

## A SCOPING REVIEW OF NUTRITION AND DIET-RELATED FACTORS IN COMBATING LEPROSY DISEASE

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### ABSTRACT

**Background:** Indonesia still faces several challenges concerning the control of neglected tropical diseases (NTDs). Leprosy is one of the bacterial infectious NTDs caused by *Mycobacterium leprae*. The most obvious risk factors include undernutrition, poverty, food scarcity, food insecurity and a lack of food diversity. According to immunity beneficiaries and preventable or protecting factors, nutrition and food are essential.

**Objectives:** To synthesize the diet and nutrition risk factors and consequences with the most substantial evidence related to leprosy disease.

**Methods:** Five databases were searched systematically, following punctuation and conventions-based keyword searches and criteria and free-text terms. Selected articles included systematic reviews and other studies involving human subjects published between 2013 and 2023. Finding articles (n=588) were interpreted using preferred reporting of items for systematic reviews and meta-analyses (PRISMA). Eligible articles (n=16) were described by author's name, publication year, study objectives, locations, study design, participants, methods, intervention and exposure, and critical findings and impacts/outputs.

**Results:** In 16 studies, there were nutrition explanations correlated to leprosy disease. Malnutrition, either undernutrition or overnutrition, may lead to a worse disease prognosis. A comprehensive approach to food security, diet quality, and dietary behaviors is needed to protect against the disease. Affected individuals tend to have lower essential nutrition serum levels to obtain multiple micronutrient supplements such as vitamins A, C, D, E, zinc and selenium.

**Conclusion:** Regarding immunity beneficiaries and impacted factors, there are several potential risk factors related to nutrition and diet in leprosy that are necessary considerations, including nutritional status, food and nutritional security (food environment-related) and dietary behavior.

**Keywords:** Food insecurity; Immune responses; Leprosy; Neglected tropical disease; Nutrition vulnerability.

### ABSTRAK

**Latar belakang:** Saat ini, Indonesia masih menghadapi beberapa tantangan dalam pengendalian penyakit tropis terabaikan, salah satunya adalah kusta atau lepra. Lepra merupakan penyakit tropis terabaikan yang menular dan disebabkan oleh *Mycobacterium leprae*. Faktor risiko yang memengaruhi timbulnya penyakit lepra adalah gizi kurang, kemiskinan, kerentanan pangan dan kurangnya keanekaragaman pangan (faktor lingkungan pangan). Hal ini berkaitan dengan peranan sistem imun sebagai faktor pencegah serta pemanfaatan zat gizi dan pangan.

**Tujuan:** Penelitian ini bertujuan meninjau secara sistematis antara faktor risiko dan/ atau dampak gizi serta diet yang memiliki bukti ilmiah pada penyakit lepra.

**Metode:** Artikel dipilih secara sistematis dari lima database menurut pencarian kata kunci, kriteria serta istilah teks bebas yang telah ditentukan. Artikel terpilih termasuk tinjauan sistematis dan penelitian yang melibatkan subjek manusia yang diterbitkan antara 2013 hingga 2023. Sebanyak 588 artikel yang ditemukan selanjutnya dianalisis berdasarkan preferred reporting of items for systematic reviews and meta-analyses (PRISMA). Artikel yang memenuhi kriteria (n=16) kemudian ditinjau secara mendalam sesuai dengan nama penulis dan tahun publikasi, tujuan, tempat penelitian, desain studi, intervensi atau paparan dan temuan kunci/dampak terkait gizi.

**Hasil:** Pada 16 studi, terdapat penjelasan terkait dengan gizi yang berkaitan dengan penyakit kusta. Malnutrisi yang didefinisikan sebagai gizi kurang dan gizi lebih dapat memperburuk prognosis penyakit. Pendekatan komprehensif mengenai ketahanan pangan, kualitas diet dan perilaku makan diperlukan sebagai upaya pencegahan. Individu terinfeksi memiliki serum zat gizi yang cenderung lebih rendah dibandingkan dengan individu sehat sehingga upaya suplementasi (vitamin A, C, D, E, seng, dan selenium) sangat diperlukan.

**Simpulan:** Ditinjau dari sisi manfaat terhadap imunitas, terdapat beberapa faktor risiko yang potensial terkait gizi dan diet pada individu terjangkit kusta, diantaranya status gizi ketahanan pangan dan gizi (terkait dengan lingkungan pangan) serta perilaku konsumsi pangan.

