Neuroendocrinology Letters Volume 35 No. 8 2014
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

Zinc in drug-naïve patients with short-illness-duration first episode major depressive disorder: impact on psychopathological features

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Submitted: 2014-02-07 Accepted: 2014-03-23 Published online: 2015-01-18

Key words: **zinc; psychopathology; major depressive disorder; drug-naïve individuals; HAMD-17; STAI**

Neuroendocrinol Lett 2014; **35**(8):741–745 **PMID:** 25702304 NEL350814A12

Abstract

OBJECTIVE: In major depressive disorder (MDD) hypozincaemia associated with symptoms severity, melancholia, anxiety and treatment-resistance is reported. Data linking zinc with specific psychopathological dimensions is limited.
METHODS: Plasma zinc was analyzed in this cross-sectional case-control study on 20 non-late-life adult, treatment-naïve MDD patients with short-illness-duration first affective episode and 20 matched healthy controls together with psychometric evaluations including Hamilton Rating Scale for Depression (HAMD-17) and Spielberger State-Trait Anxiety Inventory (STAI).
RESULTS: No significant difference in zinc levels was found between MDD subjects and controls. No significant correlations were observed between zinc concentration and the total HAMD-17 score as well as with the specific core depression, insomnia, anxiety and somatic psychopathological dimensions or STAIX-1 and STAIX-2 scores.
CONCLUSION: The study provides evidence for unchanged plasma zinc concentration at early stage of MDD and failed to demonstrate any correlation between plasma zinc and psychopathological features including severity of symptoms and specific psychopathological dimensions in MDD.

ORIGINAL ARTICLE

INTRODUCTION

Zinc ions are important neuromodulators and signalling molecules in the central nervous system influencing monoaminergic, endocrine and immune systems. A body of evidence indicates the role for zinc in the pathophysiology of the major depressive disorder (MDD) (Swardfager *et al.* 2013).

Lower concentration of zinc in peripheral blood is seen in MDD and zinc depletion corresponds with the severity of depression (Swardfager *et al.* 2013). That observation is particularly well established in patients with treatment-refractory/chronic MDD. However, some studies indicate no zinc deficiency in MDD or find no association between plasma zinc level and severity of depression (Narang *et al.* 1991; Maes *et al.* 1997; Crayton & Walsh 2007; Irmisch *et al.* 2010; Salustri *et al.* 2010; Swardfager *et al.* 2013). Hypozincaemia was also associated with specific psychopathological dimensions of major depression including anxiety, apathy, anorexia, dysphoria, anhedonia and cogni-

tive dysfunction (Russo 2011; Swardfager *et al.* 2013). However, the evidence for zinc ions being associated with specific dimensions of depression or anxiolytic effect is unclear as systematic clinical data on zinc levels in major depression according to the psychopathological profile are not available.

A case-control study in a well defined cohort of first-episode, drug-naïve, short-illness-duration MDD patients and healthy subjects was designed to examine whether and to what extent plasma zinc is interrelated to the psychopathological features including severity of symptoms and specific psychopathological dimensions.

METHODS

Subjects

The study population has been described in detail elsewhere (Cubała & Landowski 2014). Briefly, 20, first-episode, drug-naïve MDD patients were recruited and diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (First *et al.* 1997). The depression severity was evaluated using 17-item Hamilton Rating Scale for Depression (HAMD-17) (Hamilton 1960). Subjects with HAMD-17 score of ≥20 with MDD being drug-naïve for any psychotropic medication and episode duration ≤24 weeks were eligible. Anxiety was assessed with the Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger *et al.* 1970). Exclusion criteria were: any other Axis I disorder, psychotic symptoms, past and current suicidality, any somatic comorbidity, concomitant medication including dietary supplements, hormonal contraception in women, pregnancy or lactation, BMI ≤18 and ≥30, age <18 and >55 years.

The control group consisted of 20 healthy subjects matched by age, sex, menopausal status, and metabolic parameters. They were interviewed using the Structured Clinical Interview for DSM-IV, nonpatient edition (First *et al.* 1997) and were administered STAI inventory (Spielberger *et al.* 1970). A HAMD-17 score ≤5 was required for inclusion. None of them had a history of serious somatic disease or a family history of major psychiatric illness in their first-degree relatives. Exclusion criteria were: past exposure to psychotropic medication, concomitant medication including dietary supplements, hormonal contraception in women, pregnancy or lactation, unstable medical condition.

