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THE ROLE OF VITAMINS, MINERALS, AND NUTRITION IN LEPROSY PATIENTS: A REVIEW

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ABSTRACT
Leprosy, is a chronic infectious disease caused by Mycobacterium leprae, an airborne intracellular bacillus and is considered a disease of poverty. Leprosy, with its associated physical and social morbidity, results in economic conditions that lead to malnutrition. The purpose of this study was to explore the role of vitamins, minerals, and nutrition in leprosy patients. The method used in this study was to explore articles and theories related to vitamins, minerals, nutrition and leprosy patients. The results of this study are that decreased antioxidant levels can lead to increased oxidative stress and complications of infectious diseases and leprosy. Because these nutrients have regulatory effects on innate and adaptive immune responses, a perfect balance in their concentrations is important to improve the immune response to pathogens.

Keywords: diet diversity; leprosy; minerals; nutritions; vitamin

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INTRODUCTION

Leprosy is a neglected tropical disease (NTD) that predominates in resource-constrained communities of the rural tropics. Despite being eliminated as a public health concern by the World Health Organization (WHO) in 2000, nearly 200,000 active leprosy cases still occur annually. The pathogen, *Mycobacterium leprae*, prevails in low- and middle-income countries (LMICs) where socioeconomic barriers can significantly reduce treatment adherence. Prevalence of leprosy continues to rise in nonendemic regions due to increasing travel and migration; thus, the disease is of increasing relevance from a Western perspective (Klowak & Boggild, 2022). Patients experience hypopigmented cutaneous lesions, disabling sensory neuropathies and debilitating peripheral neuropathic pain (PNP), often leading to stigma and social ostracization. Standard pharmacological treatment of PNP using antidepressants, anticonvulsants and opioids results in a less than 30% reduction of pain at best. In addition, a significant side-effect profile including anticholinergic effects, dizziness, confusion, hypertension and weight fluctuation contribute to poor treatment adherence overall. Likewise, despite the development of effective therapeutics *via* multidrug therapy (MDT) for leprosy, many barriers to treatment adherence and effective immunological control of the pathogen are still evident, due to its complex relationship with both nutrition and immunity (MacRae et al., 2018).

Socioeconomic barriers, such as disability-related social stigma and rampant nutritional deficiencies, have resulted in heightened disease severity. Comprehensive systematic reviews assessing these relationships suggest that nutrient deficiency is common in leprosy-endemic regions, potentially contributing to pathogenesis and severity. Nutrient deficiencies have been shown to weaken the immune system, resulting in a diminished host immune response to invading pathogens. This phenomenon is additionally enhanced by leprosy's innate ability to increase host oxidative stress (Somar et al., 2020). Given these extensive barriers, patients with leprosy continue to experience a reduced quality of life even with adequate access to gold standard therapeutics. In the absence of effective pharmaceuticals for PNP, alternative interventions must be explored to reduce overall morbidity (Dennison et al., 2021).

Pathogen elimination is predicated upon a balanced immune response in which inflammatory mediators aid in host recovery while antioxidant substances protect the host environment. Supplementation of vitamins A, C, D, E and B12 and minerals zinc, magnesium and selenium in leprosy cohorts, where nutrient deficiency is common, has been shown to enhance the antioxidant response and decrease morbidity overall (de Oliveira et al., 2020). Nutrient supplementation has been instrumental in reducing host oxidative stress, strengthening the immune system and mitigating potential adverse events in leprosy. Likewise, dietary interventions have been specifically shown to reduce overall symptomatology and improve the quality of life of individuals suffering from PNP due to diabetes, a significant and common comorbidity of leprosy. Overall, strategies seeking to improve physiological wellness, including those that reduce inflammation and enhance immune responsiveness to neurotoxic factors, are powerful tools that can influence underlying neuropathic etiologies. This review seeks to synthesize this literature surrounding the intersection of nutrition, PNP and leprosy, providing a knowledge base for further development of nonpharmacological therapeutics for leprous PNP (Ghavami et al., 2018). The purpose of this study was to explore the role of vitamins, minerals, and nutrition in leprosy patients. Because these nutrients have regulatory effects on innate and adaptive immune responses, a perfect balance in their concentrations is important to improve the immune response to pathogens.

