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Brief report

Serum zinc level in depressed patients during zinc supplementation of imipramine treatment

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ABSTRACT

Background: Recurrent major depression is associated with decreased blood zinc concentrations that may be increased by effective antidepressant therapy. Some clinical investigations point to alterations of the zinc level in blood as a potential marker of depression.
Methods: A placebo-controlled, double blind study of zinc supplementation to imipramine therapy was conducted on sixty patients fulfilling the DSM-IV criteria for major depression (18–55 years old, 40 females, 20 males). Moreover, a group of 25 healthy volunteers was recruited (16 females, 9 males). Blood samples were drawn for the assay of serum zinc once from the control subjects and four times (before, and then 2, 6 and 12 weeks after the beginning of treatment) from the depressed subjects.
Results: We report that: 1) the serum zinc level was significantly lower (by 22%) in depressed patients than in healthy volunteers, 2) all groups demonstrated a gradual increase in zinc concentrations over the period of imipramine treatment with or without zinc supplementation, 3) treatment-resistant patients demonstrated lower concentrations of zinc (by 14%) than treatment-non-resistant patients, 4) zinc concentrations were higher in zinc-supplemented patients than in placebo-supplemented patients, 5) zinc supplementation increased zinc concentrations over the period of treatment, and 6) at a 12-week imipramine treatment, a significant negative correlation was demonstrated between the Montgomery–Asberg Depression Rating Scale and the serum zinc level together with a concomitant increase in serum zinc in patients in remission.
Conclusions: Serum zinc is a state marker of depression.

1. Introduction

Depression is considered as a chronic and recurring illness. The development of new medications for depression has been hindered by an insufficient knowledge on the pathophysiology of this disorder (Skolnick et al., 2009). Among other factors, a major obstacle in the diagnosis and

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effective therapy is the lack of biomarkers allowing assessment of the current depressive state. The discovery of such a marker could also be useful in predicting the risk of development of the disease and/or its relapse as well as its resistance to treatment. Some potential candidate markers of depression have been reported [e.g. (Dinan, 2009; Piccinni et al., 2009; Maes et al., 2010], but their relationships to the mechanisms of the pathophysiology of depression and efficacy in clinical practice are at present unclear.

Current hypotheses of depression are based on the alteration of neurotransmission, yet mostly of the mono-aminergic and amino-acidergic systems (Skolnick et al., 2001; Palucha and Pilc, 2005; Pilc and Nowak, 2005). Recent data points to the involvement of zinc – a modulator of glutamatergic neurotransmission – in mood disorders and in the mechanism(s) of antidepressant activity (Nowak et al., 2005; Szewczyk et al., 2008, 2010b). Preclinical studies have demonstrated the antidepressant-like activity of zinc in animal tests and models (Cieslik et al., 2007; Kroczka et al., 2000, 2001; Nowak et al., 2003b; Rosa et al., 2003; Sowa-Kucma et al., 2008). Moreover, zinc has been shown to enhance the activity of antidepressant drugs (Cieslik et al., 2007; Cunha et al., 2008; Kroczka et al., 2001; Szewczyk et al., 2002, 2009), while zinc deficiency produced depressive-like alterations in behavioral and neurochemical studies (Corniola et al., 2008; Takeda and Tamano, 2009; Tassabehji et al., 2008; Whittle et al., 2009). Some clinical studies have indicated the reduction of the blood zinc level in depressed patients (Amani et al., 2010; Maes et al., 1994, 1997a; McLoughlin and Hodge, 1990; Nowak et al., 1999). Our previous clinical study demonstrated that zinc enhanced antidepressant efficacy in, especially, treatment-resistant patients suffering from major depression (Nowak et al., 2003a; Siwek et al., 2009).

The present study examined the effect of zinc supplementation to imipramine treatment on the serum zinc level in depressed patients.

2. Methods

2.1. Subjects

Sixty patients admitted to the Department of Psychiatry Jagiellonian University Collegium Medicum or to the Affective Disorder Outpatients Unit and fulfilling the DSM-IV criteria for major depression were accepted for the study [18–55 years old, details described previously (Siwek et al., 2009)].