The study was carried out in agreement with the Declaration of Helsinki and was approved by the Ethic Research Committee of the Institution. For all subjects, written informed consent was obtained.

Study protocol

The study followed a cross-sectional, case-control design. All subjects fasted from midnight before the test day and arrived at the laboratory at 07:00 am. Blood was sampled for the assay of zinc at 09:00 am being immediately centrifuged. Plasma was stored at –80 °C protected from light.

Assays

The plasma zinc concentration was determined using flame atomic absorption spectrometry (Avanta Σ GBC with deuterium background correction). A linear calibration curve was performed by using certified stardard solution (Merck, Darmstadt, Germany). The measured mean concentration of zinc in quality control samples was 1.41 mg/L (n=5, RSD=3%). The analytical detection limit was 0.01mg/l.

The total HAMD-17 score was analysed followed by the exploratory analysis based on the hierarchical Cole and Motivala model (Cole *et al.* 2004) with core depression, insomnia, anxiety and somatic psychopathological dimensions. The STAI results were analysed with regard to the differentiation of the anxiety to anxiety caused by a specific condition (state subscale – STAIX-1), and anxiety as a more permanent characteristic of the personality (trait subscale – STAIX-2) (Spielberger *et al.* 1970).

Statistical analysis

Statistical procedures were performed using StatsDirect v2.7.9. Shapiro-Wilk test was used to assess normal distribution of continuous data. Normally distributed variables were compared using Student's t-test, all other continuous data were compared with nonparametric Mann-Whitney U-test. Pearson's correlation coefficient was calculated to quantify the linear association between the obtained variables. All tests were two-tailed with an alpha=0.05.

RESULTS

Table 1 summarizes the demographic and clinical variables. There was no significant difference in zinc concentration between MDD patients and controls. Post hoc analysis showed significant negative correlation between zinc concentration and age in MDD subjects (r=–0.45, p=0.046, 95%CI: –0.74 to –0.01), whereas no significant correlation was observed in controls. No significant correlations were observed between zinc concentration and depressive episode duration, melancholia, BMI and WHR, in MDD patients and with respect to age, BMI and WHR in controls. No significant correlations were observed between zinc concentration and the total HAMD-17 score as well as with regard to the specific HAM-D dimension. No significant correlations were also found between zinc concentrations and STAIX-1 and STAIX-2 scores (Table 2).

Significantly higher STAIX-1 (p<0.0001) and STAIX-2 (p<0.0001) scores were observed in MDD as related to controls. The exploratory analysis revealed significantly higher STAIX-1 (p=0.001) scores in non-melancholic major depression as related to melancholic MDD and significantly higher STAIX-2 (p=0.001) scores in melancholic major depression as related to non-melancholic MDD.

Post hoc analysis revealed the HAMD-17 score was significantly higher in melancholic patients with

Tab. 1. Demographic characteristics with psychometric variables and plasma zinc concentrations in MDD and control groups.

