Research Article

Serum Zinc and Copper Levels and their Association with Mental Distress in Postmenopausal Women

Irmiya Rachmiyani[1,2], Shofwal Widad[1], Agung Dewanto,[1]

[1]Division of Reproductive Endocrinology Fertility
Department of Obstetrics and Gynecology
Faculty of Medicine Public Health and Nursing
Universitas Gadjah Mada, Yogyakarta
[2]Department of Obstetrics and Gynecology
Faculty of Medicine Universitas Trisakti, Jakarta

Abstract

Objective: To investigate the relationship between serum zinc (Zn) and copper (Cu) levels and mental distress in postmenopausal women.

Methods: This cross-sectional study included 87 postmenopausal women. Participants with a history of hysterectomy or estrogen therapy were excluded. Mental distress was assessed using the Self-Reporting Questionnaire-20 (SRQ-20). Serum Zn and Cu concentrations were measured using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Data were analyzed using SPSS version 25, employing independent t-tests, Mann–Whitney tests, and Pearson correlation analysis.

Results: The mean serum zinc levels in participants with and without mental distress were 67.93 ± 9.03 µg/dL and 71.07 ± 12.99 µg/dL, respectively (p = 0.390). The mean serum copper levels were 129.38 ± 12.31 µg/dL in participants with mental distress and 131.78 ± 18.22 µg/dL in those without (p = 0.638). No significant correlations were found between serum zinc or copper levels and mental distress (r = -0.03, p = 0.775; r = -0.002, p = 0.984, respectively). These findings suggest that zinc and copper may not serve as reliable biomarkers for screening mental distress in postmenopausal women.

Conclusion: Serum zinc and copper levels were not significantly associated with mental distress in postmenopausal women.

keywords: copper, mental distress, postmenopausal, zinc.

Correspondence author. Agung Dewanto. Division of Reproductive Endocrinology Fertility Department of Obstetrics and Gynecology. Faculty of Medicine Public Health and Nursing. Universitas Gadjah Mada. Yogyakarta.
Email: agung.dewanto@ugm.ac.id

INTRODUCTION

Menopause represents a significant transitional phase in a woman's life, characterized by numerous physiological and psychological changes.[1]This period marks the end of one stage of life and the beginning of a new phase.[2] During menopause, women frequently experience various clinical symptoms associated with hormonal, psychological, and physical changes.[3] Approximately 90% of women experience some degree of mental distress during menopause due to these psychological fluctuations.[4] Common physical symptoms during the menopausal transition include hot flashes, vaginal dryness, headaches, and difficulty sleeping. Psychological manifestations often include stress, depression, mood swings, and anxiety,[5] which may become a concern, particularly in cases of early menopause, as it is associated with an increased risk of cardiovascular disease, myocardial infarction, osteoporosis, and higher mortality rates.[6]

Recent research has increasingly focused on nutritional interventions as alternatives to conventional treatments such as pharmacotherapy and psychotherapy. Nutritional approaches have shown promise in managing mood and anxiety disorders among women undergoing the menopausal transition and in the postmenopausal period.[7] Although digestive and absorptive functions generally remain intact in older adults, individuals with underlying conditions may

experience nutrient malabsorption. Conditions such as small intestinal bacterial overgrowth, exocrine pancreatic insufficiency, enteropathies, vascular disease, diabetes mellitus, and chronic infections are more prevalent in the elderly. Furthermore, prior surgical procedures or long-term medication use may further contribute to malabsorption in this population.[8] Among micronutrients, zinc (Zn) and copper (Cu) have received particular attention due to their roles as important modulators of glutamate transmission, which is linked to the etiopathogenesis of depression.[9]

