tests of plasma or whole blood concentration, or urinary excretion, may provide some evidence of recent intake but may not reflect whole body status or the concentration within the metabolically active intracellular compartment. As indicated above, effects of the acute-phase response in sick patients further limit the use of plasma or blood measurements. Nonetheless, recommendation must be made to permit at least some degree of assessment of status and adequacy of provision. The most commonly used indices of Zn and Cu nutriture are the circulating Zn and Cu concentrations. Measurements done in plasma and serum, a relatively accessible fluid by atomic absorption spectrophotometry, provide accurate and precise methods of quantifying Zn and Cu in biologic materials[14]. Cu is an essential part of many enzymes including cytochrome c oxidase, lysyl oxidase, Zn/Cu superoxide dismutase and ferrooxidase (or ceruloplasmin) which appears to be beneficial in scavenging free oxygen radicals generated from neutrophils and macrophages[15]. In the presence of an acute-phase reaction, low serum Cu levels suggest Cu depletion, because an elevated Cu concentration is expected. Similarly, a normal serum Cu concentration does not confirm Cu adequacy in such patients[16]. The changes in serum Cu are a direct result of increased synthesis of plasma ceruloplasmin, which is a slowly reacting acute-phase protein induced by IL-1 in rats[17], and also by IL-6[18]. In this study, 5 per cent of patients (3 with renal, 1 with infectious and 2 with GI & hepatic diseases) had serum Cu concentrations less than 12.4 μmol/L (normal mean - 2SD). It was shown, however, that the synthesis of ceruloplasmin is still able to occur in Cu-deficient rats.

We found that 26 per cent of patients had serum Zn concentrations less than 8.1 μmol/L (normal mean - 2SD). Endotoxin injection in rats has been shown to cause a fall in plasma Zn concentration associated with an increase in both the extracellular Zn and the hepatic Zn pool, as measured by ^{65}Zn studies[19]. Furthermore, IL-1 injection into rats leads to increased uptake of Zn into the liver, bone marrow and thymus, whereas Zn is lost from bone, skin and intestine[20]. Schroeder and Cousins[21] demonstrated that the effect of IL-1 is mediated through IL-6, because IL-1 alone has no effect on the metallothionein response in hepatocyte monolayer cultures. TNF injection causes an increase in hepatic metallothionein synthesis, and this also is probably mediated through IL-6[22]. Increases in intracellular Zn correlate closely with the rise in metallothionein. The benefits of these changes in plasma Zn are not entirely clear, but one possible advantage would be to increase the availability of Zn in tissues in which metallothionein is induced. Zn plays an important role in stabilizing cell membranes[23], and at least one of the roles for metallothionein is as a free radical scavenger, because it has numerous reduced sulphydryl groups [24]. Zn is also an essential component of >200 metalloenzymes such as in the pathways of protein synthesis[1]. There is some preliminary evidence that provision of increased trace elements intake (30 mg Zn, 3.3 mg Cu and 150 μg Se /24 h by intravenous infusion) may improve the outcome (better immune response and shorter hospital stay) in cases of severe burn[25].

Many investigators tried to use serum Cu/Zn ratios as markers for the diagnosis of cancer or for staging tumors such as lung cancer[8-10], ovarian malignancy[26], gynecological tumors[3] and breast cancer[27]. From our study, the Cu/Zn ratio in our patients not only with cancer but also with other diseases was significantly higher than in the normal group (Table 1). So we agree with the statement that serum Cu/Zn ratios must be interpreted cautiously in cases of suspected malignancy that are accompanied by acute or chronic infections, chronic liver diseases or other conditions known to affect serum copper and zinc[26].

(Received for publication on May 13, 1998)

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ระดับทองแดงและสังกะสีในซีรัมของผู้ป่วยไทยที่เป็นโรคต่างๆ†

ศรีวัฒนา ทรงจิตสมบูรณ์, วท.ด., สุรัตน์ โคมินทร์, พ.บ.**,*
*อรุณลักษณ์ โคมินทร์, พ.บ.***, ไสวรินทร์ กุลพงษ์, วท.ม.*,*
*อรวรรณ ภู่ชัยวัฒนานนท์, วท.ด.**, อุมาพร อุดมทรัพยากรกุล, วท.ม.**

ได้ทำการวิเคราะห์หาระดับทองแดงและสังกะสีในซีรัมของผู้ป่วยไทยจำนวน 118 ราย (ผู้หญิง 53 ราย และผู้ชาย 65 ราย) ซึ่งเข้ารับการรักษาในหอผู้ป่วยของโรงพยาบาลรามาธิบดี ผู้ป่วยเป็นโรคดังต่อไปนี้ โรคปอด 12 คน โรคไต 14 คน โรคติดเชื้อ 30 คน โรคมะเร็ง 9 คน โรคหัวใจ 22 คน โรคทางเดินอาหารและตับ 13 คนและโรคโลหิต 18 คน จากการศึกษาพบว่า ค่ามัชฌิมของระดับทองแดงในซีรัมของผู้ป่วยโรคปอด โรคมะเร็ง โรคหัวใจและโรคติดเชื้อสูงกว่าค่ามัชฌิมของคนปกติอย่างมีนัยสำคัญทางสถิติ โดยร้อยละ 75, 75, 50 และ 37 ของผู้ป่วยโรคดังกล่าวมีระดับ serum Cu สูงกว่า ค่ามัชฌิม +2SD ของคนปกติ (23.6 ไมโครโมลต่อลิตร) นอกจากนี้พบว่าร้อยละ 5 ของผู้ป่วยทั้งหมด (โรคไต 1 คน โรคติดเชื้อ 1 คน และโรคทางเดินอาหารและตับ 2 คน) มีระดับ serum Cu ต่ำบ่งชี้ถึงภาวะพร่องของทองแดง ในทางตรงกันข้าม ค่ามัชฌิมของระดับสังกะสีในซีรัมของผู้ป่วยโรคทางเดินอาหารและตับ โรคติดเชื้อ โรคไต โรคหัวใจและโรคมะเร็ง ต่ำกว่าค่ามัชฌิมของคนปกติอย่างมีนัยสำคัญทางสถิติ โดยร้อยละ 46, 37, 29, 23 และ 22 ของผู้ป่วยโรคดังกล่าวมีระดับ serum Zn ต่ำกว่า ค่ามัชฌิม–2SD ของคนปกติ (8.1 ไมโครโมลต่อลิตร) การศึกษานี้พบว่าไม่เพียงแต่ผู้ป่วยโรคมะเร็ง ผู้ป่วยโรคอื่น ๆ ก็มีระดับ serum Cu/Zn ratio แตกต่างจากคนปกติอย่างมีนัยสำคัญทางสถิติ ดังนั้นการใช้ serum Cu/Zn ratio เป็นเครื่องวินิจฉัยโรคมะเร็งหรือระดับรุนแรงของมะเร็งต้องแปลผลอย่างระมัดระวัง

คำสำคัญ : ทองแดง, สังกะสี, โรคต่าง ๆ

* สำนักงานวิจัย,
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400
*** โรงพยาบาลราชวิถี, กรมการแพทย์ กระทรวงสาธารณสุข, กรุงเทพ ฯ 10400
† การศึกษานี้ได้รับการอุดหนุนจากทุนวิจัย, คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี, มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400