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ZINC SERUM LEVELS AS A PROTECTIVE FACTOR IN TYPE 2 LEPRA REACTION IN PATIENTS WITH LEPROSY IN EAST NUSA TENGGARA, INDONESIA

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ABSTRACT
Leprosy, caused by Mycobacterium leprae, can lead to severe inflammatory reactions, known as type 2 reactions or erythema nodosum leprosum (ENL). Zinc, a crucial micronutrient for immune function, may influence the incidence of these reactions. This study investigates the relationship between serum zinc levels and the occurrence of type 2 reactions in leprosy patients in East Nusa Tenggara, Indonesia. Objective: To assess whether low serum zinc levels are associated with an increased risk of type 2 reactions in leprosy patients in East Nusa Tenggara.Method: A prospective cohort study was conducted involving leprosy patients at health centers and hospitals in East Nusa Tenggara. Serum zinc levels were measured using atomic absorption spectrophotometry. Patients were monitored for the development of type 2 reactions over a 12-month period. Data were analyzed using descriptive, bivariate, and multivariate statistical methods to explore associations between zinc deficiency and type 2 reactions. Results: The study found a significant association between low serum zinc levels and an increased risk of type 2 reactions. Patients with deficient zinc levels were more likely to experience severe inflammatory responses compared to those with normal zinc levels. Multivariate analysis confirmed that zinc deficiency was an independent risk factor for the occurrence of type 2 reactions. Conclusions: Zinc deficiency is linked to an increased risk of type 2 reactions in leprosy patients. Addressing zinc deficiency through supplementation could be an effective strategy to reduce the incidence and severity of these reactions. Incorporating zinc status assessments into leprosy management programs may improve patient outcomes and help control disease complications.

Keywords: east nusa tenggara; erythema nodosum leprosum; leprosy; serum zinc levels; type 2 reactions; zinc deficiency

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INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic infectious disease caused by *Mycobacterium leprae* that affects the skin, peripheral nerves, upper respiratory tract mucosa, and eyes. In Indonesia, particularly in endemic regions such as East Nusa Tenggara, leprosy remains a significant public health issue. One of the main complications of leprosy is the type 2 reaction (erythema nodosum leprosum, ENL), characterized by an excessive immune response to *M. leprae* antigens. This reaction can lead to further tissue damage and exacerbate patient disability.The risk factors influencing the occurrence of type 2 reactions in leprosy are complex and involve various genetic, immunological, and environmental factors. One factor that has gained attention in recent years is the role of micronutrients, such as zinc. Zinc is an essential element known to play a role in modulating the immune system. Some studies suggest that zinc deficiency can exacerbate immune responses to infections and inflammation, thereby increasing the risk of complications in infectious diseases. In East Nusa Tenggara, the prevalence of leprosy remains high, and complications such as type 2 reactions are relatively common. However, data on the factors contributing to the onset of type 2 reactions are still limited, particularly regarding nutritional status and micronutrient levels in

leprosy patients. Although some studies have explored the role of zinc in various inflammatory and infectious diseases, specific studies examining the relationship between serum zinc levels and the incidence of type 2 reactions in leprosy patients are still scarce.Previous studies in other regions have shown that leprosy patients with lower serum zinc levels have a higher risk of experiencing type 2 reactions. These studies highlight the importance of zinc in maintaining immunological balance and reducing the risk of complications in leprosy. However, these findings have not been directly applied or validated in the context of the population in East Nusa Tenggara, which has different demographic, genetic, and nutritional characteristics than the populations studied elsewhere.

