COPPER AND ZINC LEVELS IN HAIR OF BOTH SCHIZOPHRENIC AND DEPRESSED PATIENTS

BY

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ABSTRACT

The aim of this paper is to estimate hair copper and zinc levels in schizophrenic and depressed patients and to correlate these levels to the severity of schizophrenia and major depressive disorder. The study was carried on 80 male and female persons with their ages between 20 -40 years. Twenty of them were healthy and helped as control, 30 were suffering from schizophrenia (group I) and 30 were suffering from major depressive disorder (group II). Exclusion criteria included pregnancy, another co-morbid psychiatric disorders and drugs known to affect trace element metabolism. Approximately 100 mg of scalp hair samples were cut from each person. Zinc and copper levels in the hair samples were determined by atomic absorption spectrophotometry after wet ashing. The mean hair copper level was significantly higher in both schizophrenic patients (group I) and depressed patients (group II) when compared with their corresponding mean level in healthy control group. On the other hand, the mean hair zinc level was significantly lower in both schizophrenic patients (group I) and depressed patients (group II) when compared with its mean level in the healthy control group. In depressed patients, the mean hair copper level was insignificantly higher while, the mean hair zinc level was significantly lower when compared with their corresponding mean level in schizophrenic patients. From these results, it can be concluded that copper excess and zinc deficiency may have a role in the pathogenesis of either schizophrenia and/ or depressive disorders. It can also be concluded that zinc deficiency may have more important role in inducing depressive disorders. So, it is recommended to evaluate both copper and zinc hair and serum levels in schizophrenic and depressed patients especially in those resistant to the traditional therapy measures. Moreover, this may have a prognostic value. It is recommended also to use zinc supplementation during antidepressant therapy as it may improve response to therapy and/ or decrease the antidepressant dose that can minimize the side effects.

INTRODUCTION

Copper (Cu) and zinc (Zn) are two essential trace elements that have been studied in many diseases, including autoimmune, neurologic and psychiatric disor-

ders (Cramer, 1983). Whenever zinc becomes deficient, copper tends to accumulate (Yanik et al., 2004).

Copper is a component of several metalloenzymes linked to dopamine synthesis, in biochemical pathways involving either antagonism of dopamine production or catalysis of its breakdown. As dopamine is implicated in schizophrenia, copper homeostasis may be particularly relevant: an excess of copper may be associated with dopamine dys-regulation (Bowman and Lewis, 1982). Zinc is required for the structural integrity and/or catalysis of more than 200 enzymes, the majority of which are zinc metalloenzymes involved in nucleic acid and protein synthesis (Abdel-Mageed and Oehme, 1990).

The findings of previous research on the status of trace elements in patients with schizophrenia have been controversial (Herrán et al., 2000). Some authors did not find significant deviation from normal in concentrations of serum copper (Gillin et al., 1982) or found a decrease in hair copper concentrations in chronic schizophrenic females (Suzuki et al., 1992). Others demonstrated significant increase in the serum and hair concentration of Cu and significant decrease in Zn in schizophrenic patients than that of their levels in the control group (Tokedemir et al., 2003; Wolf et al., 2006; Rahman et al., 2009).

It was found also that major depressed subjects had significantly lower serum zinc concentrations than normal controls and that clinical improvement was accompanied by increments in serum zinc (McLoughlin and Hodge, 1990). Meanwhile, copper levels and Cu/Zn ratios were significantly higher in women having a history of post-partum depression (Crayton and Walsh, 2007).

This study was undertaken to estimate hair copper and zinc levels in schizophrenics and patients with depression to declare their possible role in the pathogenesis of these disorders. Also, whether the levels of these trace elements could be correlated to the severity of schizophrenic and depressive disorders would be studied.

SUBJECTS AND METHODS

Subjects:

The present study was carried on 80 male and female persons; 20 of them (10 males and 10 females) were clinically and laboratory healthy and helped as control, 30 (15 males and 15 females) were suffering from schizophrenia (group I) and 30 (15 males and 15 females) were suffering from major depression (group II). The age of all persons of the study is between 20 - 40 years with mean age 30.1 $\pm$ 5.6 y in control group, 30.26 $\pm$ 5.63 y in group I and 30.63 $\pm$ 5.54 y in group II. Exclusion

criteria for all persons selected for the study included another co-morbid psychiatric disorder, pregnancy and medical disorders (endocrine, liver cirrhosis, renal insufficiency) or intake of certain drugs (as anticonvulsants, contra-ceptives, glucocorticoids) known to affect trace element metabolism. These criteria were determined according to study of Farzin et al. (2006). The exclusion was done through history taking and routine laboratory investigations.

