Serum Copper, Zinc, Ceruloplasmin and Superoxide Dismutase in Thai Overweight and Obese

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Abstract

The serum copper, selenium, ceruloplasmin, superoxide dismutase (SOD) (specific activities of antioxidant enzymes), anthropometric measurements, including waist/hip ratio 51 male and 190 female overweight subjects (body mass index (BMI) $\geq$ 25.0 kg/m^2) compared with a 26 male and 83 female control group (BMI = 18.5-24.9 kg/m^2) Thai volunteers who attended the Out-patient Department, General Practice Section, Rajvithi Hospital, Bangkok, for a physical check-up from March to October, 1998, were investigated. There was no age difference between the overweight group and the controls. All of the anthropometric variables, except the height of the overweight group, were significantly higher than those of the normal subjects. The medians of weight and waist/hip ratio of overweight and obese males were significantly higher than those of overweight and obese females. Serum ceruloplasmin, copper were statistically significantly higher in overweight subjects than in the controls. However, serum zinc and superoxide dismutase activity in the overweight group were found to be lower than in the control group. Higher serum ceruloplasmin, copper, zinc and superoxide dismutase activity were shown in the female overweight group than in the male overweight group. Ceruloplasmin was found to correlate positively with copper concentration but negatively related with superoxide dismutase enzyme activity. A negative correlation was found between serum copper and zinc concentrations in both sexes of the overweight and obese subjects. Low SOD activity found in the overweight and obese subjects might be caused by low zinc intake.

Key word : Superoxide Dismutase, Ceruloplasmin, Serum Copper, Serum Zinc, Obesity

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The prevalence of obesity has increased dramatically over the past decade[1,2]. The fact that Thailand is rapidly approaching the status of a newly industrialised country is well reflected in some demographic and economic indicators[3]. A total of 23.6 per cent of Thai female construction site workers was reported to be obese[4]. Obesity was found in 11 per cent of the Thai elderly[5]. Moderate to severe obesity is increasingly found and might be associated with clear health risks, including hypertension, diabetes and dyslipidemia[6]. In the past few years, there have been advances in research in overweight and obese Thais. Exploratory papers have reported abnormal lipid profiles[7], serum leptin[8] and erythrocyte antioxidant enzyme[9]. Serum oxidase enzyme has been related to some trace elements, copper and selenium. Enzymatic and immunologic technics indicate the existence of a linear relation between the serum copper and ceruloplasmin and oxidase activity in pregnancy, infection and the nephrotic syndrome[10]. The serum copper concentration is elevated in many acute and chronic pathologic states. A persistent elevation after acute myocardial infarction was reported[11]. Therefore, the aim of the present study was to investigate serum copper, selenium, ceruloplasmin, and superoxide dismutase (SOD) in healthy, overweight and obese Thai people compared with apparently healthy subjects in order to provide preliminary baseline information for further studies, health promotion and nutritional intervention.

MATERIALS AND METHOD

Study Population

Fifty-one male and 190 female overweight and obese Thai volunteers, including 26 male and 83 female normal subjects, comprised the study population. Thai volunteers who attended the Out-patient Department, General Practice Section, Rajvithi Hospital, Bangkok, for a physical check-up, were enrolled in this study. They all visited the clinic voluntarily and were still fairly well, except for minor ailments and typical diseases of obese people such as hypertension, mild to moderate degrees of cardiovascular diseases and non-insulin dependent diabetes mellitus, which were diagnosed by physical and biochemical laboratory examinations for the inclusion criteria. The age, marital status, place of origin, drinking and smoking habits were assessed by standardized questionnaires. The same medical doctor conducted the physical examinations throughout the study. The study protocol was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, and informed consent was obtained from each participant.