METHOD

This study is a study by tracing articles and cases that meet the inclusion criteria of the role of vitamins, minerals and nutrition in leprosy patients. After several articles were found, conclusions were drawn from several articles by making points related to the inclusion criteria. After several articles were found, conclusions were drawn from several articles by making points related to the inclusion criteria, namely vitamins, minerals and nutrition and leprosy patients. The results of this study can be developed to the next research stage using a more accurate method in accordance with the research results desired by the researcher.

RESULT

The results of the article search found that several vitamins and minerals are related to the healing of leprosy patients.The decrease in serum vitamin E and vitamin C levels may be due to their increased use in scavenging lipid peroxides. Vitamins with low antioxidant levels may support the involvement of oxidative stress in leprosy. As the pathological spectrum of leprosy shifts from the TT stage to the LL stage, there is a progressive decrease in serum vitamin E and vitamin C levels (Klowak & Boggild, 2022). Since these vitamins are known for their immune stimulant actions and cell-mediated immunity is severely compromised in the LL leprosy group, the sharp decrease in plasma vitamin E and C concentrations may be associated with the immunocompromised state found in this leprosy group. Low antioxidant levels may expose tissues to oxidative stress-mediated modifications of cells and

biomolecules, and may mediate inflammatory episodes, organ damage, depressed cell-mediated immune responses, and neurodegeneration in leprosy patients (Trimbake et al., 2013). Antioxidants such as vitamin C, vitamin E, and carotenoids present in fresh fruits and leafy vegetables provide protection against oxidative damage to cells and biomolecules. Since leprosy patients are mostly from low socioeconomic status, they do not get antioxidant-rich foods such as fresh fruits and leafy vegetables on a daily basis. Thus, the increased lipid peroxidation observed in leprosy patients can also be attributed largely to the lack of vitamins in the diet (Klowak & Boggild, 2023; Trimbake et al., 2013).

DISCUSSION

Vitamin

Vitamin A is an important component that plays a vital role in the immune system because it regulates several immune responses. Research shows that leprosy patients have low levels of vitamin A. Vitamin A deficiency is associated with reduced phagocytic activity in macrophages and decreased Natural Killer Cell (NK) activity. A study showed lower levels of vitamin A in the MB type, especially in L patients (Vázquez et al., 2014). Vitamin A intake increases IL-10 production and induces anti-inflammatory responses, inhibiting the production of IL-12 and TNF-α, which are involved in the development of leprosy (Kimberly et al., 2024). Vitamin A can be obtained from food sources, such as chicken liver, eggs, milk, red or citrus fruits, and vegetables, as well as through oral supplementation (Klowak & Boggild, 2023; Vázquez et al., 2014). Vitamin C, as a powerful antioxidant, has an important role in improving the human immune system. Vitamin C has the potential to reduce oxidative stress and affect the phagocytic ability of macrophages, interferon production, inhibit DAMP replication, and increase T lymphocyte maturation. A study showed that leprosy patients have lower levels of vitamin C compared to healthy individuals (Khalid et al., 2022). These findings may be related to increased oxidative stress due to leprosy infection, where most leprosy patients are malnourished, as this may be a contributing factor to low serum vitamin C levels (Hazlianda et al., 2023; Khalid et al., 2022; Kimberly et al., 2024).

Like vitamin A, vitamin D can modulate the immune system to fight various pathogens, including M. leprae. Vitamin D enhances phagocytic activity and stimulates the production of antimicrobial peptides in infected macrophages and neutrophils. These peptides have immunomodulatory properties for the innate immune system and act as immunomodulators through the Vitamin D Receptor (VDR) in macrophages. Vitamin D has been shown to activate macrophages by binding to Toll-like Receptors (TLRs), thereby facilitating the elimination of Mycobacterium, resulting in inhibition of Th1 activity (reduction of IL-12, IFN-γ, IL-6, IL-8, TNF-α, and IL-9) (Klowak & Boggild, 2022), and increased Th2 activation (IL-4, IL-5, and IL-10) (Kimberly et al., 2024). In leprosy patients, there was a significant decrease in serum vitamin D levels (Garg et al., 2020). The main sources of vitamin D are food, UVB exposure, and supplements. Vitamin D is available in two forms, namely ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D3 is mainly provided by sunlight. It is recommended to get direct sunlight exposure for 10-15 minutes twice a week to get optimal vitamin D3 levels, and diet and multivitamin supplementation mainly contain vitamin D2. Food sources rich in Vitamin D include sea fish, fish oil, egg yolks, butter, cheese, meat, or oral supplements (Garg et al., 2020; Klowak & Boggild, 2023). Vitamin E is a fat-soluble antioxidant. With antioxidant properties that break the ROS chain, vitamin E can effectively protect against lipid peroxidation. Vitamin E also contains antioxidant and membrane stabilizer properties. One of the roles of vitamin E is the activity of scavenging free radicals in the aqueous phase of cells and the circulatory system to clean up the Reactive Oxygen Species (ROS) produced (Garg et al., 2020). Research shows that there is a