Zn and Cu are essential trace minerals for human health. Acting as structural ions, catalysts, and regulators of enzymatic processes, these minerals influence numerous physiological functions. They also play roles in immune response, ageing, antioxidant defense, and anti-inflammatory processes.[6] Zn has been shown to regulate Brain-Derived Neurotrophic Factor (BDNF) activity, which is associated with depression, and to reduce the production of inflammatory mediators such as C-reactive protein (CRP) and interleukin-6 (IL-6). Zinc's antioxidant properties may further explain the role of oxidative stress in the pathophysiology of depression.[10] Cu is another essential element, and both its deficiency and excess can significantly affect brain development and function. Cu plays a key role in neurotransmission, cognitive function, learning and memory processes, neurogenesis, and synaptogenesis. It also regulates the activity of dopamine β-hydroxylase.[11] Dopamine and norepinephrine are essential neurotransmitters for mood regulation, motivation, and concentration.[12]

Previous studies have suggested that higher Zn intake may be associated with a decreased frequency of depressive symptoms.[13,14] Similarly, another study reported that total zinc and copper intake may be inversely associated with depression.[11] However, other studies have not demonstrated statistically significant associations between copper, magnesium, zinc, selenium, and other trace elements and the prevalence of depressive disorders.[15] A study found that 87.9% of elderly individuals in Indonesia had zinc intake below the national dietary reference values,[16] which is consistent with a systematic review and meta-analysis showing that copper intake among Indonesian adults was below 100% of the recommended Estimated Average Requirement (EAR).[17] However, to date, no study has examined whether serum Zn and Cu concentrations are associated with mental distress in Indonesian postmenopausal women. Serum Zn and Cu levels may be decreased in postmenopausal women experiencing mental distress.

METHODS

A cross-sectional study involving 87 postmenopausal women aged 46–65 years was conducted in the Kebayoran Baru district, Jakarta, Indonesia. The sample size was calculated with a statistical power of 0.8. Consecutive sampling was applied. The sample size was estimated using the following formula:

$$n = \frac{1.96^2 \times 0.35 \times 0.65}{0.1^2} = n = 87.3 \sim 87$$

This calculation was based on an estimated proportion of mental distress of 35% among postmenopausal women.[18] Participants were recruited from the general population based on predefined inclusion and exclusion criteria. Written informed consent was obtained from all participants after a detailed explanation of the study procedures.

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Universitas Trisakti (Approval No. 008/KER/FK/III/2021). The inclusion criteria were postmenopausal women aged 46–65 years who had not experienced menstruation for at least 12 consecutive months, indicating the end of their reproductive period. The exclusion criteria included women who had undergone surgical menopause or were receiving estrogen therapy.

A 5 mL venous blood sample was aseptically collected from each participant. Serum was separated by centrifugation at 3,000 rpm for 10 minutes. Serum zinc (Zn) and copper (Cu) concentrations were measured using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). Sample preparation followed the base extraction method according to the instrument's standard operating procedures. The Agilent 7700 Series ICP-MS MassHunter Workstation software was used for data acquisition and analysis in accordance with the manufacturer's instructions. The reference ranges were 75–145 µg/dL for serum Cu and 60–130 µg/dL for serum Zn.

Mental distress was assessed using the Self-Reporting Questionnaire-20 (SRQ-20). The SRQ-20 consists of 20 dichotomous (yes/no) questions

addressing symptoms associated with common mental disorders (CMDs). Each "yes" response was scored as 1 and each "no" response as 0, reflecting the presence or absence of symptoms over the past month. A total score of ≥6 indicated the presence of anxiety and depression.[19]

Descriptive statistics were used to summarize the characteristics of the study population, presented as frequencies and percentages for categorical variables. Quantitative variables were described using median, minimum, and maximum values. Group comparisons were performed using the independent t-test and Pearson's correlation for normally distributed data. For non-normally distributed data, the Mann–Whitney test was applied, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

The total number of respondents was 87 post-menopausal women aged 46-65 years. Most of the women exhibited no signs of mental distress (81.6%) while the rest showed mental distress (18.3%)