Patients were recruited from Psychiatry Department of Mansoura University Hospital. Assessment and diagnosis of schizophrenic and depressed patients were made according to the Diagnostic and Statistical Manual of mental disorders (4^{th} division Text Revised) DSM IV TR criteria. Positive and negative syndrome scale (PANSS) for schizophrenia (Kay et al., 1987) was used as adjunct to the positive-negative symptoms assessment to provide a parallel measure of severity of schizophrenic illness. The score based on General Psychopathology Scale (ranged from 16 - 112) was used for testing of statistical correlation between severity of schizophrenic illness and zinc and copper levels in hair. Assessment of the severity of depression was made according to translated self-report rating inventory which was developed by Beck et al., (1961) that measure characteristic attitudes and symptoms of depression and its severity.

Samples collection:

Approximately 100 mg of scalp hair samples were cut from each person with stainless-steel scissors in the nape or occipital regions, as close to the scalp as possible. Hair collection was carried out in dust-free environment and hair treated with artificial color was excluded from the study. The distal ends of the hair were cut from the samples. Each hair sample was comminuted, washed consecutively in neutral detergent as ether and acetone and dried before analysis according to the procedure originally described by Sorenson, et al. (1973).

Biochemical studies:

Zinc and copper levels in hair samples were determined by atomic absorption spectrophotometry after wet ashing using reagent-grade HNO_3 and $HClO_4$ according to Eads and Lambdin (1973). For analysis the Model Varian Spectra AA - 400, atomic absorption spectrophotometer was used. Atomization signals were recorded from the digital readout. The light sources were zinc and copper hollow-cathode lamps. Uncoated graphite tubes (Varian 63 - 100015 - 00) were used for furnace. Wavelengths were set at 324.8 and 213.9 nm for copper and zinc respectively.

Statistical analysis:

Statistical analysis was done by using the Statistical Package for Social Science (SPSS) program version 12. The following

statistical parameters were utilized: arithmetic mean (x), standard deviation (± SD), Student t-test and correlation coefficient. Significance was considered at P value less than 0.05.

RESULTS

The mean hair copper levels are 29.8 ug/mg ± 5.46 in control group, 46.82 ug/mg ± 9.66 in schizophrenic patients (group I) and 48.6 ug/mg ± 15.75 in depressed patients (group II). The mean hair zinc levels are 488.23 ug/mg ± 6.56 in control group, 421.08 ug/mg ± 54.7 in schizophrenic patients (group I) and 381.47 ug/mg ± 70.75 in depressed patients (group II) (Table 1).

The mean hair copper level is significantly higher in both schizophrenic patients (group I) and depressed patients (group II) when compared with its mean levels in healthy control group. In depressed patients the mean hair copper level is insignificantly higher when compared with its mean level in schizophrenic patients (Table 1).

The mean hair zinc level is significantly lower in both schizophrenic patients (group I) and depressed patients (group II) when compared with its mean levels in healthy control group. In depressed patients the mean hair zinc level is significantly lower when compared with its mean level in schizophrenic patients (Table 1).

Results of the present study show significant positive correlation between hair copper level and the severity of illness in schizophrenics and depressed patients. On the other hand, significant negative correlation is found between hair zinc level and the severity of illness in the same cases (Table 2 and Figures 1 - 4).

The percentage of increase of mean hair copper level is more in depressed patients than that in schizophrenic patients (Figure 5). The percentage of decrease of mean hair zinc level is more in depressed patients than that in schizophrenic patients (Figure 6).

DISCUSSION

Deficiency as well as excess in either zinc or copper can produce a variety of biochemical and physiologic changes (Jun and Nancy, 2000). In addition, these two essential trace elements are neuroactive substances that can be synaptically released during neuronal activity. They have been implicated in diseases with neuropathological components (Strausak et al., 2001).

Previous observations suggested that there may be an association between elevated serum and hair Cu levels and

decreased serum and hair Zn levels and some psychiatric disorders. A relation between low concentrations of zinc and mental health problems, especially in at-risk populations has been demonstrated. Zinc deficiency induced depression-like behavior in mice that was incompletely corrected by antidepressant therapy (Whittle et al., 2009).