correlation between the bacterial index and vitamin E levels (Hazlianda et al., 2023). Increased use of vitamin E in lipid peroxide clearance may lead to decreased serum vitamin E levels. Low antioxidant levels may expose tissues to oxidative stress-mediated changes in biomolecules and cells. Antioxidants may contribute to inflammatory episodes in leprosy patients, organ damage, depressed cell-mediated immune responses, and neurodegeneration. Vitamin E can inhibit lipid peroxidation by neutralizing peroxyl radicals. Increased amounts of isolated vitamin E may have a pro-oxidant effect, leading to changes in the characteristics of free radicals; therefore, a proper balance of the concentrations of these components is required (Vijayaraghavan et al., 2005). Another study described the protective role of vitamin E in leprosy, with exogenous vitamin E supplementation being able to protect against the harm produced by ROS during disease progression and antileprosy chemotherapy. Antioxidant defenses may counterbalance the ability of multidrug Hansen's disease drug therapy to induce free radical production in leprosy patients (Hazlianda et al., 2023).

Mineral

Selenium is a micronutrient classified as an essential trace element that is closely related to complex enzymatic and metabolic functions. Selenium has several biological functions, the most important of which is its interaction with glutathione peroxide (GPxs). Glutathione catalyzes the reduction of hydrogen peroxide and organic hydroperoxides, making it important for protecting membrane lipids and other cellular constituents against oxidative injury. Selenium also influences the chemotactic and microbicidal activities of phagocytic cells, components of the innate immune response. Selenium modulates leukotriene synthesis and peroxide regulation in the microenvironment of immune-competent cells (Vázquez et al., 2014). Selenium has antiproliferative and immune-enhancing properties by enhancing innate and adaptive immune defenses. Selenium has been shown to increase the activation of NK cells, CD4+ T cells, and IFN-γ expression. A cross-sectional study found that serum selenium in leprosy patients, especially MB type, was significantly lower than in PB leprosy patients, and patients with high BI were correlated with low selenium levels (Partogi et al., 2018). Experimental studies in 2021 showed that selenium supplementation of 80 mg/kg in 60 immunosuppressed mice as an immunomodulator can reduce the secretion of nitric oxide, IL-2, and IFN-γ. However, a perfect selenium balance must be maintained, because, while phagocytosis and lymphocyte activity can be stimulated in adequate selenium supplementation, higher doses are inhibitory. The recommended dietary intake of selenium as an immunomodulator in humans as recommended by randomized controlled trials in children and adolescents ranges from 15 µg/day for children aged 1–3 years to 70 µg/day for adolescents (Klowak & Boggild, 2022, 2023)(Khalid et al., 2022; Kimberly et al., 2024).

Zinc deficiency triggers a deficiency in the Th1 response. Inflammatory cytokines, such as IFN-γ, IL-2, and TNF-α which are important for the control of intracellular pathogens (such as M. leprae) are reduced, while the production of IL-4, IL-6, and IL-10 is not affected. In contrast, prolonged Zinc supplementation increased IL-2 production and significantly decreased the incidence of respiratory infections. IL-2 is a cytokine that induces the proliferation of Th1 cells (Kimberly et al., 2024). The possible antioxidant role of Zinc may be related to the regulation of the expression of metallothionein (MT), a low molecular weight protein rich in cysteine residues, which has antioxidant properties in many conditions such as radiation, drugs, and heavy metal exposure. Zinc is a structural and catalytic component of Superoxide Dismutase (SOD), and is essential for its activity. SOD is an antioxidant enzyme that reduces the oxidant effects of ROS, converting superoxide to hydrogen peroxide, a form that minimizes the chain reaction of cell damage. There are two types of SOD, the cytoplasmic form, which contains copper-zinc in its molecule (CuZnSOD), and the

mitochondrial form, which contains manganese (MnSOD). The loss of Zinc in the cell membrane can affect its function, its flux, sodium and calcium transport channels, and the hydro- and osmotic balance of the cell. Zinc can still stabilize the reduced form of the sulfhydryl group, protecting against the effects of lipid peroxidation on the cell membrane (Khalid et al., 2022).

