Pharmacy Education (2024) 24(9) 58 - 64
https://doi.org/10.46542/pe.2024.249.5864

ICSM SPECIAL EDITION

RESEARCH ARTICLE

Correlation between micronutrients and cellular immune responses after CoronaVac vaccination in elderly people

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Keywords
Cellular immunity
Magnesium
Micronutrient
Neopterin
Vaccine
Zinc

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Abstract

Background: Elderly individuals are often at risk for deficiencies in micronutrients like zinc (Zn) and magnesium (Mg), which are essential for cellular function and immune system homeostasis. Vaccination is a crucial strategy to prevent disease, but micronutrient deficiencies may diminish vaccine effectiveness. The immune response consists of cellular and humoral components, with neopterin serving as a marker for cellular immune activity. **Objective:** This study aimed to determine whether Zn or Mg deficiencies affect the decrease of cellular immunity between six and 24 weeks after vaccination. **Method:** This study was a prospective cohort involving eighty-eight elderly individuals (aged 60 and older) who received two doses of the CoronaVac vaccine. Blood samples were collected at six and 24 weeks post-vaccination to measure serum zinc (Zn) and magnesium (Mg) levels using inductively coupled plasma mass spectrometry (ICP-MS). The immune response was assessed by the decrease in serum neopterin levels at six and 24 weeks after vaccination, measured using an enzyme-linked immunoassay (ELISA). **Result:** There was a positive correlation between Mg and a decrease in neopterin between six and 24 weeks after vaccination, with p = 0.011 and r = -0.296. However, we did not find a correlation between Zn and neopterin levels. This study showed that the lower the Mg levels, the faster the cellular immune response after vaccination disappeared. Nevertheless, the role of Zn in cellular immune response after vaccination is still unclear. **Conclusion:** Mg deficiency, but not Zn, was correlated with a more rapid reduction of cellular immune response after vaccination.

Introduction

The number of elderly people is increasing worldwide, occurring not only in developed countries but also in developing countries. In Indonesia, there were 26.82 million elderly people, or 9.92% of the population, in 2020. Indonesia has become one of the countries experiencing population ageing since it has more than 7% elderly population (Dwijayanti *et al.,* 2023). The elderly are a population group prone to various diseases such as autoimmune, malignancy, and severe infections. They also have reduced immune response to vaccines since they are ageing (Valiathan *et al.,* 2016). Additionally, elderly people have reduced appetite, altered taste function, dysphagia, and malabsorption (Aliani *et al.,* 2013; Montgomery *et al.,* 2014; Haines *et al.,* 2020; Schiller, 2020; Rodd *et al.,* 2022). Moreover, the elderly tend to get less income and are less active, thus giving them less access to nutritional food (Mustofa *et al.,* 2023). It is reported that there is up to 47.8% malnutrition in elderly people, especially in underdeveloped and developing countries (Veronese & Barbagallo, 2021). These conditions make elderly people prone to micronutrient deficiencies.

Micronutrient deficiency is common in the elderly. Zinc (Zn) and Magnesium (Mg) are two micronutrients that have an important role in maintaining immune system function (Maier *et al.,* 2021; Wessels *et al.,* 2021). Zn is an important micronutrient in the development of the immune system and modulates cytokine release (Maggini *et al.,* 2018). Zn is an essential nutrient in hematopoiesis, cell maturation, cell differentiation, cell cycle progression, and adequate function of the immune system. Zn deficiency alters the immune system and becomes similar to the ageing of the immune system. Zn deficiency alters the function of the cellular and humoral immune response and increases inflammation and thymus atrophy; thus, individuals are at risk of getting recurrent infections (Haase & Rink, 2014). The prevalence of Zn deficiency is estimated at 20% worldwide, and in the elderly, Zn deficiency is reported to be almost 30% (Wessels *et al.,* 2017). However, a study reported that 98% elderly consume inadequate food rich in Zn (Gupta *et al.,* 2017).