Analytical methods

The body weight of each individual dressed in light clothing, was measured using a carefully calibrated beam balance (Detecto®, Detecto Scale Manufacturing, USA). Height measurements were taken using a vertical measuring rod. The BMI or Quetelet's index was conventionally calculated as weight in kg/ (height in metres)^2. The classifications of BMI employed were those used by the WHO Expert Committee 1995[12], overweight grade I: BMI=25.00-29.99 kg/m^2; grade II (obese): BMI= 30.00-39.99 kg/m^2; grade III (obese): BMI $\geq$ 40 kg/ m^2. Waist and hip circumferences were also measured to calculate waist/hip ratio (normal value for females < 0.77, males <0.90)[13,14].

About twenty ml of venous blood from each of the subjects under study was drawn in the morning after an overnight fast. All samples were collected in metal-free, acid-cleaned syringes through a special stainless-steel needle. Metal-free, acid cleaned glassware was used throughout. Serum was separated from the cell one hour after collection, stored in the cold at -20°C and analyzed within ten days for copper and selenium. For the quantitative determination of ceruloplasmin, the rocket immunoelectrophoresis method was used[15]. Blood for antioxidant enzyme determination was collected in heparinized tubes and the hemolysates were prepared in the next few hours. Determination of enzymes, SOD was performed using a Randox test combination (Randox, Grumlin, UK). Hemoglobin (g/l) was measured on an STKR cell counter (Coultronics, Margency, France). Results of superoxide dismutase activity were expressed as U SOD/g hemoglobin. Serum copper and zinc were determined by using atomic absorption spectrophometric methods[16,17].

Statistical analysis

The results were expressed as median, range, and 95 per cent confidence interval (C.I.). The data were coded and analyzed by using a standard statistical method provided by the Minitab computer programme[18].

RESULT

The medians, ranges and 95 per cent confidence interval (CI) of age, anthropometric variables, waist/hip ratio, ceruloplasmin, serum copper, zinc and superoxide dismutase activity of overweight and normal subjects, and overweight and normal subjects (males and females), are shown in Table 1 and Table 2. There was no age difference between the overweight group and the controls. All of the anthropometric variables, except the height of the overweight group, were significantly higher than those of the normal subjects. The medians of weight and waist/hip ratio of the overweight and obese males were significantly higher than those of overweight and obese females. Serum ceruloplasmin and copper were statistically significantly higher in the overweight subjects than in the controls, while serum zinc and superoxide dismutase activity in the overweight group were found to be lower than in the control group. Higher serum ceruloplasmin, copper, zinc and superoxide dismutase activity were shown in the female overweight group than in the male overweight group (Table 2).

Using the cut-off point of ceruloplasmin concentration (60 mg/dl) suggested by Dati et al 1996 [19], 41.3 per cent (19 out of 46) of the overweight and obese males were found to have elevated ceruloplasmin levels, while 63.6 per cent (105 out of 165) were found to have elevated levels in the overweight and obese females (Table 3). 14.3 per cent (6 out of 42) of the male overweight and obese subjects were found, compared with 5.8 per cent (8 out of 139) of the female overweight and obese group who also had less zinc in their sera (<75 μg/dl in males and <65 μg/dl in females) (Table 3).

Ceruloplasmin was found to be positively correlated with copper concentration but negatively related with superoxide dismutase enzyme activity. A negative correlation was found between serum copper and zinc concentrations in both sexes of overweight and obese subjects (r= -0.212, p<0.01) (Table 4).

DISCUSSION

The distribution of obese subjects in the present study according to the grading of the 1995 WHO Group[12] was 34.9, 58.5 and 6.6 per cent for grades I, II and III, respectively, with a predomination of grade II (BMI=30.0-39.99 kg/m^2). This result may indicate the need for counseling and control-

Table 1. Medians, ranges and 95 per cent confidence interval (CI) of age, anthropometric variable, ceruloplasmin, copper, zinc and superoxide dismutase enzyme in overweight and control subjects.