A group of 25 healthy volunteers (normal controls) was also recruited. The normal controls (18–55 years old) were free of mental disorders and had no family history of depression or mania. In the normal controls (once) and depressed subjects (four times: before and 2, 6 and 12 weeks after beginning the treatment), blood samples were drawn at 8.00–10.00 h for the assay of serum zinc. The serum was separated, frozen and stored at −80 °C before the assay.

The study was approved by the Ethical Committee of Jagiellonian University, Collegium Medicum, Kraków and the informed consent was obtained from all participants.

2.2. Serum zinc determination

Samples were wet-digested with nitric acid and hydrogen peroxide (microwave digestion, Milestone MLS-1200 Mega Microwave Digestion System). Determination of the zinc was carried out by flame atomic absorption spectrometry (Sadlik et al., 2000).

2.3. Statistics

Assessments of the serum zinc level were evaluated with the General Linear Model mixed design ANOVA with the *test number* as a repeated factor, and *treatment* and *antidepressant treatment resistance* as between the factors, followed by Duncan's post-hoc test (Statistica 8 and SPSS 16). Data was deemed significant when $P<0.05$.

3. Results

The characteristics of the patients and the effect of the treatment on their psychopathological status were previously published by Siwek et al. (2009). The mean ages (±SD) in the volunteers and patients were 43 ± 9.1 and 45.9 ± 5.9 years, respectively, and did not significantly differ ($P=0.08$). There were no significant differences in the female/male ratio between the volunteer (16/9) and patient group (40/20) ($P=0.81$).

The analysis of zinc concentrations with ANOVA (Fig. 1) revealed that all of the groups demonstrated a gradual increase in zinc concentrations over the time of the supplementation (the main factor of the test number). Secondly, the treatment-resistant patients appeared to demonstrate lower concentrations of zinc than treatment-non-resistant patients (the main factor of the treatment resistance). Thirdly, zinc was higher in zinc-supplemented patients than in placebo-supplemented patients (the main factor of the treatment). The interaction between the test number and treatment was also significant, suggesting that zinc supplementation increased zinc concentrations over the time of the treatment. The zinc concentration data was subjected to analysis of covariance (ANCOVA) with gender, age, education, smoking status, years of illness, illness episode, and final drug (imipramine) dose as covariates. Levene's test demonstrated an equality of error variances. ANCOVA revealed not only a significant between-subjects factor of treatment $F(1,39)=8.278$, $P=0.006$ (as in ANOVA, Fig. 1A) but also a significant between-subjects factor of length of episode (Fig. 1B). ANCOVA revealed also not only a significant ($F(3,117)=5.541$, $P=0.001$) within-subjects interaction between the test number and treatment (as in ANOVA, Fig. 1A), but also the test number and smoking status interaction $F(3,117)=2.859$, $P=0.04$.

The data concerning the zinc levels was also subjected to a number of regression analyses. At the beginning (baseline), 2 or 6 weeks of treatment there were no correlations between the depression assessment scores (e.g. Montgomery–Asberg Depression Rating Scale, MADRS) and serum zinc level (data not shown). Zinc levels negatively and significantly correlated with the MADRS scores at week 12, when either all (Fig. 2A; $R^2=0.199$, $P=0.001$) or the zinc-supplemented patients were taken into analysis (data not