Magnesium is a cofactor for various enzymes and has a role in energy metabolism. It is known that Mg plays a role in the synthesis of antibodies, macrophage response, and immune cell adherence. Mg also modulates the immune response, innate and adaptive (Barbagallo *et al.,* 2021). Mg deficiency alters enzymatic reactions and cell function, including the immune system (Iddir *et al.,* 2020). Mg deficiency also caused thymus involution, altered polymorphonuclear cell function, and phagocytosis activation. Furthermore, Mg deficiency may cause chronic inflammation and increased oxidative stress, similar to inflame ageing. Mg deficiency is reported to contribute to the ageing process (Barbagallo *et al.,* 2021). Mg deficiency is reported in 10 – to 30% of the population and is predominantly among the elderly. National Health and Nutrition Survey reported Mg deficiency in adults approximately 31 – 36.3% of the population (DiNicolantonio *et al.,* 2018). Moreover, 47% of elderly individuals are reported to have an inadequate diet of Mg (Gupta *et al.,* 2017).

When the COVID-19 pandemic hit the world, the elderly were at risk of more severe disease and also increased risk of mortality (Pietrobon *et al.,* 2020; Al-Zahrani, 2021; Surendra *et al.,* 2021). Vaccination has become one of the key preventive strategies. However, it was reported to be less effective in the elderly (Crooke *et al.,* 2019; Pereira *et al.,* 2020). This may be caused not only by ageing in the elderly but also by Zn and Mg deficiency. Studies about the effect of Zn and Mg on the immune response to the vaccine in the elderly are still limited, especially in cellular immune response (Kreft *et al.,* 2000; Hamza *et al.,* 2012). However, the cellular immune response is also important because of its role in protecting against severe COVID-19 and other virus variants that escape from neutralising antibodies (Wherry & Barouch, 2022). Thus, a study about Zn and Mg's effect on cellular immune response after the vaccine is still needed. Immune response to vaccines is divided into humoral and cellular responses. Pro-inflammatory cytokines such as interferon-gamma and tumour necrosis factor-alpha can measure cellular immune activity. However, they have a short half-life. Neopterin, pteridine produced by macrophages, is one of the markers of cellular immune activity. Neopterin is superior to interferon-gamma since it has a longer half-life and is more stable (Gieseg *et al.,* 2018). Thus, the authors conducted serum neopterin levels as a cellular immunity marker.

The purpose of this study is to provide information on the importance of Zn and Mg in immune response to vaccines, especially in the elderly. This study will focus on the role of Zn and Mg in cellular immune response after the vaccine in the elderly.

Methods

Design

This study was approved by the ethics committee of Universitas Brawijaya with ethic number 134/EC/KEPK – S3/06/2023. The study was conducted using an analytical observational study with a prospective cohort design. Inclusion criteria are elderly (age ≥ 60) who get a second COVID-19 vaccination with inactivated COVID-19 vaccine in Malang, East Java, Indonesia. Exclusion criteria are subjects that have already suffered from COVID-19 before, have gotten a third vaccination dose, or have chronic kidney disease. The number of subjects in this study was determined based on Dahlan's non-experimental correlation sample size formula to provide better results. The minimum number of subjects required is 47 subjects, but the aim was to get at least 80 subjects. All subjects signed written informed consent forms before taking blood samples. A venous blood sample was taken six and 24 weeks after vaccination and then will be centrifuged. The serum will be separated and stored at -80 °C.

Assessment

Blood samples were taken six weeks after vaccination and tested for Zn, Mg, and Neopterin serum. 24-week blood samples were tested for Neopterin serum. Zn and Mg serum were measured using the inductively coupled plasma mass spectrometry (ICP-MS) method in PT. Angler BiochemLab Surabaya, East Java, Indonesia. Normal serum Zn level is 60 – 120 µg/dL, while normal serum Mg level is 1.7 – 2.2 mg/dL (Barman *et al.,* 2020; Sabah *et al.,* 2023). Neopterin serum was measured using an enzyme-linked immunosorbent assay (ELISA) kit from BT Lab® in the Parasitology Laboratory of Universitas Brawijaya. Results from ICP-MS and ELISA were tabulated manually in Microsoft Excel and then analysed with SPSS 26.0 for Windows. The ethics committee of Universitas Brawijaya approved this study with ethic number 134/EC/KEPK – S3/06/2023.