Table 1. The Mean Difference between Characteristic and the Mental Distress Category Based on the SRQ Scores

Parameter	Mental Distress Category Based on SRQ		*P-value*
	YES (n = 16)	**No (n = 71)**	
Age (year, median [min-max])	55 (49-68)	59 (50-71)	0.122#
Systolic (mmHg, mean ± SD)	132.29±15.75	137.94±25.49	0.426*
Diastolic (mmHg, mean ± SD)	80.21±9.00	79.55±11.21	0.835*
BMI (kg/m2, mean ± SD)	26.29±4.81	26.19±4.86	0.942*

* Independent t-test, # Mann-Whitney

The normality test of data from both groups for systolic, diastolic and BMI was normally distributed (sig. > 0.05) while the normality test of data from age was not normally distributed. The characteristic subjects in both groups with and without mental distress were not significant.

Table 2. The Mean Difference between Mineral and the Mental Distress Category Based on the SRQ Scores

Parameter	Mental Distress Category Based on SRQ		*P-value*	Size Effect	95% CI (Lower-Upper)
	Yes (n = 16)	**No (n = 71)**			
Zinc (µg/dL, mean ± SD)	67.93±9.03	71.07±12.99	0.390*	-0.252†	-0.824 – 0.322
Copper (µg/dL , mean ± SD)	129.38±12.31	131.78±18.22	0.638*	-0.138†	-0.709 – 0.435
Total SRQ (median [min-max])	8.5 (6-13)	1 (0-5)	<0.05#	-0,647‡	-0,755 – (-0,505)

* Independent t-test, # Mann-Whitney; † Cohen's d. ‡ r coefficient

The normality test of data from both groups for Zn and Cu was normally distributed (sig. > 0.05) while the normality test of data from total SRQ was not normally distributed. The mean serum Zn in the mental distress group was lower than in the no mental distress group. The mean serum Cu level was lower in the mental distress group than in the no mental distress group. The difference serum zinc between the groups with and without mental distress showed a small effect size (Cohen's d = −0.252 [95% CI −0.824 to 0.322]). The difference serum copper levels between the two groups showed a very small effect size (Cohen's d = −0.138 [95% CI −0.709 to 0.435]). The difference in SRQ total scores between the groups with and without mental distress showed a large effect size (r = −0.647 [95% CI −0.755 to −0.505]). The median SRQ-20 score in the mental distress group was 8.5 (range: 6–11), whereas in the no mental distress group, the median was 1 (range: 0–5).

Table 3. The Mean Difference between Ratio Zn/Cu and the Mental Distress Category Based on the SRQ Scores

Mental Distress Category Based on SRQ	Mean	Std. dev	Min	Max	95% CI (Lower-Upper)	*P-value*
Yes	1.94	0.36	1.48	2.71	1.75 – 2.13	0.504#
No	1.86	0.40	1.09	3.15	1.76 – 1.95	

Mann-Whitney

The average Zn/Cu ratio in the mental distress group was slightly higher (1.94) than in the no mental distress group (1.86). However, the data distribution (SD) across the two groups was relatively similar (0.36 vs. 0.40). Zn/Cu values in mental distress group ranged from 1.48–2.71, while in the no mental distress group they ranged from 1.09–3.15. The normality test of data from mental distress group was normally distributed (sig. > 0.05) whereas in the no mental distress group was not normally distributed (sig. < 0.05). There was no significant association between ratio Zn/Cu and mental distress (p = 0.504).

Table 4. Correlation between copper, and zinc levels with SRQ scores

Parameter	Correlation coefficient	*P-value†*
Zinc (µg/dL)	-0.031	0.775∫
Copper (µg/dL)	-0.002	0.984∫

∫ Pearson test

Our analysis did not demonstrate any correlation between levels of Zn (r = -0.031, p > 0.05) or Cu (r = -0.002, p>0.05) and mental distress.