Nutrition

Mycobacterium leprae is an intracellular microorganism, so cell-mediated immune responses are important in human host defense. Protein-energy malnutrition, as well as inadequate vitamin and/or mineral intake are associated with reduced cell-mediated immunity. Lower nutrient intakes have placed leprosy patients at risk for reduced cell-mediated immunity. When the immune response is restored after a period of suppression, the immune system will begin to respond to infections present in the body (Wagenaar et al., 2015). Leprosy patients tend to have less favorable within socioeconomic aspect, health, and nutritional conditions than control populations. Lower per capita food expenditure, lower BMI, lower Dietary Diversity Score (DDS), and lack of household food stocks are the main factors associated with increased risk of developing leprosy (Wagenaar et al., 2015). Chronic malnutrition is considered an important risk factor that makes a person susceptible to leprosy, and affects the response to treatment. They also found an association between malnutrition and a greater risk of disability, even after completion of treatment, as well as a greater risk of leprosy reactions (Jindal et al., 2022). A systematic review showed a consistent association between leprosy and poor socioeconomic conditions. At the personal level, individuals who are male, live in the same house as someone with leprosy, live in a densely populated area, and have experienced food shortages in the past increase the risk of leprosy, ecological level, population density, sanitation, and poverty are thought to have a fairly strong association with the risk of developing leprosy although the exact mechanism is not yet known (Pescarini et al., 2018).

A diet consisting mostly of rice or high in carbohydrates and low in protein and fiber indicates that the consumption of non-rice nutritious foods is relatively low, which may explain the low DDS. Research shows that the diversity of household foods characterized by high DDS scores increases with increasing food expenditure, and especially the intake of animal-based foods and fruits increases sharply with increasing food expenditure, which is strongly related to income (Wagenaar et al., 2015). Inadequate dietary intake leads to reduced intake of carbohydrates, proteins, fats, vitamins, and minerals; and malnutrition weakens the immune system against infection (Wintergerst et al., 2007). Although the risk of subclinical infection is not necessarily related to dietary deficiency, it does facilitate the progression of infection to clinical disease. It has previously been reported that protein deficiency combined with inadequate or low intake of foods rich in vitamins and minerals from various food groups is associated with reduced cell-mediated immunity (Ferguson and Griffin, 2000), placing leprosy patients at risk for impaired immunity. The course of infection is dependent on host genetic factors and is influenced by environmental and nutritional status . Malnutrition is common in leprosy endemic areas, so it is likely that the clinical presentation is a result of malnutrition along with environmental and genetic factors of the host. Nutrition and dietary supplements are known to influence the immune response in many diseases, vitamin and trace element deficiencies affect both innate and adaptive immune responses (Dwivedi et al., 2019). Poverty associated with food insecurity is an important risk factor for leprosy susceptibility, but the underlying mechanisms of this relationship other than malnutrition still need to be identified, where research related to nutrition in leprosy patients often experiences obstacles due to several conditions such as strong stigma in society (Oktaria et al., 2018), causing recall

and response bias. Especially for people who are very poor with unstable incomes, their average income is difficult to estimate. In addition to recall or remembering their food intake in the last 24 hours, last year, and over a longer period, which causes recall and response bias, and biomarkers for micro and macro nutrients in blood, urine, and/or feces can be analyzed to assess food intake more objectively (Oktaria et al., 2018; Wagenaar et al., 2015).