Parameter	Total				P-value*
	Overweight (N=240)		Control (N=109)		
	Median (range)	95%CI	Median (range)	95%CI	
Age (yrs)	39.0 (18.0-58.0)	38.0-41.0	39.0 (18.0-60.0)	36.0-40.0	0.546
Weight (kg)	78.5 (54.0-165.0)	74.5-78.5	54.2 (42.5-78.0)	52.8-55.9	0.000
Height (m)	1.56 (1.43-1.85)	1.56-1.58	1.58 (1.43-1.85)	1.56-1.59	0.222
BMI (kg/m^2)	31.56 (25.08-57.77)	30.26-31.23	21.90 (18.47-24.97)	21.55-22.22	0.000
Waist (cm)	92.0 (66.5-128.0)	90.0-94.0	72.5 (60.0-89.0)	71.2-74.0	0.0000
Hip (cm)	109.0 (86.5-151.5)	107.0-110.0	92.0 (82.0-102.0)	92.0-94.0	0.0000
W/H ratio	0.84 (0.67-1.01)	0.83-0.85	0.78 (0.65-0.93)	0.77-0.80	0.0000
Ceruloplasmin (mg/dl)	63.8 (38.2-170.0	61.9-67.2	46.5 (25.8-102.3)	44.1-50.2	0.000
Serum copper (μg/dl)	102.7 (31.3-230.7)	98.8-111.7	96.6 (37.3-173.1)	89.1-100.9	0.001
Serum zinc (μg/dl)	190.0 (25.0-656.0)	170.0-216.1	240.0 (70.0-690.0)	230.0-260.0	0.001
SOD U/gHb	1582.8 (220.8-16312.1)	1389.0-1886.0	2670.5 (315.8-13880.6)	2370.0-3074.0	0.000

BMI = body mass index, SOD = superoxide dismutase enzyme
*Mann-Whitney U-Wilcoxon Rank Sum W Test (Two-Tailed)

Table 2. Medians, ranges and 95 per cent confidence interval (CI) of age, anthropometric variable, ceruloplasmin, copper, zinc and superoxide dismutase enzyme in overweight and control subjects compared between male and female.

Parameter	Male				p-value	Female				p-value
	Overweight (N=51)		Control (N=26)			Overweight (N=190)		Control (N=83)		
	Median (range)	95% CI	Median (range)	95% CI		Median (range)	95% CI	Median (range)	95% CI	
Age (yrs)	41.0 (18.0-56.0)	39.0-46.0	35.5 (19.0-54.0)	30.0-42.0	0.0810	38.0 (18.0-58.0)	34.0-42.0	37.0 (18.0-55.0)	34.0-40.0	0.6171
Weight (kg)	86.5 (62.4-114.8)	82.0-91.6	61.75 (50.7-78.0)	58.9-64.7	0.0000	76 (54.0-130.2)	74.5-78.6	52.5 (42.5-67.0)	51.62-54.18	0.0000
Height (m)	1.69 (1.50-1.84)	1.67-1.72	1.66 (1.57-1.86)	1.65-1.70	0.5392	1.55 (1.45-1.69)	1.54-1.56	1.56 (1.43-1.69)	1.54-1.58	0.0473
BMI (kg/m^2)	30.92 (25.35-38.75)	29.30-32.20	21.73 (18.68-24.61)	20.61-23.22	0.0000	31.63 (25.19-53.78)	30.94-32.54	21.91 (18.68-24.92)	21.03-22.07	0.0000
Waist (cm)	100.0 (65.0-123.5)	95.0-104.0	81.0 (64.0-89.0)	75.6-83.7	0.0000	90.5 (71.0-127.0)	89.0-92.5	71.0 (60.0-83.0)	70.0-72.0	0.0000
Hip (cm)	105.0 (89.5-129.0)	103.4-109.5	94 (87.0-102.0)	91.3-95.4	0.0000	110.0 (86.5-151.5)	107.0-110.5	92.0 (82.0-101.1)	91.0-93.0	0.0000
W/H ratio (cm)	0.93 (0.67-1.01)	0.92-0.94	0.87 (0.72-0.93)	0.82-0.88	0.0000	0.83 (0.70-0.99)	0.82-0.84	0.77 (0.65-0.88)	0.76-0.78	0.0000
Ceruloplasmin (mg/dl)	56.85 (38.2-137.6)	55.1-61.9	41.4 (1.8-25.8)	37.7-46.3	0.0000	67.2 (42.3-170.0)	63.7-70.2	50.1 (27.6-102.3)	46.5-53.9	0.0000
Serum copper (μg/dl)	99.1 (48.5-219.9)	90.6-118.5	72.4 (37.3-134.7)	57.5-90.0	0.0032	103.3 (31.3-230.7)	98.9-112.1	98.8 (42.3-173.1)	93.5-106.0	0.0476
Serum zinc (μg/dl)	172.5 (35.0-210.0)	120.0-213.8	240. (95.0-405.0)	213.5-306.3	0.0215	195.0 (25.0-656)	177.0-223.0	240.0 (70.0-690.0)	220-260.0	0.0075
SOD (U/gHb)	1437 (234-6624)	1264-2383	2751 (1316-23881)	2241-3472	0.0325	1591 (235-16312)	1332-1970	2596 (1111-11395)	2234-3114	0.0000