DISCUSSION

In this study, we found that the mean serum Zn level was lower in the mental distress group than in the non–mental distress group; however, the difference was not statistically significant (r = −0.031, p > 0.05). The postmenopausal period is characterized by an increased risk of nutritional deficiencies, particularly zinc (Zn), due to hormonal changes, especially estrogen depletion. Estrogen functions as an antioxidant; therefore, reduced estrogen levels may lead to decreased antioxidant capacity. Estrogen deficiency in postmenopausal women may increase the risk of zinc deficiency, which could potentially be mitigated by zinc supplementation.[20]

Serum zinc levels may indicate the presence of depressive conditions, although they are not necessarily associated with the severity of depressive symptoms. In addition, the regulation of zinc homeostasis plays an important role in the mechanisms underlying antidepressant therapy.[21] Although serum testing is technically simple, it has several limitations. Normal serum zinc levels do not necessarily reflect adequate intracellular zinc levels, as severe depletion may cause cellular release of zinc into circulation. Conversely, low serum zinc levels may reflect an inflammatory response, as zinc is redistributed from serum to the liver during immune activation, resulting in hypozincemia. Other factors, such as hypoalbuminemia and hormonal therapies, may also influence serum zinc levels by increasing urinary excretion. Additionally, zinc released from erythrocytes during intra- and extravascular hemolysis can increase serum concentrations.[22]

Serum zinc levels may also fluctuate by up to 20% within a day. After food intake, zinc levels rise rapidly and then decline within two to four hours, followed by a gradual increase until the next meal. The highest serum zinc levels are typically observed in the morning after several hours of fasting.[23] Epidemiological studies have shown that serum zinc levels are significantly lower in patients with Major Depressive Disorder (MDD), that dietary zinc deficiency increases the risk of onset, and that zinc supplementation may improve symptoms and reduce risk. Zinc supplementation (25–30 mg/day) as monotherapy has been reported to be effective for mild to moderate depression, particularly in overweight or obese individuals. In combination with antidepressants such as selective serotonin reuptake inhibitors (SSRIs), zinc may enhance therapeutic efficacy, especially in treatment-resistant cases, with a dose-dependent effect.[24]

A complex interaction may exist between serum copper and depressive symptoms. Depression has been described as a pro-inflammatory state, which activates the inflammatory response system and may lead to increased serum copper levels. On the other hand, depression is also strongly associated with oxidative stress. Evidence suggests that patients with depression exhibit elevated levels of reactive oxygen species (ROS), along with increased superoxide dismutase (SOD) activity.[25]

In the present study, the mean serum Cu level in the mental distress group was lower than in the non–mental distress group; however, the difference was not statistically significant ($r = -0.002$, $p = 0.984$). Similar findings have been reported in other studies, which found no significant differences in serum copper concentrations between patients with current depressive episodes and healthy controls, or between those in remission and controls. These findings suggest that the role of copper in the pathophysiology of major depressive disorder (MDD), and its potential as a clinical biomarker, remains unclear.[25] Overall, these findings suggest that zinc and copper may not serve as reliable biomarkers for screening mental distress in postmenopausal women.

Furthermore, previous studies have highlighted the importance of the zinc-to-copper (Zn/Cu) ratio, suggesting that elevated serum copper and reduced serum zinc levels play a role in the pathogenesis of MDD.[26] Depressed patients often exhibit increased levels of reactive oxygen species (ROS) along with elevated superoxide dismutase (SOD) activity. Copper plays an important role in this process, as it is a component of the copper–zinc superoxide dismutase (Cu/Zn-SOD) enzyme and can influence its activity. Additionally, copper and its complexes may exert antioxidant effects.[25] An imbalance between zinc and copper has been associated with several conditions, particularly psychiatric disorders. Therefore, the Zn/Cu ratio may provide a more sensitive and reliable indicator than either element alone. However, in this study, no significant relationship was found between the Zn/Cu ratio and mental distress ($p > 0.05$).