Results

Eighty-eight elderly people were enrolled in this study in week six following vaccination. However, in week 24, only 73 subjects participated in this study since the rest had already caught COVID-19 or had already gotten a third dose of the vaccine. The characteristics of the subjects are shown in Table 1. There is no significant difference in the number of females and males among all subjects. Forty-eight of 88 subjects have comorbidities, listed below in Table 1. Among 88 subjects, 79 (89.8%) had Zn deficiency or insufficiency, while Mg deficiency was found in 65 (73.9%).

Table I: Characteristics of the subjects

Variables	N = 88	*P*-value
Age (year old), mean (min-max)	68.91 (60-94)	
Gender		
Female, n (%)	50 (56.8)	0.201
Male, n (%)	38 (33.2)	
Comorbidities, n (%)		
Hypertension	28 (31.8)	
Diabetes mellitus	11 (12.5)	
Dyslipidemia	3 (3.4)	
History of CVA or ACS	4 (4.5)	
Asthma	2 (2.3)	
None	40 (45.5)	
Zn level (µg/dL), N (%)		
Deficiency (< 60 µg/dL)	79 (89.8)	
Insufficiency (60 – 80 µg/dL)	5 (5.6)	
Normal (80 – 120 µg/dL)	2 (2.3)	
High (> 120 µg/dL)	2 (2.3)	
Mg level (µg/dL), N (%)		
Deficiency (< 1,700 µg/dL)	65 (73.9)	
Normal (1,700 – 2,200 µg/dL)	21 (23.9)	
High (> 2,200 µg/dL)	2 (2.3)	

ACS = arterial coronary syndrome; CVA = cerebrovascular accident

The mean, standard deviation, minimum, and maximum levels of Zn and Mg serum levels are shown in Table II. The mean levels of Zn and Mg are both low-considered subjects in this study, and they predominantly have Zn and Mg deficiency. The Spearman correlation test between Zn and Mg shows a significant positive correlation between Zn and Mg with a p-value < 0.001 and r = 0.439.

Table II: Characteristics of the subjects

Parameter	Mean	SD	Min	Max
Zn (µg/dL)	42.626	32.55	10.5	236
Mg (µg/dL)	1,560.13	338.55	712	3,260

SD = standard deviation

Neopterin levels in weeks six and 24 after vaccination are shown in Table III. Wilcoxon test between week six and 24 neopterin level shows a significant difference with p-value < 0.05. This means there is a significant decline in neopterin levels between week six to week 24. The decline of the neopterin level is calculated by subtracting the week six neopterin level from the week 24 neopterin level.

Table III: Neopterin levels among elderly subjects

Parameter	Mean	SD	Min	Max	*P*-value
Week 6 (nmol/L)	6.29	4.36	0.03	24.55	0.003*
Week 24 (nmol/L)	4.79	2.86	0.11	17.69	

SD = standard deviation, *p-value is significant.

Table IV and Figure 1 show the correlation between the decline of neopterin level after 18 weeks and Mg. The decline of neopterin level is negatively correlated with the Mg level. This means Mg deficiency is correlated with a faster decline of neopterin level, although Zn deficiency did not show a similar result.

Table IV: Correlation between decline of neopterin level with zinc and magnesium

Correlations	*P*-value	R
The decline of Neopterin and Zn	0.839	0.024
The decline of Neopterin and Mg	0.011*	-0.296

*P-value is significant.