BMI = body mass index, SOD = superoxide dismutase enzyme

*Mann-Whitney U-Wilcoxon Rank Sum W Test (Two-Tailed)

Table 3. Number and percentage of individuals with overweight, hypertension and abnormal ceruloplasmin, trace elements and superoxide dismutase enzymes.

Parameter	Male		Female		Total	
Grading of overweight by BMI (kg/m^2)	N/Total	%	N/Total	%	N/Total	%
Grade I (BMI=25.0-29.99)	21/51	41.2	63/190	33.2	84/241	34.9
Grade II (BMI=30.0-39.99)	29/51	56.8	112/190	58.9	141/241	58.5
Grade III (BMI ≥ 40.00)	1/51	2.0	15/190	7.9	16/241	6.6
Ceruloplasmin >60 mg/dl	19/46	41.3	105/165	63.6	124/212	58.5
Trace elements Cu <75 μg/dl	6/33	18.2	15/130	11.5	21/163	12.9
Zn Male <75 μg/dl Female < 65 μg/dl	6/42	14.3	8/139	5.8	14/181	7.7
Superoxide dismutase enzymes SOD ≤ 2,866 (U/gHb)	23/33	69.7	97/133	72.9	120/166	72.3

BMI = body mass index, Cu= serum copper concentration, Zn =serum zinc concentration, SOD = superoxide dismutase enzyme

Table 4. Correlation coefficients of age, anthropometric variables, ceruloplasmin, superoxide dismutase enzyme, trace elements in overweight both males and females (BMI ≥ 25.0 kg/m^2).

Parameter	SOD	Ceruloplasmin	Cu	Zn
Age	-0.124	0.014	-0.003	-0.021
Weight	-0.138*	0.343**	0.120	-0.175
Height	0.095	-0.306**	-0.229**	0.019
BMI	-0.172**	0.488**	0.230**	-0.187**
SOD	1.000	-0.239**	0.062	-0.004
Ceruloplasmin	-0.039	1.000	0.409**	-0.042
Cu	0.034	0.409**	1.000	-0.212**
Zn	-0.021	-0.042	-0.212**	1.000

BMI = body mass index, Cu= serum copper concentration, Zn =serum zinc concentration, SOD = superoxide dismutase enzyme

Significant difference: *p<0.05, **p<0.01

ling transformation from grade II to grade III. Over 80 per cent of the obese subjects had a waist/hip ratio higher than the cut off point. Although overweight can be estimated from anthropometric measurements (BMI), waist/hip ratio has been shown to be closely correlated with more direct measurements of visceral fat in women, especially in Asian women[20]. It has been shown that Vietnamese women appear to have a low waist/hip ratio, and also a low BMI, and this has been noted in other Asian women[21], whereas, lean women in China tended to have a higher waist/hip ratio of 0.8, while mean BMI was relatively low. Therefore, the identification of obesity should use both indicators, BMI and waist/hip ratio, because the relatively high waist/hip ratio means that with increasing weight gain they could reach unacceptable levels of abdominal obesity leading to an increased risk of diabetes mellitus and heart disease[22].

