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The role of Zinc Intake Serotonin and Cortisol Level in Patient with Depression

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Short Running Title: Zinc in serotonin and cortisol level in depression.

ABSTRACT

Background: Low zinc levels affects the relationship between the glutamatergic and serotonergic systems in major depressive disorders that cause stress and inflammation. Decreased zinc in the hippocampus can activates the HPA axis associated with an increase in cortisol. Several studies documented the relationship between zinc and clinical depression, however further research including biological measurements is needed to support these studies.
Objective: To observe the correlation between zinc intake with serotonin and cortisol serum in patient with depression
Methods: This was an observational study with cross sectional design. Subjects were patients with depression who came to Dr. Kariadi Hospital, Tugurejo Hospital, Diponegoro National Hospital and Permata Medika Hospital met the inclusion and exclusion criteria. The food frequency questionnaire (FFQ) was used to assess daily zinc intake. The levels of serum serotonin and cortisol were measured using ELISA technique.
Results: Of the 53 subjects, there was significant correlation between zinc intake with serotonin serum level (p=0,038), however there was no correlation between zinc intake with cortisol serum level (p=0,845)
Conclusion: The higher zinc intake the higher serotonin serum level, however there was no correlation between zinc intake with cortisol serum level in patients with depression.

Keywords: cortisol; depression; FFQ; serotonin; zinc intake

BACKGROUND

Depression is a mental disorder that is associated with decreased productivity, poor psychosocial outcomes and decreased quality of life and wellbeing. According to the World Health Organization (WHO), the total number of people living with depression in the world is about 350 million. Nearly half of these people live in the South-East Asia and Western Pacific.[1] In Indonesia, with a variety of biological, psychological and social factors with diversity in the population, the total estimated number of cases of mental disorders increased this may result burden and decrease in human productivity. Data of Basic Health Research of Ministry of Health of the Republic of Indonesia in 2018 showed the prevalence of depression among the population of aged 15 years and above was about 14 million people or 6.1%, with a prevalence of 4.7% in Central Java.[2] Although there are many effective treatments for depression, pharmacotherapy is usually costly and has potential side effects and psychotherapy requires time and commitment. Take the widely promoted monoaminergic antidepressant for example more than 30% of the patients did not respond to this treatment.[3] Therefore, there is a need to investigate alternative treatment or prevention strategies. Recent research has focused on the role of micronutrient in various mental health disorders including depression.[4,5] Zinc is one of micronutrients that essential for optimal function of the human body, especially the brain and neural structures, where it is found at the highest concentration in the hippocampus and amygdala regions of the brain.[6]

The essential trace ion zinc participates in numerous biological processes. Zinc regulates intracellular signal transduction and contributes to efficient synaptic transmission in the central nervous system.[7] Zinc deficiency is a recognized global public health concern in developing countries and is also becoming a prevalent concern in the ageing population of developed countries.[8] Zinc insufficiency is also associated with neuropsychiatric manifestation including cognitive and behavior changes and depression.[9] A case control study showed that serum zinc level in patients with depression were significantly lower than in normal controls.[10]

The interaction of zinc and the serotonergic receptor 5-hydroxytryptamine 1A (5-HT1A) in a mouse test with reduced antidepressant administration showed that zinc modulates serotonergic receptors that can improve depression.[11] Serotonin is involved in various functions of the central nervous system to regulate pain, sleep, blood pressure, mood, and behaviour. The role of serotonergic transmission in depression is well known so that it is one of the mechanisms of action in anti-depressant drugs. Effect on serotonergic receptors is one of the explanations of the antidepressant-like properties of zinc, which are observed in both preclinical and clinical studies. Satała et al. extensively explored the pharmacological profile of zinc at the 5-HT_{1A} receptors using the agonist of 5-HT_{1A}, [3H]-8-OH-DPAT.[12] The interaction of zinc with glutamate and the specific N-methyl-D-aspartate (NMDA) receptor is another mechanism in reducing symptoms of depression.[13] Low zinc levels disrupt the relationship between the glutamatergic and serotonergic systems in major depressive disorders causing stress and inflammation.[14] Some studies showed that increased glucocorticoids in stress and inflammation in the dysregulation of the Hypothalamic Pituitary Adrenal (HPA) axis produce symptoms of depression. Decreased zinc level in the hippocampus activates the HPA axis associated with increased cortisol.[15] The role of dietary zinc intake in serotonin and cortisol levels has never been reported in depression patients.