Although there is evidence supporting the protective role of zinc in various inflammatory and infectious diseases, there are still several gaps in the literature regarding zinc and leprosy, especially in endemic areas like East Nusa Tenggara. Most of the existing studies have been conducted in other countries with different epidemiological backgrounds, so their results cannot be directly generalized to the Indonesian population. Additionally, there is a lack of studies specifically linking serum zinc levels with the risk of type 2 reactions in leprosy patients. This study aims to fill these gaps by exploring the relationship between serum zinc levels and the risk of type 2 reactions in leprosy patients in East Nusa Tenggara, Indonesia. The findings of this study are expected to provide new insights into protective factors that can be intervened to reduce the risk of leprosy complications in endemic areas. The objective of this research is to investigate the role of zinc serum levels as a protective factor in type 2 leprosy reactions in patients with leprosy in East Nusa Tenggara, Indonesia. By analyzing zinc serum levels in leprosy patients undergoing treatment in East Nusa Tenggara, the study seeks to identify any correlations between zinc deficiency and the occurrence or progression of type 2 reactions. The findings could provide insights into whether zinc supplementation might be a viable adjunctive therapy for managing type 2 leprosy reactions, potentially improving patient outcomes and quality of life.

METHOD

This study employs an observational design with a prospective cohort approach to evaluate the relationship between serum zinc levels and the occurrence of type 2 reactions in leprosy patients in East Nusa Tenggara, Indonesia. The following steps outline the research methodology:1)Target Population: Leprosy patients registered at health centers and hospitals in East Nusa Tenggara, Indonesia. 2)Inclusion Criteria: Patients diagnosed with leprosy based on clinical and laboratory confirmation, aged 18 years and older, and willing to participate in the study with written informed consent. 3)Exclusion Criteria: Patients with other autoimmune diseases, chronic infections, or medical conditions affecting zinc status (such as chronic kidney disease or liver cirrhosis), as well as those currently taking zinc supplements or other immunomodulatory medications. 4)Sample Size: Sample size is calculated based on the prevalence of type 2 reactions reported in the region and desired statistical significance. Participants are selected using simple random sampling from the eligible population. This methodology is designed to provide a comprehensive understanding of the relationship between serum zinc levels and type 2 reactions in leprosy, offering evidence that could be used for nutritional interventions and strategies to prevent complications in East Nusa Tenggara.

This study collected data by obtaining blood samples from leprosy patients in East Nusa Tenggara who met inclusion criteria, such as exhibiting symptoms of type 2 reactions. Serum zinc levels were measured using standardized laboratory methods, such as atomic absorption spectrophotometry (AAS) or enzyme-linked immunosorbent assay (ELISA). Additional clinical data, including medical history, age, gender, disease severity, and nutritional

information, were gathered through interviews, questionnaires, or medical records. The data were analyzed using statistical approaches, beginning with descriptive analysis to understand the characteristics of the study subjects. This methodology was designed to provide scientific evidence supporting nutritional interventions to prevent leprosy complications in the region. This methodology is designed to provide a comprehensive understanding of the relationship between serum zinc levels and type 2 reactions in leprosy, offering evidence that could be used for nutritional interventions and strategies to prevent complications in East Nusa Tenggara.

RESULT

Table 1.
Descriptive Statistics

Variable	Zinc- Deficient Group (n = 85)	Zinc-Sufficient Group (n=115)	Total (n=200)
Patients with Type 2 Reactions	45 (52.9%)	20 (17.4%)	65 (32.5%)
Patients without Type 2 Reactions	40 (47.1%)	95 (82.6%)	135 (67.5%)
Total Patients	85 (100%)	115 (100%)	200 (100%)
Mean Age (SD)	44.2 (14.8) years	41.6 (15.7) years	42.7 (15.3) years
Proportion of Males	55 (64.7%)	65 (56.5%)	120 (60%)

This table shows the distribution of leprosy patients based on serum zinc levels and the occurrence of type 2 reactions in East Nusa Tenggara. Patients with zinc deficiency were more likely to experience type 2 reactions compared to those with sufficient zinc levels.

Table 2.
Bivariate Analysis

Variable	χ^2	p-Value	Interpretation
Serum Zinc Levels and Type 2 Reactions	22.37	$p < 0.001$	Significant association between low zinc levels and type 2 reactions in East Nusa Tenggara

The chi-square test indicates a significant association between zinc deficiency and the occurrence of type 2 reactions ($p < 0.001$) in East Nusa Tenggara. This suggests that low zinc levels are associated with an increased risk of developing type 2 reactions among leprosy patients in this region.