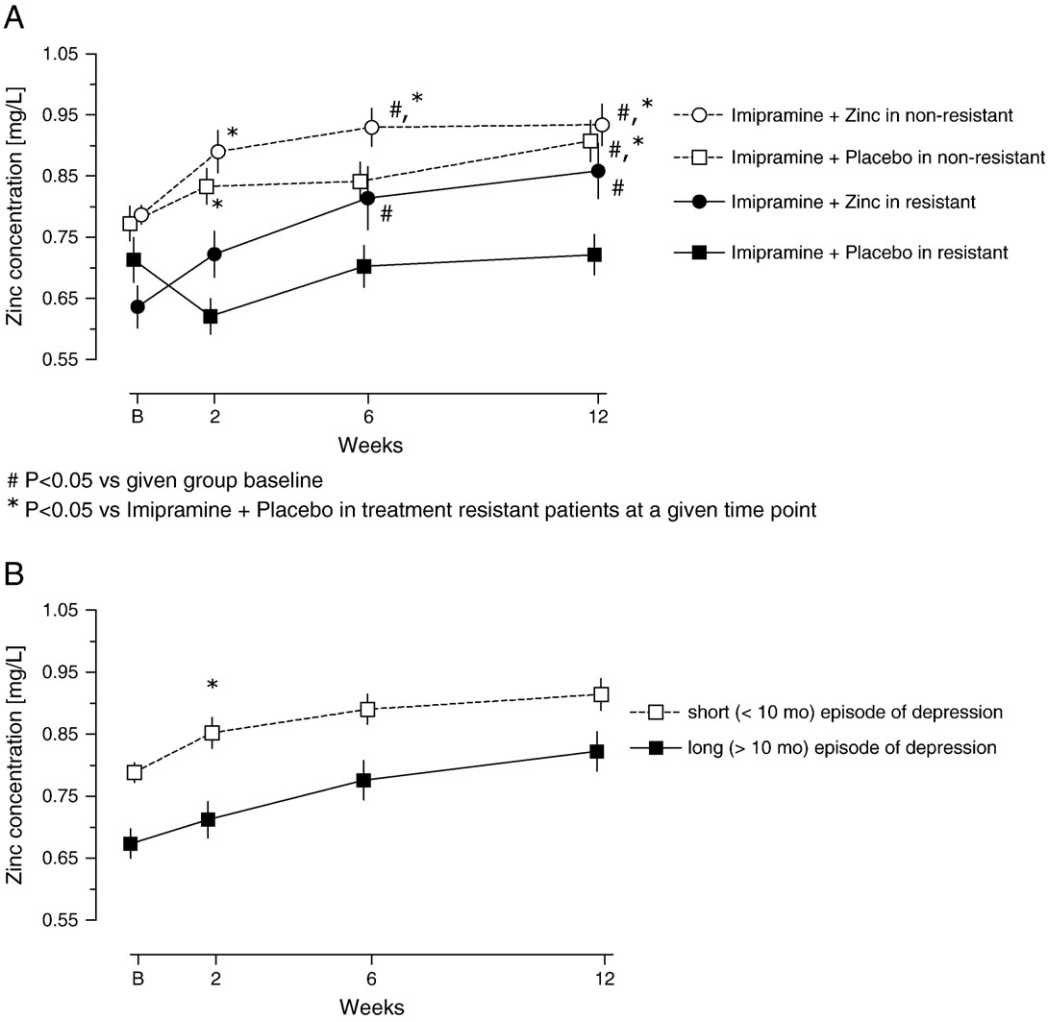

Fig. 1. A) Effect of duration of treatment with imipramine and zinc supplementation on zinc serum levels in treatment-resistant and non-resistant depressive patients. Data represents the mean ± SEM zinc serum level of 9 treatment-resistant patients treated with imipramine + placebo, 15 treatment-non-resistant patients treated with imipramine + placebo, 12 treatment-resistant patients treated with imipramine + zinc and 15 treatment-non-resistant patients treated with imipramine + zinc. Mixed-design ANOVA demonstrated the following values: treatment: $F(1,47) = 5.46$, $P<0.025$, treatment resistance: $F(1,47) = 31.766$, $P<0.001$ and test number: $F(3,141) = 15.503$, $P<0.001$. The interaction between test number and treatment was also significant: $F(3,141) = 4.276$, $P<0.01$. Post-hoc Newman–Keul's test revealed that zinc-supplemented groups (circles) demonstrated a significant increase in zinc serum levels at weeks 6 and 12 when compared with the baseline, a similar increase was noted for the imipramine + placebo group at week 12 (# symbol). B) Effects of the duration of depressive illness on zinc serum concentrations during the time of measurement: ANCOVA: $F(1,39) = 4.372$, $P = 0.043$. Parameter estimates calculated using regression analysis revealed that the duration of depressive illness affected zinc concentrations only at week 2: $t = -2.06$, $P<0.05$.

shown, $R^2 = 0.1932$, $P = 0.0218$). Moreover, patients with remission demonstrated a significantly higher serum zinc level at 12-weeks of treatment (Fig. 2B) but not at 6-weeks (data not shown), compared to those patients without remission.