OBJECTIVE

This study aimed to characterize the correlation between dietary zinc intake and serotonin and cortisol level among depression population.

METHODS

This was an observational study with cross sectional design. Subjects participated in this study were patients with depression under treatment who came to Psychiatry Clinic at Kariadi Hospital, Tugurejo Hospital, Permata Medika Hospital, Diponegoro National Hospital between January - December 2019. Subjects signed consent approved by our institutional review board 014/EC/KEPK-RSDK-2018. Subjects filled the demographic questionnaires including sex, occupation, marital status, education, income, and history of psychosocial stressors. Subjects underwent a full medical evaluation which involved a medical history, physical and psychiatric examination. Subjects who had diabetes mellitus, cardiovascular disease, renal disease, gastrointestinal disease, malignancy, smoking, pregnant and breastfeeding were excluded. Body weight and height were measured to calculate the body mass index (BMI).

Zinc intake was calculated from dietary intakes assessment using food frequency questionnaires (FFQ).[16] FFQ was administered by trained physician and data conversion was carried by nutritionist. Zinc daily intake of each participant was obtained from the conversion of FFQ in gram. Zinc daily intake level was categorized as insufficient when the zinc intake below 77% of daily requirement and normal when the zinc intake above or the same as daily requirement.[17,18]

Serum were obtained from peripheral blood vein and Sandwich ELISA method was applied to measure the serotonin and cortisol level. Normal serum serotonin level ranging from 101-283 ng/ml and normal serum cortisol level ranging from 10-20 g/dL.[19]

The normality test was carried out using the Saphiro-Wilk test. The correlation between zinc intake and serotonin and cortisol levels was. Pearson test was done to analyze the role of age in serotonin and cortisol level and the Spearman correlation test to analyse the role of occupation, marital status, education, monthly income, length of therapy, stressor, nutritional status, sex, and BDI-II score in serum serotonin and cortisol level. The p value is considered significant if $p<0.05$.

RESULTS

Subjects participated in studies at Kariadi Hospital, Tugurejo Hospital, Diponegoro National Hospital and Permata Medika Hospital between January and December 2019. The subjects include 53 patients who met criteria with mean age 35.91 SD 13.26 (19 to 60 years) with mean BDI-II score 21.15 SD 11.41 (1 to 53), mean body weight 60.85 kg SD 9.32 (45 to 85), mean height 156.87 cm SD 8.12 (140 to 176), mean body mass index 24.77 SD 3.59 (17.4 to 34.4). The characteristics of the study subjects are shown in table 1. Serum serotonin levels were measured with levels ranging from 8,12 ng/mL to 327,66 ng/mL (mean 91,15 ± SD 63,00). Cortisol serum levels ranging from 1,7 g/dL to 16,4 g/dL (mean 8,26 ± SD 3,65).

Table 1 Demographic Characteristics of Subjects

Characteristics	Mean ± SD (min-max)
Age	35,91 ± 13,26 (19-60)
Height (cm)	156,87 ± 8,12 (140-176)
Weight (kg)	60,85 ± 9,32 (45-85)
BMI (kg/m^2)	24,77 ± 3,59 (17,4-34,4)
BDI-II	21,15 ± 11,41 (1-53)
Serum serotonin level	91,15 ± 63,00 (8,12-327,66)
Serum cortisol level	8,26 ± 3,65 (1,7-16,4)

SD = Standard Deviation; min = minimum; max = maximum

Table 2 summarizes the correlation between zinc intake and serum serotonin and cortisol levels. It showed that there was significant positive correlation between zinc intake and serum serotonin level (p=0,038) but not with serum cortisol level (p=0,0845).

Table 2. Correlation between zinc intake and serum serotonin level

		Zinc Intake
Serum serotonin level	r	0,285
	p	0,038*
Serum cortisol level	r	-0,027
	p	0,845

r= correlation coefficient; p= p-value

Table 3 showed the result of the bivariate analysis between occupation, marital status, education, monthly income, length of antidepressant therapy, stressor, nutritional status, sex, age and BDI-II on serum serotonin and cortisol levels. From this analysis, we found that there was a negative significant correlation between body mass index and serum serotonin levels in the subjects. (p=0,039) with weak level of coefficient correlation (r=-0,284). The higher the body mass index, the lower the serum serotonin levels. There was a significant negative correlation between the length of therapy and serum cortisol levels of subjects (p=0,042) and there was a significant negative correlation between gender and serum cortisol levels (p=0,001).