The results of the present work showed significant increase in the mean hair copper level and significant decrease in the mean hair zinc level in schizophrenic patients compared with their corresponding mean levels in healthy control group.

Similar results were found in the study of Rahman et al. (2009). Another earlier study found that serum copper and ceruloplasmin were elevated in schizophrenia (Wolf et al., 2006). Nechifor et al. (2004) observed also that Cu/ Zn ratios were increased in patients with acute paranoid schizophrenia episode. In addition, they found that Zn levels but not plasma Cu was found to improve after 3 weeks of antipsychotic treatment. In criminal schizophrenic subjects, Tokedemir et al. (2003) found that serum copper values were significantly higher while zinc values were significantly lower than non-criminal subjects.

In disagreement of the present results, the study of Gillin et al. (1982), who found that patients with acute and chronic schizophrenia, on or off treatment with various major tranquillizers, did not show any significant deviation from normal in concentrations of zinc or copper in serum, urine, or gastric fluid, in serum ceruloplasmin or in hair zinc. Suzuki et al. (1992) found also a decrease in hair copper concentrations in chronic schizophrenic females. Nechifor et al. (2004) explained this heterogeneity of the data by heterogeneity of patients and presence of many forms of schizophrenia.

The role of copper and ceruloplasmin in schizophrenia remains unclear. Although elevation of copper and ceruloplasmin may be related to other factors and are insufficient alone to infer pathogenic causality, copper abnormalities may play a role in schizophrenia by exacerbating or perpetuating dopaminergic dysregulation (Bowman and Lewis, 1982). However it is unknown at this stage whether the copper contributes to the mental illness or the body attempts to store more copper in response to the illness. Herrán et al. (2000) postulated that elevated Cu levels may be a consequence of antipsychotic treatment which may affect absorption, plasma protein binding, storage and/ or excretion of these metals (Rand and Murray, 2000). Contradictory to this postulation, Gillin et al. (1982) concluded that patients on various major tranquillizers did not show any significant deviation from normal in concentrations of zinc or copper.

The results of the present work showed also significant increase in the mean hair copper level and significant decrease in the mean hair zinc level in depressed patients compared with their mean levels in healthy control group. In addition, zinc levels were significantly lower in depressed patients compared to schizophrenic patients. Similarly, Manser, et al. (1989) and Narang, et al. (1991) found that Cu levels were significantly higher in depressives than in the normal and after recovery from depression. Others found that major depressed subjects had significantly lower serum zinc concentrations than normal controls (McLoughlin and Hodge, 1990). Even lower serum Zn was considered a marker of treatment resistance and of the immune/inflammatory response in depression (Maes et al., 1997). Also, copper levels and Cu/Zn ratios were significantly higher in women having a history of post-partum depression (Crayton and Walsh, 2007).

Changes in plasma Cu and Zn contents can cause health problems because they can oxidize proteins and lipids, bind to nucleic acid and enhance the production of free radicals (Rand and Murray, 2000). Copper/zinc superoxide dismutase coenzyme concentrations in postmortem prefrontal cortical regions of the brain was significantly increased in patients with recurrent depressive disorder evidencing oxidative stress in the pathophysiology of depressive disorder (Michel et al., 2007).

The significant negative correlation that was found in the present work between hair zinc level and the severity of both schizophrenic illness and depression support the study of Pfeiffer and Braverman (1982) who stated that zinc has been employed with success to treat specific types of schizophrenia. These coincide also with McLoughlin and Hodge (1990) who found that clinical improvement of major depressed subjects was accompanied by increments in serum zinc. However, Maes et al. (1997) concluded that, there were no significant effects of antidepressant treatment on serum Zn, whereas serum Cu was significantly reduced.

The clinical efficacy of current antidepressant therapies is unsatisfactory; antidepressants induce a variety of unwanted effects, and, moreover, their therapeutic mechanism is not clearly understood (Szewczyk et al., 2008). Zinc and magnesium exhibit antidepressant activity in laboratory animals. The efficacy of pharmacotherapy is enhanced by supplementation with zinc and magnesium particularly in patients previously non-responsive to antidepressant pharmacotherapies (Cunha et al., 2008 and Siwek et al., 2009).

From the results of the present work, it can be concluded that copper excess and

zinc deficiency may have a role in pathogenesis of both schizophrenia and depressive disorders. It can also be concluded that zinc deficiency has more important role in inducing depressive disorders.