In the present study, higher serum ceruloplasmin and copper concentrations were found in the overweight and obese subjects than in the control group. The copper concentration was also positively correlated with ceruloplasmin ($r = 0.409$, $p < 0.01$, Table 4). It has been reported that high copper concentrations were found in healthy adults (BMI > 25.0 kg/m^2) living in Bangkok and surrounding districts[23]. Furthermore, subjects with hypertension had serum copper levels significantly higher than those with normotension[24]. Therefore, high copper levels in the obese might be related to the physiological effects of hypertension, a major result of obesity. However, further investigations are needed.

Ceruloplasmin is an acute phase reactant protein exhibiting moderate responses to various stresses. It is thought to possess extracellular antioxidant properties in humans and other mammals[25]. This protein is a monomeric (2-glycoprotein that contains more than 95 per cent of the total circulating copper in healthy human adults. Conforti et al[26] reported a clear correlation between increases in ceruloplasmin and serum copper concentration in normal rats and animals with experimental inflammation. Similar findings have also been reported in humans[27-29]. Factors that can increase serum concentrations of ceruloplasmin in humans

include physical exercise, third trimester pregnancy, ovarian hyperfunction, arteriosclerosis, epilepsy, chronic inflammatory processes (eg. alcoholic and biliary liver cirrhosis, active chronic hepatitis, rheumatoid arthritis, pyelonephritis and rheumatoid spondylitis) and malignant tumors (eg. of the stomach, lung and bone, and Hodgkin's disease)[30]. Transitory reversible increases have been reported in women taking oral contraceptives and persons with acute myocardial infarction[31]. It has been proposed that ceruloplasmin may have a role in copper transport, conversion of Fe^{+2} to Fe^{+3} (ferrooxidase) for subsequent uptake by transferrin and exhibition of pro-oxidant activity towards low density lipoproteins under some circumstances[32-34]. Recently H_2O_2-removing activity (peroxidase) of human ceruloplasmin in the presence of reduced glutathione has also been reported[35]. For this reason, a negative correlation was also found between ceruloplasmin concentration and superoxide dismutase (SOD) which is the enzyme that destroys the free oxygen radical (superoxide) by successive oxidation and reduction of the transition metal ion at the active site in a PingPong type mechanism with remarkably high reaction rates[36], to hydrogen peroxide in overweight and obese subjects (Table 4). Superoxide dismutase has at least three forms, namely Cu/Zn SOD, mitochondria Mn-SOD (containing one manganese atom), and extracellular SOD[37,38]. Although Mn-SOD is more essential for life than Cu/Zn-SOD, the Cu/Zn-SD contents were two times as large as the Mn-SOD contents. Low activity of total SOD (all forms of SOD) was found in the overweight and obese subjects, compared with the control subjects (Table 1). This finding indicated that lower immune responses and impairment of antioxidant defenses were found in overweight and obese subjects. An impairment production of antioxidant defenses plays a role in the pathogenesis of a number of diseases such as ischemia/reperfusion injury, atherosclerosis, neurodegenerative diseases, cancer and allergy in overweight and obese subjects.