A previous study reported that as women age, they tend to experience fewer depressive symptoms and less negative mood, with the highest levels observed during the menopausal transition.[27] However, our study did not account for the duration of menopause or other nutritional factors that may have influenced these findings. Additionally, this study did not assess other micronutrients, did not exclude comorbid conditions that could affect mineral levels, and included participants with relatively similar sociodemographic backgrounds. Mental distress was assessed using a self-report instrument (SRQ-20), which may introduce reporting bias.

CONCLUSION

Within the limitations of this cross-sectional study, serum zinc and copper levels were not significantly correlated with mental distress in postmenopausal women. However, zinc and copper supplementation in postmenopausal women with mild to moderate mental distress may improve outcomes. Future research should employ longitudinal designs, include multi-center studies across broader geographical settings, examine additional factors contributing to mental distress, and incorporate measurements of other nutrients that may influence depressive symptoms. Further studies should also explore the effects of supplementation interventions.

REFERENCES

1. Yadav V, Jain A, Dabar D, et al. A meta-analysis on the prevalence of depression in perimenopausal and postmenopausal women in India. Asian J Psychiatr. 2021;57(102581):1-8. doi:10.1016/j.ajp.2021.1025812.
2. Suheimi HK. Pola Hidup untuk Meningkatkan Kualitas Wanita Menopause. Indones Obstet Gynecol Indones. 2006;30(2):82-91.doi:https://doi.org/10.32771/inajog.v30i23.
3. Di YM, Yang L, Shergis JL, et al. Clinical Evidence of Chinese Medicine Therapies for Depression in Women During Perimenopause and Menopause. Complement Ther Med. 2019;47(102071). doi:10.1016/j.ctim.2019.03.0194.
4. Nazari F, Hekmat K, Iravani M, Haghighizadeh MH, Boostani H. The Relationship between Serum Zinc and Magnesium Levels and Depression in Postmenopausal Women. J Biochem Tech. 2019;(4):108-114.5.
5. Octavani C, Meiyanti M. The relationship of menopause with depression among women over 50 years old. JKKI. 2019;10(1):50-56. doi:10.20885/jkki.vol10.iss1.art86.
6. Ningsih E, Affandi B. Stimulasi ovarium dan hubungannya dengan usia terjadinya menopause. Indones J Obstet Gynecol.2008;32(4):242-9.doi: https://doi.org/10.32771/inajog.v32i47.
7. Grigolon RB, Ceolin G, Bambokian A, Koning E, Fabe J. Effects of nutritional interventions on the severity of depressive and anxiety symptoms of women in the menopausal transition and menopause: a systematic review, meta-analysis, and meta-regression. Menopause. 2023;30(1):95-107.8.
8. Schiller LR. Maldigestion Versus Malabsorption in the Elderly. Curr Gastroenterol Rep. 2020;22(33):1. doi:10.1007/s11894-020-00771-59.
9. Szkup M, Jurczak A, Brodowska A, et al. Analysis of Relations Between the Level of Mg, Zn, Ca, Cu, and Fe and Depressiveness in Postmenopausal Women. Biol Trace Elem Res. 2017;176(1):56-63. doi:10.1007/s12011-016-0798-910.
10. Kluza K, Zawlik I, Janowska M, et al. Study of Serum Copper and Zinc Levels and Serum Cu/Zn Ratio among Polish Women with Endometrial Cancer. Nutrients. 2024;16(144):1-17. doi:10.3390/nu16010144