It is recommended to evaluate both copper and zinc hair and serum levels in schizophrenic and depressed patients especially in patients resistant to therapy as this may have a prognostic value. It is recommended also to use zinc supplementation during antidepressant therapy as it may improve response to therapy and/ or decrease the dose that can minimize the side effects of antidepressants. Frequent psychiatric assessment is recommended for individuals chronically exposed to cupper. Zinc rich food as meat is advised to minimize liability to develop depressive disorders. Zinc supplementation is recommended especially in resistant cases.

Table (1): Comparison between mean hair copper and zinc levels (ug/mg) in all groups of the study.

Parameters \ Groups		Control Group	Group (I)	Group (II)
Hair copper level (ug/mg)	**Mean ± SD**	29.8 ± 5.46	46.82 ± 9.66	48.6 ± 15.75
			↑	↑
	P_1		< 0.001*	< 0.001*
				↑
	P_2			0.638
Hair zinc level (ug/mg)	**Mean ± SD**	488.23 ± 6.56	421.08 ± 54.7	381.47 ± 70.75
			↓	↓
	P_1		< 0.001*	< 0.001*
				↓
	P_2			< 0.05*

* Significant if $P < 0.05$, ↑ = higher, ↓ = lower, Group I: Schizophrenic patients, Group II: Depressed patients, P_1: Schizophrenics and depressed patients versus control and P_2: Depressed patients versus Schizophrenics.

Table (2): Correlation between hair copper and zinc levels and severity of schizophrenic symptoms assessed by PANSS and severity of depressive symptoms assessed by Beck score.

		Hair copper level	Hair zinc level
PANSS (for schizophrenia)	r	0.984	0.943
	P	0.000*	0.000*
	n	30	30
Beck score (Depression severity)	r	0.994	0.973
	P	0.000*	0.000*
	n	30	30

*Correlation is significant at 0.01 level (2-tailed)

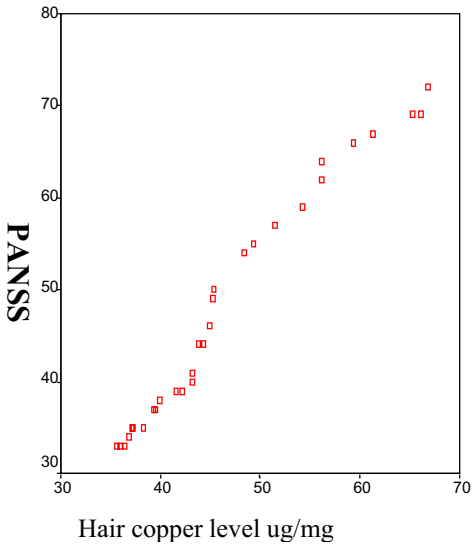

Fig. (1) : The statistical correlation between hair copper level and severity of schizophrenic symptoms assessed by PANSS.

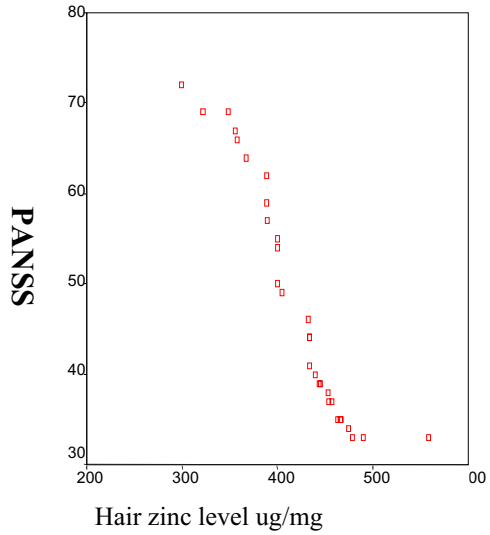

Fig. (2) : The statistical correlation between hair zinc level and severity of schizophrenic symptoms assessed by PANSS.

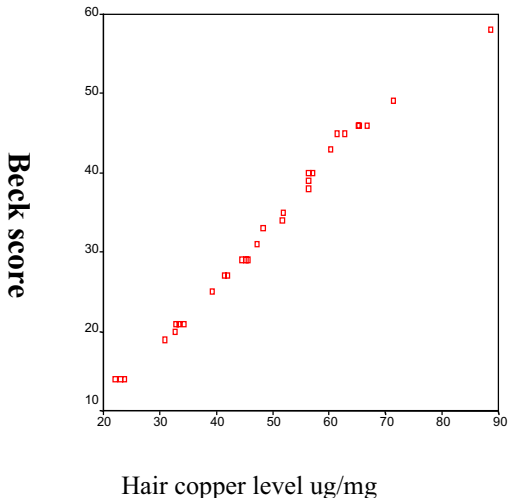

Fig. (3) : The statistical correlation between hair copper level and severity of depressive symptoms assessed by Beck score.