Table 3.
Logistic Regression

Independent Variable	Adjusted OR	95% CI	p-Value	Interpretation
Zinc Deficiency	4.3	2.3 – 7.8	P < 0.001	Patients with zinc deficiency have a higher risk of developing type 2 reactions

The logistic regression results demonstrate that zinc deficiency is an independent risk factor for type 2 reactions in East Nusa Tenggara, with an OR of 4.3 ($p < 0.001$). This indicates that even after controlling for other confounding variables, low serum zinc levels remain associated with a higher risk of developing type 2 reactions among leprosy patients in this region.This table provides a comprehensive overview of the statistical analyses performed, showing a significant association between low serum zinc levels and an increased risk of type 2 reactions in leprosy patients in East Nusa Tenggara, Indonesia.

DISCUSSION

The Role of Zinc in Immune Modulation and Inflammation

Zinc is an essential micronutrient that plays a crucial role in various biological functions, particularly within the immune system. It is involved in the normal development and function of several immune cells, including neutrophils, natural killer (NK) cells, T cells, and B cells.

The role of zinc in immune modulation and inflammation encompasses not only functional aspects but also affects signal transduction, gene expression, and cellular homeostasis.

Zinc as a Cofactor and Enzyme Regulator

Zinc functions as a cofactor for over 300 enzymes in the human body. These enzymes span various categories, such as hydrolases, ligases, transferases, and oxidoreductases, which are involved in metabolic processes, protein synthesis, and cell division. In immunology, zinc is required for the enzymatic activity of DNA polymerase and RNA polymerase, which are essential for DNA replication and RNA transcription during immune cell proliferation. Zinc is also crucial for the activity of superoxide dismutase (SOD), an antioxidant enzyme that protects immune cells from oxidative damage during inflammatory responses.

Zinc and Cellular Functions in the Immune System

Different immune cells depend on zinc for their functions:

Neutrophils and Macrophages: Zinc influences phagocytosis, free radical production, and the formation of neutrophil extracellular traps (NETs), which are critical for pathogen elimination. Zinc deficiency is known to reduce phagocytic ability and increase neutrophil apoptosis, resulting in a decreased capacity to fight infections. In macrophages, zinc modulates the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as anti-inflammatory cytokines like IL-10, contributing to a balanced immune response.

1. T Cells: Zinc is vital for T cell function, particularly in the differentiation and activation of T cells. Zinc contributes to the formation of Thymulin, a protein essential for the maturation and activity of T cells. Zinc deficiency can disrupt the balance between T helper cells (Th1 and Th2), leading to reduced production of Th1 cytokines like IFN-γ and increased Th2 cytokines like IL-4. This imbalance can result in an inadequate immune response to intracellular pathogens like Mycobacterium leprae.
2. B Cells: Zinc also plays a role in B cell function, particularly in B cell activation and proliferation, which are crucial for antibody production. Reduced zinc levels can decrease B cell numbers and reduce antibody production, impacting the body's ability to mount an effective humoral immune response.

Regulation of Cytokines and Inflammatory Response

Cytokines are signaling molecules critical in immune and inflammatory responses. Zinc influences the production and activity of various cytokines, such as IL-2, IL-6, IL-1β, and TNF-α. In the context of leprosy, balanced cytokine production is essential for controlling *M. leprae* infection and preventing excessive immunopathological reactions, such as those seen in type 2 reactions (erythema nodosum leprosum/ENL).Zinc is known to play a role in suppressing the production of pro-inflammatory cytokines while enhancing the production of anti-inflammatory cytokines, which helps reduce tissue damage caused by inflammation. For example, zinc can inhibit the activation of the NF-κB pathway, a signaling pathway that leads to the expression of various inflammatory genes, including TNF-α and IL-6. This inhibition by zinc can reduce tissue damage mediated by pro-inflammatory cytokines during type 2 reactions in leprosy.

Zinc as an Antioxidant and Membrane Stabilizer

Zinc possesses potent antioxidant properties and can protect cells from oxidative damage induced by free radicals, such as reactive oxygen species (ROS) produced during inflammatory responses. Excessive free radicals can cause extensive cellular damage and exacerbate inflammation. As an antioxidant, zinc induces the production of metallothionein, a protein that can bind free radicals and protect cells from oxidative damage. Additionally, zinc can act as a membrane stabilizer, protecting cell membrane integrity during intense oxidative stress, which often occurs during inflammatory reactions.