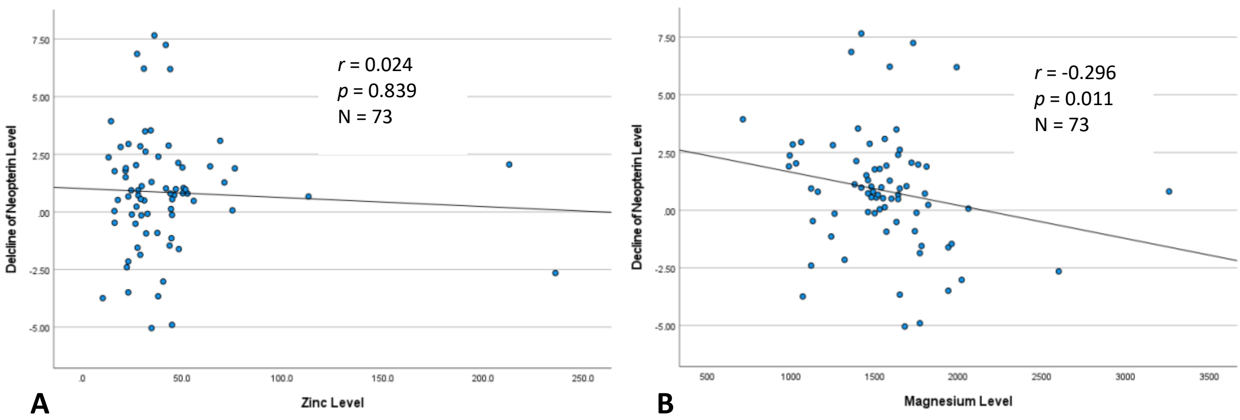

Figure 1: Scatter plot correlation between decline of neopterin level with (A) serum zinc level and (B) serum magnesium level

Discussion

From this study, the authors found that almost 90% of the elderly population have Zn deficiency, and more than 70% of the elderly have Mg deficiency. This finding is far greater than other studies that reported the prevalence of Zn deficiency is 28-61% (Haase *et al.,* 2006) and the prevalence of Mg deficiency is 27-29% in the elderly (Gautam & Khapung, 2021; Kisters *et al.,* 2021). However, there are some different methods used in those studies and the current study. A review by Haase and colleagues reported two studies that observed elderly patients hospitalised in Belgium and France, which are developed countries, differ from this study in Indonesia (Haase *et al.,* 2006). A study by Gautam and Khapung and by Kisters and colleagues observed elderly patients in hospitals in Nepal and Germany, respectively; thus, it is different from the subjects in this study (Gautam & Khapung, 2021). On the other hand, patients may have some diseases that can alter Zn or Mg metabolism, but they are checked routinely by medical healthcare; thus, nutritional status can be maintained.

Thus, the result of that study could be different from that of this study. Also, the subjects of this study are predominantly elderly with low socioeconomic status, not to mention their educational background (supplementary data). In Indonesia, dietary habits are low in carbohydrates and protein (Boedhi-Darmojo, 2002; Rachmi *et al.,* 2021). Thus, there is only a limited amount of Zn, which is abundant in meat-based food. Plant-based foods rich in Zn also contain high phytate, inhibiting Zinc absorption (Hambidge & Krebs, 2007; Ahmad *et al.,* 2018; Maares & Haase, 2020).

On the other hand, foods rich in Mg are predominantly plant-based. Unfortunately, they also contain high phytates, which inhibit Mg absorption (Razzaque, 2018). Moreover, chicken meat contains less Zn and Mg than red meat, which is more expensive and thus less affordable (Djinovic-Stojanovic *et al.,* 2017). This fact is in line with the result of the study in which the authors found Zn deficiency is more frequent than Mg deficiency in elderly with poor socioeconomic status. A previous study by Boedi-Darmojo found that elderly reported that the elderly tended to reduce their diet and also consume rice with mostly vegetables every day (Boedhi-Darmojo, 2002). The authors found a positive correlation between Zn and Mg levels in this study. This finding may be caused by decreased absorption of Zn and Mg because of dietary habits with a plant-based diet that contains high phytate. Also, Zn and Mg shared dietary resources and absorption mechanisms.

