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# Serum Level of Copper, Zinc and Manganese in Somatization Disorder Patients

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## Abstract

*Objective: The purpose of the study is to determine the serum concentrations of trace elements of somatization disorder patients and to find out the relationship between trace elements level with their nutritional status and socioeconomic factors.*

*Method: The study was conducted among 46 somatization disorder patients and 45 healthy volunteers. Each patient was selected from different hospitals by random sampling. Serum trace elements concentrations were determined by flame atomic absorption spectroscopy. Statistical analysis were done using independent t-test, Pearson's correlation analysis, regression analysis and ANOVA.*

*Result: Mn, Zn and Cu concentrations of somatization disorder patients were 1.133±0.45 (mg/L), 1.216±0.352 (mg/L) and 1.491±0.499 (mg/L), while these were 0.987±0.216 (mg/L), 1.209±0.277 (mg/L) and 0.962±0.684 (g/L) in control subjects respectively. The serum concentration of Mn and Cu increased significantly (P=0.00; P=0.022 respectively) in somatization disorder patients while the concentration of Zn (P=0.954) remained unchanged. Socioeconomic data reveals that most of the patients were poor, middle- aged and unmarried. Mean BMI of the patients (20.26±3.04) and the control subjects (23.56±2.03) was in normal range. Pearson's Correlation analysis suggested that only Cu concentration of patients had a significant inverse correlation with the BMI ($r = -0.462$, $p = 0.010$), which was further justified from the regression analysis ($R^2 = 46.3\%$; $t = -2.876$; $p = 0.003$) and one-way ANOVA test ($F = 8.135$; $p = 0.010$).*

*Conclusion: This study depicted a significant increase in the serum concentration of Cu and Mn in somatization disorder patients than that of its control counter parts, which may provide prognostic tool for the diagnosis of this disease. Still the authors suggest further studies to confirm these findings (German J Psychiatry 2007; 10: 41-45).*

*Keywords: somatization disorder; trace elements; flame atomic absorption spectroscopy; clinical significance*

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## Introduction

Somatization disorder (SD) is the physical manifestation of mental pain (Adler et al, 1989). It represents a psychiatric condition because the physical symptoms present in this disorder cannot be explained fully by a medical disorder, or another mental disorder (Fink et al., 1999). Of all patients attending the family physician, 16% have a somatization disorder as described by DSM-IV (Arnold et al, 2006). Therefore, it is a frequently occurring psychiatric disorder. Individuals with somatization disorder claim to suffer constantly and for many years from many physical illnesses, yet they do not have any specific, diagnosed medical illnesses that can explain their symptoms (Francois, 2004). Symptoms of somatization provide a challenge to the physicians to differentiate it from other mental illness. Frequent concomitants of somatization are major depressive

disorders, anxiety disorders, and personality disorders. Several recent studies found that 61 to 72 percent patients with somatization disorder also have co-occurring personality disorders (Turkson and Asamoah, 1999). In general terms, somatization refers to the condition wherein mental states and experiences are expressed as bodily symptoms. The term conversion, commonly used as a synonym for somatization, usually implies that unconscious defence mechanisms are operative (Francois, 2004). Very little work has been done on somatization disorder to know the possible etiology of the disease and still the diagnosis of somatization disorder remain cumbersome.

Trace elements are required for numerous metabolic and physiological processes in the human body (Mertz et al, 1981). They play a part in the synthesis and structural stabilization of both proteins and nucleic acids. Therefore, imbalances in the optimum levels of trace elements may adversely affect biological processes, and are associated with many diseases (Muralidhar et al, 2004). Trace elements like manganese (Mn), copper (Cu), zinc (Zn) etc. have been studied in many diseases, including autoimmune diseases, neurological disorder, and psychiatric disorders. These elements are incorporated into the structures of proteins, enzymes, and complex carbohydrates. They take part in biochemical reactions together with enzymes. For example, copper is an important component of several metalloenzymes, including tyrosinase and dopamine hydroxylase (Livesay et al, 2003). It also plays a vital role in neurological disorders (Wallwork, 1987). Copper is essential for maintaining the strength of the skin, blood vessels, and epithelial and connective tissue throughout the body. Deficiencies of copper can result in hernias, aneurysms, and blood vessel breakage manifesting as bruising or nosebleeds (Ruegger et al, 1995).

Zinc is important for the functioning of more than 200 enzymes; some of them are related with DNA and RNA synthesis (Vallee et al, 1991; Vallee et al, 1993)). It plays a vital role in immune system and is essential for the optimal function of a variety of biochemical and physiological processes (Tudor et al, 2005).