Serum zinc concentration was lower in the overweight and obese subjects compared with the control subjects (Table 1). Zinc concentration was also negatively correlated with copper concentration ($r = -0.212$, $p < 0.01$, Table 4). Zinc is known to be an essential metal for the activity of Cu/Zn-SOD, because two identical subunits of this enzyme contain a metal cluster, the active site, constituted by a copper and a zinc atom bridged by a histamine residue[39-41]. As shown in rats, a deficiency of zinc had a marginal effect on the expression of Cu/Zn SOD in erythrocytes[42]. There are many factors that may modify zinc absorption, and they may be considered as activators or inhibitors of this process. Among absorption activators there are picolinic acid secreted by the pancreas, vitamin B6 that increases picolinic acid secretion, and citrate and amino acids such as glycine, histidine, lysine, cysteine and methionine[43-45]. In the group of absorption inhibitors there are phytic and oxalic acids, tannins, fibre, selenium, tin, copper, iron and calcium[46-50]. Imbalance in both absorption activators and inhibitors in the overweight and obese subjects may have occurred. Therefore, one reason for the low SOD activity found in the overweight and obese subjects may be low zinc intake. Further research in the pathophysiology of trace elements and antioxidant enzymes might be needed for more information on this relationship.

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ทองแดง สังกะสี เซอรูโลพลาสมิน ซุปเปอร์ออกไซด์ดีสมิวเตส ในคนที่มีน้ำหนักเกินและอ้วนไทย

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คณะผู้วิจัยได้ทำการศึกษาปริมาณทองแดง สังกะสี เซอรูโลพลาสมิน รวมทั้งปริมาณเอนไซม์ซุปเปอร์ออกไซด์ดีสมิวเตสในเม็ดเลือดแดง และดัชนีชี้วัดสัดส่วนของร่างกายในผู้มีน้ำหนักเกินและอ้วนชายจำนวน 51 คน หญิงจำนวน 190 คน (BMI $\geq$ 25.0 กิโลกรัม/เมตร^2) เปรียบเทียบกับอาสาสมัครผู้มีน้ำหนักปกติ (BMI =18.5–24.9 กิโลกรัม/เมตร^2) ชายจำนวน 26 คน และหญิง 83 คนซึ่งได้มาทำการตรวจร่างกายประจำปี ที่แผนกผู้ป่วยนอก โรงพยาบาลราชวิถี กรมการแพทย์ กรุงเทพฯ ผลการศึกษาพบว่าดัชนีชี้วัดสัดส่วนของร่างกายของผู้มีน้ำหนักเกินและอ้วนมีความแตกต่างอย่างมีนัยสำคัญทางสถิติโดยเฉพาะค่าอัตราส่วนของเส้นรอบเอว/เส้นรอบสะโพก ในกลุ่มผู้มีน้ำหนักเกินและอ้วนพบค่าของปริมาณทองแดงและเซอรูโลพลาสมินสูงกว่าในกลุ่มคนปกติ ในขณะที่ค่าปริมาณสังกะสีและเอนไซม์ซุปเปอร์ออกไซด์ดีสมิวเตสในกลุ่มผู้มีน้ำหนักเกินและอ้วนต่ำกว่ากลุ่มคนปกติอย่างมีนัยสำคัญทางสถิติ เมื่อเปรียบเทียบในกลุ่มผู้มีน้ำหนักเกินและอ้วนพบว่าในเพศหญิงอ้วนค่าซีรั่มทองแดง สังกะสี เซอรูโลพลาสมินและซุปเปอร์ออกไซด์ดีสมิวเตสสูงกว่าในเพศชาย ในกลุ่มคนที่มีน้ำหนักเกินและอ้วนยังพบว่าเซอรูโลพลาสมินมีความสัมพันธ์ในทางบวกกับปริมาณทองแดงในซีรั่มแต่มีความสัมพันธ์ในทางลบกับซุปเปอร์ออกไซด์ดีสมิวเตส นอกจากนั้นยังพบว่าปริมาณสังกะสีมีความสัมพันธ์ในทางลบกับปริมาณทองแดงในซีรั่มในทั้งสองเพศ ปริมาณซุปเปอร์ออกไซด์ดีสมิวเตสต่ำอาจจะสัมพันธ์กับการได้รับสังกะสีต่ำในกลุ่มคนที่มีน้ำหนักเกินและอ้วน

คำสำคัญ : ทองแดง, สังกะสี, เซอรูโลพลาสมิน, ซุปเปอร์ออกไซด์ดีสมิวเตส, คนอ้วน

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