Table 3. Correlation between variables and serum serotonin and cortisol levels

Variable	F	Serotonin	Cortisol
Occupation		p=0.283, r=-0,150[a]	p=0.744, r=0.046[a]
None	8	113.16 (61.62 -180.85)	9.2(3.9 – 14.3)
Housewife	18	66.11 (17.48 – 229.47)	6.6 (2.1 – 15.4)
Student	10	71.57 (39.24 – 154.02)	8.4 (3.5 -14.9)
Entrepreneur	16	88.07 (8.12 – 327.66)	8.9 (1.8 -18.7)
Civil servant	1	10.91 (10.91 – 10.91)	9.3 (9.3-9.3)
Marital Status		p=0.200, r=-0.179[a]	p=0.090, r=-0.235[a]
Single	23	87.72 (39.24 – 254.26)	9 (3.5-18.7)
Married	27	70.87 (8.12 -327.66)	6.9 (1.8 -16.4)
Separated	3	58.92 (37.97 -116.78)	9.9 (4.4 -12.8)
Education		p=0.634, r=0.067[a]	p=0.233, r=-0.167[a]
Elementary	10	74.32 (17.72 -156.41)	5.8 (2.1 -12.8)
Junior High	6	48.14 (8.12 -130.75)	8.4 (1.8 -16.4)
Senior High	20	90.16 (17.48 -327.66)	9.7 (2.6 -18.7)
College/University	17	74.8 (10.91 -254.26)	7.9 (3.5 -14.9)
Monthly income		p=0.100, r=-0.228[a]	p=0.219, r=-0.172[a]
Under minimum wage	31	84.05 (17.48 -327.66)	9 (2.1 -18.7)
Same as minimum wage	19	61.62 (37.97 -254.26)	6.3 (1.8 -15.4)
Above minimum wage	3	10.91 (8.12 -93.39)	12.5 (9.3 -16.4)

Variable	F	Serotonin	Cortisol
Length of antidepressant therapy		p=0.349, r=-0.131[a]	p=0.042, r=-0.281
< 1 Month	7	90.08 (41.20 -254.26)	11.9 (7.1 -14.9)
>1 Month	46	76.15 (8.12 – 327.66)	8 (1.8 -18.7)
Stressor		p=0.059, r=0.262[a]	p=0.977, r=0.004[a]
Occupation	5	58.92 (8.12 -156.41)	9.9 (6.3 -16.4)
Psychosocial and environment	8	58.82 (37.97 -254.26)	8 (1.8-14.9)
Primary Support Group	27	86.06 (10.91 -327.66)	8 (2.1 – 18.7)
Health condition	4	110.05 (84.05 -157.55)	7.4 (5.9 -9.2)
Education	7	77.51 (40.33 -180.85)	9.5 (6.7 -13.5)
Financial	2	95.79 (50.54 -141.05)	6.3 (2.2 -10.5)
Nutritional status		p=0.039, r=-0.284[a]	p=0.930, r=-0.012[a]
Underweight	1	90.08 (90.08 -90.08)	10.7 (10.7 -10.7)
Normal	19	86.06 (17.48 -327.66)	7.9 (2.1 -14.3)
Overweight	13	87.72 (25.07 -243.87)	8.7 (3.5 – 18.7)
Obesity	20	53.11 (8.12 -229.47)	8.2 (1.8 – 16.4)
Sex		p=0.185, r=0.185[a]	p=0.001, r=-0.430[a]
Male	13	72.27 (8.12 -157.55)	10.7 (7.2 – 16.4)
Female	40	85.05 (17.48 -327.66)	7 (1.8 – 18.7)
Age		p=0.119, r=-0.217[a]	p=0.091, -0235[b]
BDI-II		p=0.758, r=0.043[a]	p=0.058, r=0.262[a]
Minimum	14	87. 06 (17.48-198.13)	7.4 (1.8 -11.5)
Mild	12	66.07 (38.93 -327.66)	7 (2.1 -12.8)
Moderate	11	77.51 (8.12 -243.87)	9.3 (4.4 -18.7)
Severe	16	76.98 (17.72 -254.26)	9.2 (3.3 -14.9)