4. Discussion

The present study reports the first analysis of the changes in the serum zinc level in depressed patients receiving zinc supplementation of the uniform treatment regime (imipramine + placebo or zinc). All previous studies enrolled patient groups treated with various antidepressant drugs and a combination therapy (McLoughlin and Hodge, 1990; Schlegel-Zawadzka et al., 2000; Maes et al., 1996, 1997b, 1999).

The fact that significantly lower serum zinc concentrations existed in patients diagnosed with depression when compared to that of healthy individuals has already been demonstrated (Maes et al., 1994, 1997a, 1999; McLoughlin and Hodge, 1990; Nowak et al., 1999).

In the present study, the serum zinc level did not correlate with the MADRS (or Hamilton Depression Rating Score, HDRS) ratings from either the beginning or that at 2 and 6 weeks of the treatment, which suggests that the magnitude of serum zinc decline did not reflect the severity of the depression. This is in line with that of Maes et al. (1997a) and is in contrast to the studies of both Nowak et al. (1999) and Maes et al. (1994), which detected a statistically significant correlation between zinc level and the HDRS score on the day of the patients' inclusion in the study. These differences can

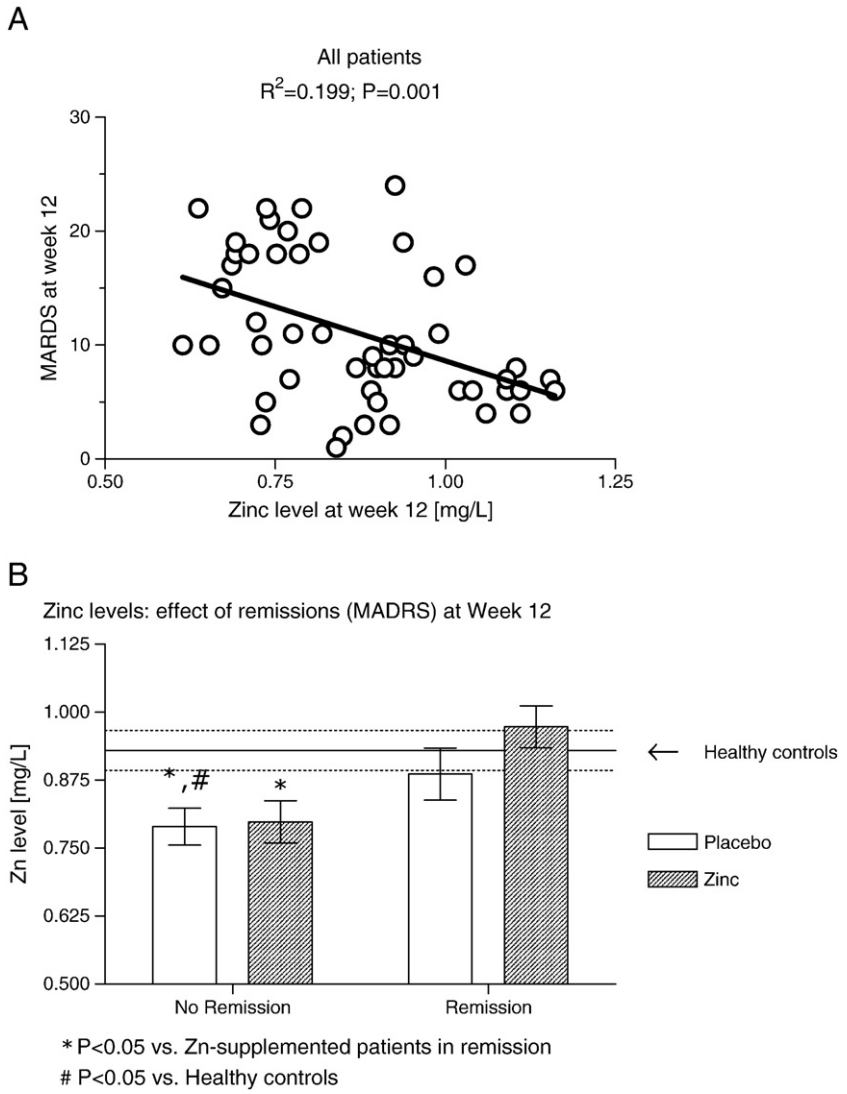

Fig. 2. A) The relationship between the Montgomery–Asberg Depression Rating Scale (MADRS) scores and serum zinc levels in depressed patients measured at 12 weeks of the trial. Analysis of all patients ($N=51$): $R^2=0.199$; $F(1,49)=12.22$; $P=0.001$. B) Serum zinc level at week 12 depends on whether the patients demonstrated remission in the MARDS or not; the treatment appeared to be not involved. Two-way ANOVA showed the following values for treatment, remission and interaction: $F(1,42)=1.359$, NS; $F(1,42)=10.93$; $P<0.01$ and $F(1,42)=0.91$, NS. Symbols: * $P<0.05$ vs. zinc-supplemented patients showing remission. The solid and dotted lines represent mean ± SEM serum levels of healthy controls. One-way ANOVA $F(4,70)=3.336$, $P<0.05$ demonstrated differences among groups. The post-hoc Dunnett's test revealed that placebo-treated patients not in remission demonstrated significantly lower (#, $P<0.05$) levels of serum zinc vs. healthy controls.

probably be explained by the exclusion of treatment-resistant patients from both above-cited trials, when compared to the present study. The presently reported lack of correlation between the lowered serum zinc level and MADRS or HDRS scores can also be attributed to a marked severity of depression (e.g. mean HDRS score 22.9 ± 3.3) and its small variability in the patients enrolled to the study (Siwek et al., 2009).