		Controls	MDD	MDD	
				melancholic	non-melancholic
N		20	20	9	11
Women (%)		60	55	55	54
Age (years)#	Median (IQR)	33.5 (30.3, 35.8)	30.5 (24.5, 37.5)	30## (25, 31)	31 (24, 44)
BMI	Mean (95%CI)	23.9 (22.6, 25.3)	22.8 (21.4, 24.1)	21.5* (19.9, 23.2)	23.8 (21.6, 25.9)
WHR	Mean (95%CI)	0.82 (0.79, 0.86)	0.82 (0.73, 0.85)	0.82 (0.77, 0.87)	0.82 (0.77, 0.87)
Episode duration (weeks)	Mean (95%CI)	–	14.5 (12.2, 16.7)	14.9 (11.1, 18.7)	14.1 (10.9, 17.3)
HAMD-17#	Median (IQR)	1 (0, 2)	22.5 (21, 24)	24### (23, 25)	21 (20, 22)
Core# depression	Median (IQR)	–	5 (5, 5)	5 (5, 5)	5 (5, 5)
Insomnia#	Median (IQR)	–	3 (3, 4)	4#### (3, 5)	3 (3, 4)
Anxiety#	Median (IQR)	–	7 (6, 7)	7##### (7, 7)	6 (6, 7)
Somatic#	Median (IQR)	–	7 (6, 8)	8###### (7, 8)	7 (6, 7)
STAIX-1#	Median (IQR)	33 (30, 37)	54& (52, 58)	52&&& (50, 52)	57 (54, 59)
STAIX-2#	Median (IQR)	36 (34, 39.5)	48.5&& (46.5, 50.5)	51&&&& (50, 52)	47 (43, 48)
plasma zinc (mg/l)	Mean (95%CI)	0.77 (0.71, 0.83)	0.81 (0.73, 0.89)	0.80 (0.66, 0.94)	0.81 (0.71, 0.92)

MDD – Major Depressive Disorder; BMI – Body Mass Index; WHR – Waist-Hip Ratio; HAMD-17 – Hamilton Rating Scale for Depression; STAI – Spielberger State-Trait Anxiety Inventory; IQR – interquartile range; 95%CI – 95% confidence interval
Shapiro-Wilk W $p<0.05$
vs. Control: $p=0.015$, Mann-Whitney U test, median difference (95%CI)=–5 (–1, –10)
vs. Non-melancholic: $p=0.002$, Mann-Whitney U test, median difference (95%CI)=3 (2, 4)
####vs Non-melancholic: $p=0.043$, Mann-Whitney U test, median difference (95%CI)=1 (0, 2)
#####vs. Non-melancholic: $p=0.009$, Mann-Whitney U test, median difference (95%CI)=1 (1, 2)
######vs. Non-melancholic: $p=0.031$, Mann-Whitney U test, median difference (95%CI)=1 (0, 2)
&vs. Control: $p<0.0001$, Mann-Whitney U test, median difference (95%CI)=21 (18, 24)
&&vs. Control: $p<0.0001$, Mann-Whitney U test, median difference (95%CI)=12 (9, 14)
&&& vs. Non-melancholic: $p=0.001$, Mann-Whitney U test, median difference (95%CI)=–6 (–9, –3)
&&&&vs. Non-melancholic: $p=0.001$, Mann-Whitney U test, median difference (95%CI)=4 (2, 7)
*vs Control: $p=0.035$, two-tailed, unpaired t-test, mean difference (95%CI)=–2.4 (–0.17, –4.60)

Tab. 2. Pearson's correlation coefficient between plasma zinc concentration and psychometric variables in MDD.

	HAMD-17 total	HAMD-17 Core depression	HAMD-17 Insomnia	HAMD-17 Anxiety	HAMD-17 Somatic	STAIX-1	STAIX-2
Plasma Zn	0.24	0.15	0.42	0.10	–0.04	0.26	–0.20

HAMD-17 – Hamilton Rating Scale for Depression; STAI – Spielberger State-Trait Anxiety Inventory

regard to the subpopulation of non-melancholic MDD ($p=0.002$). Post hoc analysis on the specific HAMD-17 dimensions revealed significantly higher insomnia ($p=0.043$), anxiety ($p=0.009$), and somatic ($p=0.031$) subscores in MDD with melancholia as related to non-melancholic patients.

There were no significant differences in terms of gender, age, BMI or WHR between patients with MDD and controls. Post hoc analysis revealed that melancholic MDD subjects were younger ($p=0.015$) and had lower BMI score ($p=0.035$) as related to controls.

DISCUSSION

No significant difference in zinc levels was found between depressed subjects and controls. Zinc concentration was uncorrelated with the severity of depressive symptoms or episode duration in MDD. No correlations were seen between plasma zinc and core depression, insomnia, anxiety and somatic psychopathological dimensions as well as state and trait anxiety measure in MDD. Lower STAIX-1 scores in melancholia with regards to non-melancholic MDD found post hoc seem to correspond with melancholic features related to emotional blunting while the inverse observation with STAIX-2 may be hypothetically associated with psychological traits with negative affect predisposing the one for melancholic MDD.