* Significant (p < 0,05);
[a] Spearman's correlation
[b] Pearson correlation

DISCUSSION

This study showed that there was a significant correlation between zinc intake and serum serotonin levels in patients with depression. A publication demonstrates that there are differences in serum concentrations in patient with depression.[10] In the aetiology of depression there is a monoamine hypothesis which states that depression is associated with a decrease in the amount or function of serotonin in cortex and limbic system. In this study the measured zinc intake was obtained from interview using food frequency questionnaire that is similar to a study conducted by Li et al which assessed total zinc level by using a 24-h recall survey.[20] Serotonin levels play a role in the mechanism of action of antidepressant. The relationship between zinc intake and depression can be explained by various mechanisms. Zinc homeostasis in the brain is regulated by the food intake containing zinc. Zinc has a synergistic effect like SSRIs that can regulate 5-HT1A receptors that can inhibit agonist and antagonist binding at synapses. Zinc can also affect serotonin neurotransmission, NMDAR activation and BDNF activity which are involved in depression.[21] In addition, zinc also has anti-inflammatory and antioxidant properties that contribute to depression.[22]

Zinc plays a significant role with respect to the stress response. Proper maintenance of zinc status can help stabilize serum cortisol levels over time and zinc intake has been shown to temporarily inhibit cortisol secretions.[15] However, in turn, prolonged stress will deplete zinc concentrations in the blood. Zinc deficiency has been demonstrated to increase plasma cortisol and pro-inflammatory cytokine of interleukin-6 (IL-6), IL-1 and nitric oxide levels. The mechanism of food consumption induced cortisol stimulation is not known, it may be due to stimulation of pituitary ACTH secretion by amino acid products or protein digestion, release of gut messengers that secondarily release ACTH or release locally generated ACTH from the intestine. The results also indicated that there was no significant correlation between zinc intake and serum cortisol levels in patients with depression. This may be because cortisol is a biological marker of stress general and not a specific marker for depression.[23] We found that almost all subjects had normal serum cortisol levels which was possible because the subjects were already on antidepressant treatment and were not currently exposed to stressful stimuli. Across multiple mental health-related measure, a polymorphism (5-HTTLPR) within the promoter of the serotonin transporter gene has been associated with differential psychological sensitivity to stressful experience. The short/short genotype of the 5-HTTLPR is associated with greater cortisol reactivity to social threat. When short/short individuals experience stressful life events, they might be at greater risk for the adverse psychological and physical health consequences associated with heightened cortisol exposure.[24]

Although acute or chronic stress can be measured in physiological parameters such as heart rate, blood pressure, and various metabolic hormones, it is difficult to understand whether changes in levels of circulating stress mediators such as cortisol can reflect acute, chronic or diurnal stress.[23,25] In the analysis of confounding variables on serotonin levels, it was found that serum serotonin levels were correlated by body mass index. Abnormal body mass index is also related to the availability of serotonin transporters that disrupted in individual with obesity. This is consistent with a study assessed the correlation between plasma tryptophan levels and body mass index with symptoms of depression.[26] Decreased serotonin levels is one of the pathophysiology mechanism of depression. Serum cortisol levels was influenced by the length of therapy. This can be because the use of long terms antidepressants can affect the HPA axis through changes in glucocorticoid and mineralocorticoid receptors so that serum cortisol levels will decrease. Changes in these receptors affect the effectiveness of therapy. Long term use of antidepressants for both SSRI and non-SSRI can reduce the intensity of HPA axis activity that eventually reduce serum cortisol levels.[27]

CONCLUSION

From the study we conclude that there was a significant correlation between zinc intake and serum serotonin levels, thus the higher the zinc intake the higher the serum serotonin levels. There was no significant correlation between zinc intake and serum cortisol levels. The demographic characteristics of the subjects showed that body mass index has a significant correlation to serum serotonin levels. The length of time the subjects received antidepressant therapy and gender had a significant correlation with serum cortisol levels. Further research is needed to assess other risk factors that can affect serum serotonin and cortisol levels.

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