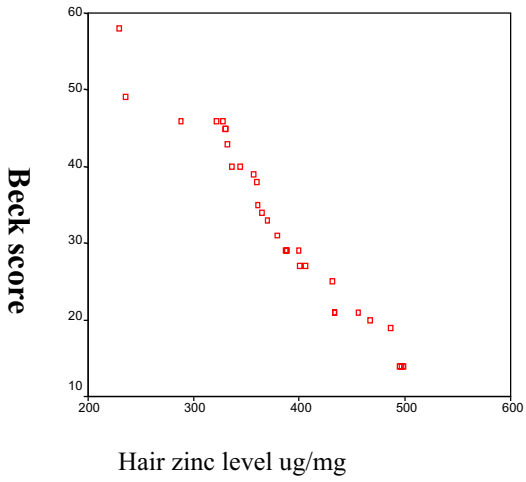

Fig. (4) : The statistical correlation between hair zinc level and severity of depressive symptoms assessed by Beck score.

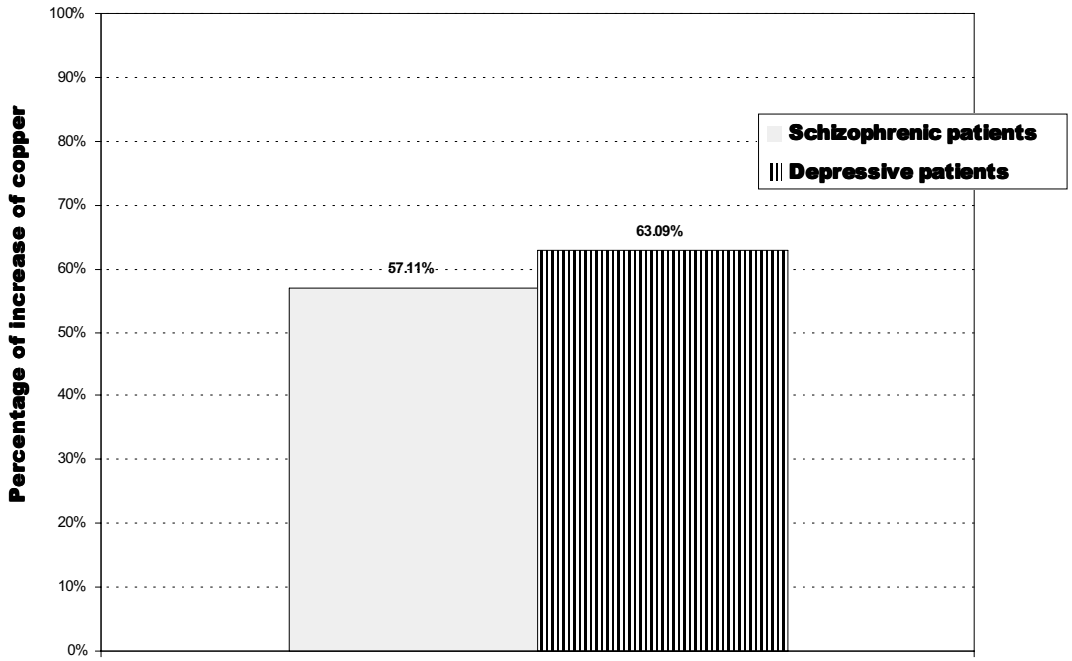

Fig. (5) : Percentage of increase in mean hair copper level in both schizophrenic and depressed patients.