The Role of Vitamins, Minerals and Nutrition in Leprosy Patients

The main defense against microbial infection in leprosy is the macrophage system. Microbial killing by macrophages is associated with a burst of activity that causes the production of free radicals called ROS. The main target of peroxidation by ROS is Polyunsaturated fatty acids (PUFA) or polyunsaturated fatty acids in membrane lipids. PUFA is degraded by free radicals to form malondialdehyde (MDA). MDA levels in serum function as a marker of cell damage due to free radicals. MDA levels in PB and MB leprosy patients increased significantly compared to healthy people (Garg et al., 2020). This shows that increased lipid peroxidation due to ROS-mediated processes occurs in leprosy patients. Increased lipid peroxidation can occur if the rate of reactive oxygen species production is higher or antioxidant levels are low. Antioxidant defense mechanisms against ROS; among these antioxidants are vitamins, enzymes C and E such as superoxide dismutase and catalase. One of the roles of Vitamins C, A, and E is to clean up free radicals in the water and lipid phases of cells and the circulatory system to clean up the ROS produced. Oxidative Stress (OS) is a term used to describe a variety of damaging processes resulting from an imbalance between the free radical generation and scavenging systems. OS causes metabolic disorders and cell death. This occurs when ROS are not adequately scavenged by antioxidants (Trimbake et al., 2013).

Related to lipid peroxidation, selenium as a micronutrient has several biological functions, the most important of which is its interaction with Glutathione Peroxide (GPxs). Glutathione catalyzes the reduction of hydrogen peroxide and organic hydroperoxides and is therefore essential for protecting membrane lipids and other cellular constituents against oxidative injury. Selenium also influences the chemotactic and microbicidal activities of phagocytic cells, components of the innate immune response. Selenium modulates leukotriene synthesis and peroxide regulation in the microenvironment of immunocompetent cells (Vázquez et al., 2014). Selenium has antiproliferative and immune enhancing properties by enhancing innate and adaptive immune defenses. Selenium has been shown to enhance activation of NK cells, CD4+ T cells, and IFN-γ expression. Zinc is a structural and catalytic component of Superoxide Dismutase (SOD), and is essential for its activity. SOD is an antioxidant enzyme that reduces the oxidant effects of ROS, converting superoxide to hydrogen peroxide, a form that minimizes the chain reaction of cell damage. There are two types of SOD, the cytoplasmic form, which contains copper-zinc in its molecule (CuZnSOD), and the mitochondrial form, which contains manganese (MnSOD). Loss of Zinc in the cell membrane can affect its function, flux, sodium and calcium transport channels, and the hydro-osmotic balance of the cell. Zinc can still stabilize the reduced form of sulfhydryl groups, protecting against the effects of lipid peroxidation on the cell membrane (Khalid et al., 2022). Because of the complexity of the clinical presentation, the many factors involved in the management of M. leprae, leprosy remains a major challenge for clinicians and researchers. Immunologically, leprosy is a spectral disease model involving components of both humoral and adaptive immune responses. These components contribute not only to protection but also to pathogenesis, with skin lesions and neurological deficit.

CONCLUSION

Because of the complexity of the clinical presentation, the many factors involved in the

management of M. leprae, leprosy remains a major challenge for clinicians and researchers. Immunologically, leprosy is a spectral disease model involving components of both humoral and adaptive immune responses. These components contribute not only to protection but also to pathogenesis, with skin lesions and neurological deficit. Several risk factor associated with leprosy clinical manifestation. Chronic malnutrition is considered an important risk factor that makes a person susceptible to leprosy, and affects the response to treatment. They also found an association between malnutrition and a greater risk of disability, even after completion of treatment, as well as a greater risk of leprosy reaction. At the personal level, individuals who are male, live in the same house as someone with leprosy, live in a densely populated area, and have experienced food shortages in the past increase the risk of leprosy, ecological level, population density, sanitation, and poverty are thought to have a fairly strong association with the risk of developing leprosy although the exact mechanism is not yet known. Micronutrient such as Selenium, Zinc combined with antioxidants such as vitamin C, vitamin E, carotenoids present in fresh fruits and leafy vegetables provide protection against oxidative damage to cells and biomolecules.

Since leprosy patients are mostly from low socioeconomic status, they do not get antioxidant-rich foods such as fresh fruits and leafy vegetables on a daily basis. Thus, the increased lipid peroxidation observed in leprosy patients can also be attributed largely to the lack of vitamins in the diet. Poverty associated with food insecurity is an important risk factor for leprosy susceptibility, but the underlying mechanisms of this relationship other than malnutrition still need to be identified, where research related to nutrition in leprosy patients often experiences obstacles due to several conditions such as strong stigma in society, causing recall and response bias. Especially for people who are very poor with unstable incomes, their average income is difficult to estimate. In addition to recall or remembering their food intake in the last 24 hours, last year, and over a longer period, which causes recall and response bias, and biomarkers for micro and macro nutrients in blood, urine, and/or feces can be analyzed to assess food intake more objectively.

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