Iron (Fe), apart from its presence in all body cells, plays a role in the oxygenation of tissues as it is incorporated in the haeme structure of haemoglobin. Low serum iron has been reported in a variety of neuropsychiatric motor disorders (Peralta et al, 1999). Low level of iron affects dopaminergic system. Many researchers found abnormal iron deposits in the brains of schizophrenics (Weiser et al, 1994). Dopamine (DA), serotonin, norepinephrine (NE) and 5-hydroxytryptamine (5-HT) depletion occur in relation to manganese in schizophrenics (Donaldson et al, 1987). Amyotrophic lateral sclerosis (ALS) patients also have very low level of manganese (Nagata et al, 1985).

Any sort of disorder (negative or positive) in the concentration level of these trace elements may help in developing psychiatric disorders. For instance, it was found that plasma Cu concentrations were significantly higher ($p < 0.01$) and Mn and Fe concentrations were lower ($p < 0.05$) in schizophrenic patients than in controls (Yanik et al, 2004). These observations suggest that alterations in essential trace elements like Mn, Cu and Zn may play a role in the pathogenesis of neurological and psychiatric diseases.

As no work has been reported regarding trace elements concentration in somatization disorder patients, this work was undertaken to find out the relationship between trace element level and the disorder.

# Materials and Method

Forty-six somatization disorder patients (24 males and 22 females of mean age 29.39±7.8 years) were randomly recruited from Bangladesh Medical College Hospital, BSMMU and National Mental Institute. The patients were diagnosed by a psychiatrist using DSM-IV. A specialist who was trained in the use of Diagnostic and Statistical Manual of Psychiatric Disorders (Fourth Edition) conducted the diagnosis and interviewed the patients with somatization disorder. Forty-five healthy volunteers comprising 25 males and 20 females of mean age 28.46±8.8 years were recruited purposively as control. The study subjects were briefed about the purpose of the study and written consent was obtained from each of them. All subjects had to go through clinical examination to find out existence of other diseases that might alter trace element level. Subjects were also under gone a routine physical check up including their organ activity, weight, nutritional condition, blood pressure, chest X-ray and ECG. Hematocrit, blood urea, nitrogen, creatinine, glucose and liver enzyme tests were done for all subjects to find out their actual pathological condition. These subjects did not have diabetes, kidney failure, or other disease nor had they been treated with drugs, which can interfere with nutritional status of the elements (diuretics, antihypertensive drugs or mineral supplements, etc.). Patients who were mentally retarded and suffered from co-morbid psychiatric disorders, those with substance disorder were also excluded from the study. Socio-demographic data were collected in a questionnaire form. That contains several information, socio-economic data, history of illness and family history etc. Ethical approval was obtained from the Bangladesh Medical Research Council (BMRC).

Five ml of venous blood was drawn from each patients and controls after overnight fasting using a plastic syringe fitted with stainless steel needle. The blood sample was collected into a metal-free plastic tube and allowed to clot at room temperature for one hour, so that clotting factors could be removed from the serum. Then the blood sample was centrifuged at 3000 rpm for 15 minutes at room temperature to extract the serum. The serum was aliquoted into the eppendorf tube and stand at −80°C until analysis. Blood collection and serum separation were carried out in dust free environment.

Analysis of the trace element was carried out by using flame atomic absorption spectrometry (Varian SpectraAA 220) according to the method of Falchuk et al. Serum samples were diluted by deionized water by a factor of 30. Different concentrations (0.5, 1.0, 2.0, 5.0 and 10.0 mg/L) of trace elements were used for calibration of standard graphs. Absorbances were read at 324.7nm, 213.9 nm, and 279.5 nm for copper, zinc and manganese respectively in the atomic absorption spectrometer. To verify the assay accuracy and to

**Table 1. Serum trace elements concentrations of somatization disorder patients (n=46) and controls (n=45)**

| Trace elements (mg/L) | Patients n (%) | Mean ± SD | Controls n (%) | Mean ± SD |
|---|---|---|---|---|
| **Mn**[a] | | | | |
| 0.1–0.8 | 18 (39.1) | | 30 (66.7) | |
| 0.8–1.4 | 18 (39.1) | 1.13 ± | 9 (20.0) | 0.987 ± |
| 1.4–1.9 | 10 (21.7) | 0.45 | 6 (13.3) | 0.216 |
| **Zn**[b] | | | | |
| 0.5–0.9 | 10 (21.7) | | 12(26.7) | |
| 0.9–1.4 | 21 (45.6) | 1.22 ± | 27(60.0) | 1.209 ± |
| 1.4–2.0 | 15 (32.6) | 0.35 | 6 (13.3) | 0.277 |
| **Cu**[c] | | | | |
| 0.6–0.9 | 10 (21.7) | | 6 (13.3) | |
| 0.9–1.5 | 12 (26.1) | 1.49 ± | 15 (33.3) | 0.962 ± |
| 1.5–2.5 | 24 (52.1) | 0.50 | 24 (53.3) | 0.684 |

Significance p<0.05
a: p=0.000
b: p=0.954
c: p=0.022

maintain quality, the standard solutions were run for every 10-test sample. A software package (SpactrAA software) was used to calculate concentrations of copper, zinc and manganese. The precaution for both collection and subsequent handling of serum were taken in order to avoid or minimize trace elements contamination.