Neopterin is pteridine produced by macrophages when it is stimulated by interferon-gamma. Neopterin is superior to interferon-gamma since it is more stable, has a longer half-life, and is small and thus can be found in peripheral blood. Increased neopterin level strongly correlates with cellular immune activity (Gieseg *et al.,* 2018). Increased neopterin levels are found after measles, mumps, rubella, and virus vaccine vaccination. It is reported that increased neopterin levels reflected cytotoxic T-cell activity. Elevated neopterin level is reported to be correlated with successful vaccination (Eisenhut, 2013).

This study found a negative correlation between Mg level and decline of neopterin level between weeks six and 24 after vaccination. After vaccination with an inactivated viral vaccine, antigen-presenting cells will activate CD4 or CD8 T cells to initiate a cellular immune response and B cells to produce antibodies (Liu & Ye, 2022). Coman and colleagues reported hypomagnesemia reduces CD4 and CD8 T cell activation (Coman *et al.,* 2023). CD4 and CD8 T cells are two of the main producers of interferon-gamma (Jorgovanovic *et al.,* 2020), which later activate macrophages and produce neopterin (Gieseg *et al.,* 2018). Altogether, these findings show that Mg is important in regulating cellular immunity. However, until now, no evidence has been reported about the role of Mg in the cellular immune response to vaccines. This study may be the first study reporting a correlation between deficient Mg and a faster decline of the cellular immune response, measured by neopterin, after vaccination.

This study found no correlation between Zn level and decline of neopterin level between weeks six and 24 after vaccination. Neopterin is a product of activated macrophage by interferon-gamma in inflammatory conditions. However, in deficiency Zn, macrophage's inflammatory response can still be elicited by activating aberrant immune cells or altering promoter methylation. Also, Zn increases the lifespan of macrophages but does not affect macrophage signalling to interferon-gamma (Gao *et al.,* 2018). Thus, Zn deficiency may not alter neopterin levels. So far, Zn deficiency is associated with reducing immune function, but when it is associated with vaccines, most studies only correlate Zn level with antibody level. A study by Albert and colleagues reported that Zn supplementation improves seroconversion after the oral cholera vaccine (Albert *et al.,* 2003). A study by Das and colleagues found that Zn status is correlated with an immune response after the vaccine in children (Das *et al.,* 2021). However, in the study by Das and colleagues , the immune response was measured at the antibody level (humoral immune) and did not measure the cellular immune response. Kreft and colleagues also found that Zn deficiency alters immune response after the diphtheria vaccine in elderly with chronic kidney failure (Kreft *et al.,* 2000). However, unlike our study, Kreft and colleagues study, the immune response measured is the humoral immune response. Furthermore, subjects are not healthy (chronic kidney disease); thus, it may influence immune response after the vaccine. Moreover, Kreft and colleagues only studied 16 subjects, a relatively small number of subjects. In this study, the authors also measured neopterin levels as a cellular immunity marker. Thus, this is the first study report on the correlation between Zn level and cellular immune response. Zn has previously been reported to influence humoral vaccine response. Still, in this study, the authors did not find a correlation between Zn level and decreased cellular immune response after the vaccine.

This study has limitations since Zn and Mg levels are measured only in serum and are not intracellular. Biologically active Zn is found intracellular, including immune cells. Mg is predominantly found intracellular; thus, serum Mg does not reflect the actual level of Mg in the body. However, most subjects have low Zn and Mg levels in serum; thus, this will not affect the analysis. Additionally, this study only measured neopterin levels and not immune cell activity. Further study is needed to analyse the correlation between T cell activity and Zn and Mg levels.

Conclusion

The prevalence of Mg deficiency is correlated with a faster decline of neopterin levels after vaccination. Zn deficiency is not correlated with a decline in neopterin level after the vaccine. As far as the authors know, this is the first study that reports the association between Zn and Mg with neopterin, reflecting a cellular immune response to the vaccine. This finding may suggest the importance of enough magnesium to boost the neopterin level as a marker of cellular immune response to vaccines.

Acknowledgement

All authors thank the Bhirawa Bhakti Hospital Malang staff for their help in this study.

Source of funding

This study is supported by the Ministry of Education, Culture, Research and Technology of Indonesia.

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