Substantial evidence exists for lower concentration of zinc in peripheral blood in MDD and zinc depletion corresponds with the severity of depression (Swardfager *et al.* 2013). However, the study results are not unforeseen. Similar results were obtained by Narang *et al.* (1991), Crayton and Walsh (2007) and Irmisch *et al.* (2010) with no evidence for significant difference between controls and depressed patients with regard to plasma zinc concentrations while Maes *et al.* (1997) found no association between serum zinc and severity of depression.

Hypozincaemia in major depression was sometimes questioned in the company of a variety of methodological issues being particularly important with regard to the studied populations. However, the recent metaanalysis by Swardfager *et al.* (2013) demonstrated strong evidence for low peripheral blood zinc concentration in MDD being associated with the greater depressive symptom severity, melancholia or treatment-resistance. Yet, systematic clinical data on zinc levels in major depression according to the psychopathological dimensions and profile are very limited.

In humans, hypozincemia is associated with dysphoria, lethargy, anxiety, maladaptive affect regulation, anhedonia, anorexia, impairment of taste and smell, and impaired cognitive function (Prasad 1985; Russo 2011; Swardfager *et al.* 2013). However, little is known on the impact of plasma zinc concentration on clinical features of depression. The high levels of depressive mood and anxiety seem to be associated with lower levels of serum zinc in MDD subjects. The only systematic study on plasma zinc levels in depression exploring the psychopathological profile found significant negative correlations between plasma zinc concentration, severity of depression, and anxiety (Russo 2011). There is also evidence for hypozincaemia being associated with the diagnosis of anxiety disorders (Russo 2011). The hypothesized link between zinc concentration and anxiety level was not found in our study as well as no correlations were observed with regard to the psychopathological features including severity of symptoms as well as specific psychopathological dimensions in MDD patients

It seems high zinc level associated with anxiolytic effect occurs with dietary supplementation in individuals already experiencing zinc homeostasis dysregulation at the latter stage of the disorder and zinc itself may not possesses anxiolytic characteristics (Russo 2011). Symptoms associated with zinc homeostasis dysregulation in MDD may be non-specific and embrace a wide spectrum of phenomena including anhedonia, dysphoria, anxiety and cognitive dysfunction.

The present study on drug-naïve patients with short-illness-duration first episode MDD exhibiting no treatment-resistance supports hypothesis on hypozincaemia being secondary depression-related phenomenon rather than the cause or the trait of the disease. Besides, hypozincaemia in MDD impacting some specific psychopathological dimensions may correspond to drug-resistance, pronounced anxiety or chronic course of the disorder (Maes *et al.* 1997; Swardfager *et al.* 2013).

The negative correlation observed between zinc concentration and age in MDD may be associated with both depression and age. As age is generally the predisposing factor for the development of hypozincaemia it may hypothetically predispose vulnerable individuals for the development of zinc deficiency and immune dysregulation in MDD (Swardfager *et al.* 2013). Lower BMI score in melancholic MDD with respect to controls along with higher depression severity with corresponding higher psychopathological dimensions scores in that group as related to non-melancholic MDD subjects seem to be associated with the traits of melancholia.

As the number of participating subjects was relatively few, the study may be underpowered. The cross-sectional study design leaves uncertainty as to whether the observed associations represent actual causal relationships between the investigated parameters. The depression might have been accompanied by decreased appetite and influence overall dietary intakes. Nutritional assessment might be important for data interpretation. Finally, the study results apply to drug-naïve patients with short-illness-duration first-episode MDD who were free of comorbid Axis I and II conditions and suicide history with closely matched controls. The selection of study subjects may be reflected in the outcome and further studies investigating the relationship between hypozincaemia, depression, and its psychopathological profile are certainly necessary.

The present study provides evidence for unchanged plasma zinc concentration at early stage of MDD. A cross-sectional analysis failed to demonstrate any correlation between plasma zinc concentrations and psychopathological features including severity of symptoms and specific psychopathological dimensions in MDD.

ACKNOWLEDGMENTS

This project was supported by a research grant MN-10 from the Medical University of Gdańsk, Poland.

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