# Statistical Analysis

The results were expressed as mean ± SD by using SPSS (Windows Version 11.5) software. Differences between groups means were determined by independent sample t-test. The significance level was set at P<0.05. Pearson's correlation analysis was performed to find the correlation of BMI and socioeconomic factors with the trace elements concentrations of the patients. A multiple regression analysis and one-way analysis of variance (ANOVA) were also performed to determine the extent of involvement of socioeconomic factors and BMI to affect the level of trace elements.

**Table 2. Correlation of serum concentration of Mn, Zn and Cu with BMI, income and age of somatization disorder patients**

| Parameter | Mn | Zn | Cu |
|---|---|---|---|
| **BMI (kg/m$^2$)** | r = -0.061 | r = 0.853 | r = -0.462 |
| | p = 0.653 | p = 0.442 | p = 0.010 |
| **Income** | r = 0.065 | r = 0.321 | r = 0.435 |
| **(US$ per month)** | p = 0.790 | p = 0.743 | p = 0.812 |
| **Age (year)** | r = -0.039 | r = -0.560 | r = -0.548 |
| | p = 0.923 | p = 0.312 | p = 0.521 |

# Results

In this experiment the sample size was 91 (46 for somatization disorder patients & 45 for control healthy volunteers). It was observed that most of the patients were literate (69%), unmarried (59%) and poor (60 US$ or less per month) with mean age 29.39±7.8 years (Hossain et al, 2006).

Serum trace elements concentrations are presented in Table 1. Only the serum concentration of Mn and Cu were increased significantly ($p<0.05$) in somatization disorder patients compared to that of the controls, while the change of concentrations of Zn was not significant ($p>0.05$).

Correlative analysis was also performed using the data of serum concentration of trace elements and BMI, age and income of somatization disorder patients. It was found that only the serum concentration of Cu was significantly inversely correlated with BMI of somatization disorder patients ($r = -0.462$, $p = 0.010$), while other factors had no significant relationship between them (Table 2). Regression analysis was also carried out using serum Cu concentration of patients' as dependent variable and BMI and income as independent variable. Regression analysis depicted that the concentration of Cu changed significantly with BMI ($R^2 = 0.463$; $t = -2.876$; $p = 0.003$). Finally, an ANOVA was done with the same parameters that showed a significant relationship between BMI and serum Cu concentration of the patients ($F = 8.135$; $p = 0.010$).

# Discussion

Somatization disorder is a psychiatric disorder representing a group of disorders characterized by physical symptoms suggesting a medical disorder (Ford et al, 1995 ). In many studies, it was established that patients with neurological disease had higher rate of being attacked by somatization disorder (Hansen et al, 2006). Although there are some evidences of communication impairment of brain cells in left hemisphere because of decreased neurotransmitter release, etiology of this disorder has yet to be known (Wexler et al, 1980). Some reports also showed that symptoms of the left side of the body might indicate that the right hemisphere of the brain is involved more than the left side (Naga et al, 2004). Preliminary evidence indicates that patients with somatization disorder may have an abnormality in cortical functioning (Rief et al, 1998). A few investigators reported serum trace element level involvement in some disorders such as schizophrenia, mania, depression, anxiety etc (Tiwari et al, 1989; Bergquist et al, 1993). We have reported here the changes in serum trace element levels in somatization disorder patients, and its correlation with nutritional status and socioeconomic factors.

Analysis of socioeconomic information showed that somatization disorder was prevalent in poor, young and unmarried people, which is in good match with previous findings (Mullick et al, 2002; Bates et al, 1995).

Analysis of serum trace elements indicated that only serum concentrations of Cu and Mn were found to be increased significantly ($p<0.05$) in somatization disorder patients compared to that of the controls. Copper has a very strong role in developing chronic mental illness. Excessive copper and zinc levels may cause brain dysfunction (Nolan et al, 1983). It also alters the concentration of neurotransmitters. Copper level is generally higher in depressed patients than in normal individual (Narang et al, 1991). Higher concentration of Mn was found in compulsive behavior, emotional lability and hallucinations (Barceloux et al, 1999). These studies of trace elements levels in various neuropsychiatric disorders support our finding of Cu and Mn level in somatization disorder. In various various neuropsychiatric disorders the level of Zn was reported to be decreased significantly (Pfeiffer et al, 1982). In this study, interestingly, we found no statistical difference in Zn levels between somatization disorder patients and controls.

Pearson's correlation analysis revealed that only the serum concentration of Cu had inverse relationship with BMI of somatization disorder patients. This finding was further strengthened by regression analysis and one-way ANOVA test that showed significant relationship with serum Cu concentration and nutritional status of the patients.

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