Based on studies conducted so far, it appears unlikely that the low blood zinc level results from the hypothalamic–pituitary–adrenal axis hyper-stimulation or loss of appetite associated with losing body weight, frequently accompanying depression (Maes et al., 1994, 1997a, 1999). The most probable cause of the drop in blood zinc during the depression episode is the activation of inflammatory processes. Some studies revealed that serum zinc concentration in depressed patients was positively correlated with the levels of albumin, transferrin and dipeptidyl peptidase IV and was negatively correlated with IL-6 and neopterin activities and with the CD4/CD8 ratio [see Szewczyk et al., 2010a for review]. Therefore, the decline in the blood zinc level might well be due to: 1) a decrease in the level of its main plasma carrier, albumin, during the depression episode; and 2) an increase in IL-6 activity, responsible for modification of metallothionein gene expression and induction of blood zinc sequestration in the liver and spleen (Maes et al., 1995b).

In patients not showing signs of treatment resistance during the manifestation of an acute depressive symptom, the

serum zinc concentration was significantly lower than that in healthy volunteers. The zinc level significantly raised when the depressive symptoms were subsiding, and when the therapeutic response or remission was achieved. In contrast, the serum zinc level in treatment-resistant patients and supplemented with placebo either did not differ from the initial value or slightly increased during the treatment but did not normalize. Moreover, the zinc level was negatively correlated with the duration of the depression episode.

The changes in the zinc level during antidepressant therapy and the differences in the concentrations of this element between responders and non-responders to the treatment may depend on immunological processes preceding depression. Clinical studies conducted so far have demonstrated the normalization of some immunological factors (e.g. polymorphonuclear leukocyte elastase (PMNE), TNFα, IL-6 and CRP activities) indicating the extinguishing or alleviation of inflammatory response when acute depressive symptoms were subsiding (Basterzi et al., 2005; Bekaroglu et al., 2000; Maes et al., 1995a; Sluzewska et al., 1996).

It can be inferred that normalization of the serum zinc level in treatment-non-resistant patients was the result of the abatement of inflammatory processes during remission of the depression episode. On the other hand, the lack of normalization of the serum zinc level in zinc non-supplemented patients who did not demonstrate a therapeutic response can be attributed to the persistence of pathophysiological processes, such as immune activation and inflammatory reaction, accompanying the acute depressive episode (Nieto et al., 2000). Therefore, one can agree with the conclusion that treatment resistance in depression is attributable to inflammatory processes which utilize blood zinc ions (Maes et al., 1997a; Nowak et al., 1999; Szewczyk et al., 2010a).

The significant lowering of serum zinc concentration during an acute depressive episode and normalization of zincemia after efficient pharmacotherapy indicates that the changes in the serum zinc level can be a state marker of depression and remission.

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Conflict of interest

The authors have no conflict of interest.

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