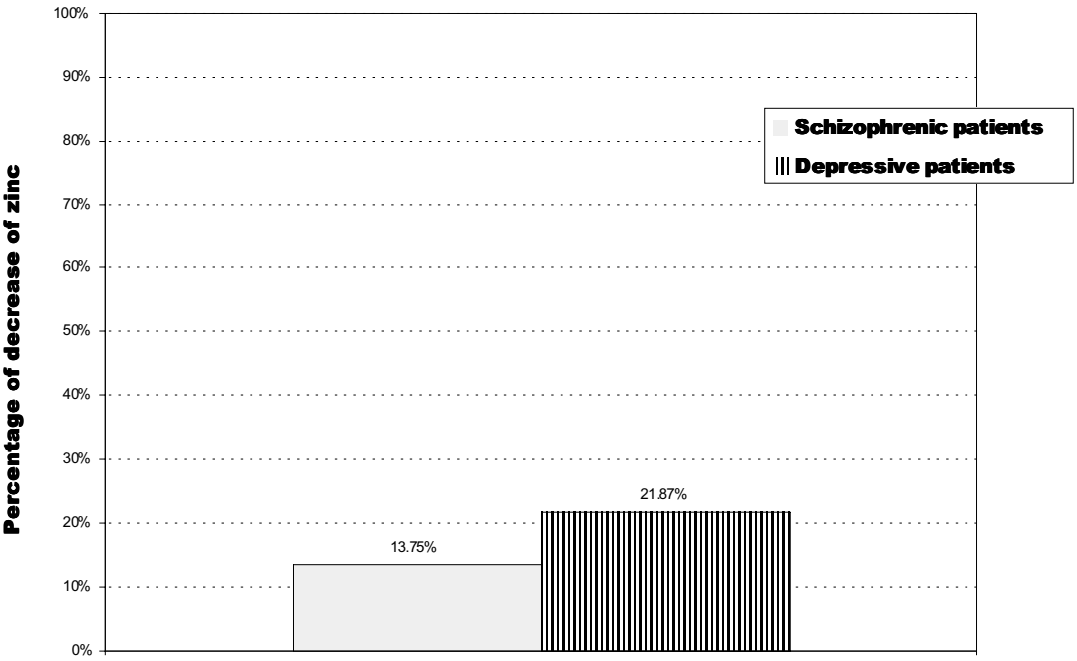

Fig. (6) : Percentage of decrease in mean hair zinc level in both schizophrenic and depressed patients.

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مستوى النحاس والزنك فى شعر كلا من مرضى الفصام والاكتئاب

المشتركون فى البحث

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أجريت هذه الدراسة على ٨٠ شخصاً من الذكور والإناث تتراوح أعمارهم بين ٢٠ و ٤٠ عاماً، منهم ٢٠ شخصاً من الأصحاء واعتبروا كمجموعة ضابطة (١٠ من الذكور و١٠ من الإناث)، ٣٠ منهم يعانون من مرض الفصام (١٥ من الذكور و١٥ من الإناث) وإعتبروا المجموعة الثانية، عند اختيار الأشخاص التى أجريت عليهم الدراسة تم إستبعاد الأشخاص المعرضون لأحوال تؤثر على أيض العناصر النادرة مثل الحمل والاضطرابات الطبية والنفسية الأخرى وبعض الأدوية. تم قص حوالى ١٠٠ مجم من شعر فروة الرأس وتم تحديد مستويات النحاس والزنك فى عينات الشعر بالامتصاص الذرى بجهاز مقياس الطيف الضوئى، ووجد أن متوسط مستوى النحاس مرتفعاً بقيمة ذات دلالة إحصائية فى عينات شعر كل من مرضى الفصام والاكتئاب عنه فى عينات شعر الأشخاص الأصحاء، كما وجد فى عينات شعر مرضى الاكتئاب أن متوسط مستوى النحاس كان مرتفعاً بقيمة ليست ذات دلالة إحصائية ومتوسط مستوى الزنك كان أكثر إنخفاضاً بقيمة ذات دلالة إحصائية عند مقارنتهم بمتوسط مستويات النحاس والزنك فى شعر مرضى الفصام.

وعلى ضوء هذه النتائج يمكن إستنتاج أن زيادة مستوى النحاس ونقص الزنك قد يكون له دور فى نشأة كل من مرض الفصام والاكتئاب كما يمكن إستنتاج أن نقص الزنك له دور أكبر فى إحداث الاضطرابات الإكتئابية، وعلى ضوء ذلك ينصح بتقييم مستوى النحاس والزنك فى الشعر وفصل الدم فى مرضى الفصام والاكتئاب وخاصة فى الحالات المقاومة للعلاج مما قد يكون له قيمة فى التكهن بنتائج العلاج، كما ينصح أيضاً بإضافة الزنك أثناء العلاج بمضادات الاكتئاب حيث أنه من الممكن أن يحسن الاستجابة للعلاج بها ويساعد على تقليل جرعتها وتقليل آثارها الجانبية.