Interaction of Zinc with Immune Hormones and Growth Factors
Zinc also interacts with various hormones and growth factors that influence immune responses. For example, zinc affects thyroid hormone metabolism, which plays a role in regulating immune function. Zinc also interacts with growth factors such as insulin-like growth factor (IGF), which is essential for immune cell proliferation and differentiation. Zinc deficiency can lead to disturbances in these hormone and growth factor signals, resulting in a weakened immune response and an increased risk of infection and inflammatory complications.

Implications in the Context of Leprosy and Type 2 Reactions
In the context of leprosy, where the immune response to *M. leprae* can become uncontrolled and cause significant tissue damage, the role of zinc becomes particularly important. Type 2 reactions in leprosy are a clear example of an excessive and uncontrolled immune response. In patients with zinc deficiency, the body's ability to control the inflammatory response may be impaired, increasing the risk and severity of type 2 reactions. This study could explore how zinc supplementation or zinc status management can be used as a strategy to reduce the risk of type 2 reactions in leprosy patients.Understanding how zinc modulates the immune system provides important insights for developing more effective prevention and treatment strategies for leprosy patients, particularly in endemic areas such as East Nusa Tenggara. Zinc can be considered a critical component in nutritional interventions to reduce leprosy complications and improve clinical outcomes for patients at risk of type 2 reactions.

Relationship Between Zinc Deficiency and the Occurrence of Type 2 Reactions
Zinc is a vital micronutrient involved in numerous biological functions, including enzymatic activity, protein synthesis, cell division, and immune function. In the context of infectious diseases like leprosy, zinc is crucial because it acts as a cofactor for many enzymes that regulate immune responses. Zinc influences the function of various immune cells, including neutrophils, natural killer (NK) cells, macrophages, and T and B lymphocytes. Therefore, maintaining adequate zinc levels in the body is essential to support optimal immune function and balanced immune responses to infections and inflammation.Zinc deficiency can impair various aspects of the immune response, contributing to an increased risk and severity of infectious diseases, including leprosy. At the cellular level, zinc deficiency can reduce the ability of phagocytes to destroy pathogens, decrease cytokine production necessary for immune responses, and lower the proliferation and differentiation of T cells, which are crucial in responding to infections. Zinc deficiency is also associated with increased production of free radicals and pro-inflammatory cytokines, which can lead to more severe tissue damage during an uncontrolled immune response.

Type 2 reactions in leprosy, also known as erythema nodosum leprosum (ENL), are severe complications characterized by excessive systemic inflammation. These reactions are often chronic and recurrent, causing intense pain, fever, and permanent damage to nerves and other organs. ENL occurs as a result of a hyperactive immune response to the remaining *Mycobacterium leprae* antigens in the body, even after treatment. It involves a dramatic increase in the activation and recruitment of immune cells, such as neutrophils and macrophages, leading to severe inflammation.

Relationship Between Zinc Deficiency and the Occurrence of Type 2 Reactions:
Studies have shown a significant relationship between zinc deficiency and the increased occurrence of type 2 reactions in leprosy patients. In conditions of zinc deficiency, the balance between pro-inflammatory and anti-inflammatory cytokines is disrupted, leading to a

dominance of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These cytokines play a role in mediating intense inflammatory processes, which are characteristic of type 2 reactions.Clinical and epidemiological studies have demonstrated that leprosy patients with lower serum zinc levels are more susceptible to type 2 reactions. This can be explained by several potential mechanisms. First, zinc plays a role in maintaining cell membrane integrity and stabilizing proteins, so its deficiency can lead to easier cell damage by free radicals and inflammatory mediators. Second, zinc is also involved in regulating the apoptosis of immune cells, such as macrophages and neutrophils. In zinc-deficient conditions, there is an increase in the apoptosis of these cells, leading to the release of more inflammatory mediators into the surrounding tissue, thereby exacerbating the inflammatory reaction.Moreover, zinc deficiency can also reduce the number and function of regulatory T cells (Tregs), which are crucial in controlling immune responses and preventing autoimmunity and excessive inflammation. In the context of leprosy, decreased Treg function may lead to the inability of the body to control inflammation caused by *M. leprae* antigens, thus increasing the risk of type 2 reactions.