11. Li Z, Wang W, Xin X, Song X, Zhang D. Association of total zinc, iron, copper and selenium intakes with depression in the US adults. J Affect Disord. 2018;228(2018):68-74. doi:10.1016/j.jad.2017.12.004
12. Milano W, Ambrosio P, Carizzone F, et al. Depression and Obesity: Analysis of Common Biomarkers. Diseases. 2020;8(23):21-19. doi:10.3390/diseases8020023
13. Nguyen TTT, Miyagi S, Tsujiguchi H, et al. Association between lower intake of minerals and depressive symptoms among elderly japanese women but not men: Findings from shika study. Nutrients. 2019;11(389):1-13. doi:10.3390/nu11020389
14. Miki T, Kochi T, Eguchi M, et al. Dietary intake of minerals in relation to depressive symptoms in Japanese employees: The Furukawa Nutrition and Health Study. Nutrition. 2015;31(5):686-90. doi:10.1016/j.nut.2014.11.002
15. Wieder-Huszla S, Zabielska P, Kotwas A, et al. The severity of depressive and anxiety symptoms in postmenopausal women depending on their magnesium, zinc, selenium and copper levels. J Elem. 2020;25(4):1305-17. doi:10.5601/jelem.2020.25.1.1997
16. Mutiara DS, Sunardi D, Dewiasty E. Correlation between Hair Zinc Level and Cognitive Function in Elderly. World Nutr J. 2019;3(1):26. doi:10.25220/wnj.v03.i1.0007
17. Agustina R, Mufida R, Lasepa W, et al. Nutrient Intake Adequacy among Adults in Indonesia and Malaysia: A Systematic Review and Meta-Analysis. Curr Dev Nutr. 2025;9(106010):1-43. doi:10.1016/j.cdnut.2025.106010
18. Jia Y, Zhou Z, Xiang F, Hu W, Cao X. Global prevalence of depression in menopausal women: A systematic review and meta-analysis. J Affect Discord. 2024;1(358):474-82.
19. Renaldo E, Suryani E. Gambaran gangguan mental emosional pada penduduk Desa Banfanu, Timor Tengah Utara, Provinsi Nusa Tenggara Timur. Jur Biomedika Kes. 2020;3:49-7. doi:10.18051/JBiomedKes.2020
20. Vázquez-Lorente H, Molina-López J, Herrera-Quintana L, et al. Erythrocyte Zn concentration and antioxidant response after supplementation with Zn in a postmenopausal population. A double-blind randomized trial. Exp Gerontol. 2022;162:1-8. doi:10.1016/j.exger.2022.111766
21. Huang D, Lai S, Zhong S, Jia Y. Association between serum copper, zinc, and selenium concentrations and depressive symptoms in the US adult population, NHANES (2011–2016). BMC Psychiatry. 2023;23(1):1-13. doi:10.1186/s12888-023-04953-z
22. Hawrysz Z, Woźniacka A. Zinc: an undervalued microelement in research and treatment. Adv Dermatol Allergol. 2023;40(2):208-214. doi:10.5114/ada.2023.127639
23. Roohani N, Hurrell R, Kelishadi R, Schulin R. Zinc and its importance for human health: An integrative review. J Res Med Sci. 2013;18(2):144-157.
24. Li Y, Lu Y, Lin X, Zhao L. The role of zinc homeostasis in major depressive disorder: heterogeneous pathological mechanisms and therapeutic implications. Ann Med. 2026;2611191(1):1-48. doi:10.1080/07853890.2025.2611191
25. Styczeń K, Sowa-Kućma M, Siwek M, et al. Study of the Serum Copper Levels in Patients with Major Depressive Disorder. Bio Trace Elem Res. 2016;174(2):287-293. doi:10.1007/s12011-016-0720-5
26. Liu X, Zhong S, Li Z, et al. Serum copper and zinc levels correlate with biochemical metabolite ratios in the prefrontal cortex and lentiform nucleus of patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2020;99(109828):1-16. doi:10.1016/j.pnpbp.2019.109828
27. Campbell KE, Dennerstein L, Finch S, Szoeke CE. Impact of menopausal status on negative mood and depressive symptoms in a longitudinal sample spanning 20 years. Menopause.2017;24(5):490-6.