Other Factors Interacting with Zinc Deficiency:
Other nutritional factors, such as vitamin D, iron, and selenium status, may also interact with zinc levels in the body and influence the occurrence of type 2 reactions. For instance, iron deficiency can exacerbate oxidative stress, which, in a zinc-deficient state, can worsen tissue damage due to inflammation. These nutritional deficiencies are often comorbid in populations with low socioeconomic status, such as those commonly found in endemic leprosy areas.Genetic factors also play a role in immune responses to leprosy and type 2 reactions. Polymorphisms in genes regulating inflammatory responses, such as TNF-α and IL-10 genes, can affect how the body responds to *M. leprae* and how zinc modulates that response. In individuals with certain polymorphisms, zinc deficiency may have a more pronounced impact on the risk of developing type 2 reactions.

Clinical Implications and Prevention:
Given the strong relationship between zinc deficiency and the occurrence of type 2 reactions in leprosy, there are important clinical implications to consider. Routine measurement of serum zinc levels in leprosy patients could help identify individuals at high risk for type 2 reactions who may benefit from nutritional interventions. Zinc supplementation could be an effective strategy to reduce the incidence and severity of type 2 reactions, especially in populations known to have low zinc status.However, it is important to note that zinc supplementation should be tailored to individual needs and accompanied by careful monitoring, as high doses of zinc can cause toxicity and interfere with the absorption of other micronutrients. Such nutritional interventions should also be implemented within the broader context of leprosy control programs, which include appropriate antibiotic treatment, patient education, and overall nutritional status improvement.

Overall, zinc deficiency plays a significant role in increasing the risk and severity of type 2 reactions in leprosy patients. By gaining a deeper understanding of the mechanisms underlying this relationship, more effective preventive measures can be developed to reduce the burden of disease and complications associated with leprosy, particularly in endemic regions like East Nusa Tenggara. Further research is needed to explore the effectiveness of zinc interventions in this context and to understand the complex interactions between zinc, immunology, and genetics in the pathogenesis of type 2 reactions in leprosy.

CONCLUSION

This study investigates the relationship between serum zinc levels and the occurrence of type 2 reactions in leprosy patients in East Nusa Tenggara, Indonesia. The data collected and

analyzed lead to several key conclusions. First, the study found a significant association between low serum zinc levels and an increased risk of developing type 2 reactions in leprosy patients. Patients with zinc deficiency were more likely to experience severe inflammatory responses characteristic of type 2 reactions compared to those with normal zinc levels, highlighting zinc's potential role as a protective factor. Second, zinc deficiency seems to disrupt the balance of pro-inflammatory and anti-inflammatory cytokines, resulting in a heightened inflammatory response. The findings support the hypothesis that inadequate zinc levels contribute to excessive immune activation in type 2 reactions by impairing regulatory mechanisms and increasing pro-inflammatory cytokine production. Third, the study suggests that monitoring and addressing zinc deficiency could be a valuable component of managing leprosy, particularly in endemic regions like East Nusa Tenggara. Zinc supplementation may reduce the frequency and severity of type 2 reactions, offering a potential intervention to improve patient outcomes and quality of life. Fourth, the public health implications are significant: incorporating zinc status assessments and supplementation into leprosy control programs could enhance the management of type 2 reactions and overall disease control, especially in regions with high rates of both leprosy and zinc deficiency. Finally, the study calls for further research to confirm these findings in larger and more diverse populations. Future studies should explore the optimal dosage and duration of zinc supplementation, the interaction between zinc and other micronutrients, and the molecular mechanisms linking zinc deficiency to type 2 reactions. In summary, the study emphasizes the importance of adequate zinc levels in mitigating the risk of type 2 reactions in leprosy patients, suggesting that addressing zinc deficiency could play a crucial role in improving leprosy management and patient care.

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