**Kata kunci:** Kerawanan pangan, Respon imun, Lepra, Penyakit tropis yang terabaikan, Kerentanan gizi

## BACKGROUND

Indonesia has faced a double burden regarding infectious disease control. Despite being in a COVID-19 pandemic, as a tropical country, Indonesia has become an inhabitable environment for disease-causing microorganisms and disease vectors. Based on Fauziyah *et al.* (2021), Indonesia still has several challenges in controlling neglected tropical diseases (NTDs). NTDs have been defined by the Centers for Disease Control and Prevention (CDC) as several parasitic, viral, bacterial, fungal, and non-communicable diseases affecting more than one billion people worldwide and causing severe illness. Leprosy is one of the bacterial infectious NTDs caused by *Mycobacterium leprae*.<sup>1</sup>

According to data from 2019 by World Health Organization databases, Brazil, India, and Indonesia reported more than 10,000 new cases, while 13 other countries (Bangladesh, the Democratic Republic of the Congo, Ethiopia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria, the Philippines, Somalia, South Sudan, Sri Lanka and Tanzania) each reported 1,000 to 10,000 new cases. Ninety-nine nations reported fewer than 1000 new cases, while 45 reported no incidents. Indonesia is one of the top three countries with the global highest number of cases of leprosy, after India and Brazil, with around 8% of world cases in 2020. Based on the Leprosy data validation report in 2021 conducted by the Ministry of Health Republic Indonesia, the number of active cases in Indonesia in 2021 was 12,288 cases, and new leprosy cases during 2021 were 10983 in 464 regencies/districts.

*M. leprae* infects macrophages and Schwann cells.<sup>2</sup> Binary fission is a process used by *M. leprae* to reproduce. It requires a temperature between 27 and 30°C to remain viable.<sup>3</sup> Additionally, *M. leprae* is a microbe that prefers the skin and nerves. This bacillus may exist for up to 46 days in wet soil and up to 5 months in dry circumstances.<sup>4</sup> Furthermore, *M. leprae* has a long incubation period that lasts an average of 4–5 years.<sup>5</sup> Skin, eyes, peripheral nerves and upper respiratory tract mucosa are the body's main areas impacted by leprosy. The body's main areas impacted by leprosy are skin, eyes, peripheral nerves and upper respiratory tract mucosa. Skin growths (nodules) can initially come up, followed by other symptoms such as painless foot ulcers, eyebrow loss, dry or thick skin and pigmented spots on the skin.

World Health Organization (WHO) operational classification and the Ridley-Jopling system are the two primary categorization systems used for leprosy patients. The Ridley-Jopling categorization system combines bacteriologic index, histopathologic characteristics and clinical

symptoms.<sup>6,7</sup> It helps the classification of the many leprosy subtypes along a spectrum, including polar tuberculoid leprosy, borderline tuberculoid leprosy, mid-borderline leprosy, borderline lepromatous leprosy and lepromatous leprosy. Depending on one's cell-mediated immune response, one's position within this classification model varies for afflicted individuals.<sup>8</sup> The WHO's Expert Committee on Leprosy determined in 1998 that treatment could begin before the conclusion of smear tests; as a result, a practical, quick method of classification was devised for global use without the need for diagnostic tools and without placing medical personnel at risk. Paucibacillary cases have no more than five skin lesions, while multibacillary cases have six or more skin lesions.

WHO stated that nasal and oral droplets transmit the disease. Leprosy must be acquired through months of close, continuous contact with an infected patient. Leprosy cannot be contracted by simply shaking hands, hugging, eating together, or sitting near someone with the disease. In addition, once therapy starts, the patient stops spreading the illness. WHO published the global leprosy strategy 2021–2030, which aligns with the road map for NTDs. The Strategy encourages a vision “Zero Leprosies” with the disease's elimination (defined as the termination of transmission) as its endpoint and net leprosy-related infection, sickness, disability, stigma and discrimination. The four key objectives of the Strategy are preventing new disabilities, eliminating stigma, promoting human rights and controlling leprosy and its complications. Scaling-up leprosy prevention alongside integrated active case detection.<sup>9</sup>

Leprosy is a curable disease. Dapsone, rifampicin and clofazimine are the currently recommended treatment combination, a multi-drug therapy (MDT).<sup>10</sup> Treatment lasts six months until twelve months based on the classification of cases. MDT eliminates the infection while curing the patient. Early detection and timely treatment are critical in preventing disability.<sup>11</sup> Current therapy of leprosy disease is very complicated and costly including various antibiotics. Treatment and duration range from six months for paucibacillary leprosy to a year for multibacillary leprosy, depending on the bacillary loads. Whereas these medicines are intentionally available in accordance with WHO recommendations, many rural individuals over the world cannot access them.

The most evident predisposing factors are poverty, under-nutrition, food shortage, food insecurities and lack of food diversities.<sup>12</sup> Furthermore, a case-control investigation conducted in Indonesia disclosed that the dietary variations

between newly diagnosed individuals and control subjects are immune-related. Leprosy incidence is largely steady despite the use of MDT and chemoprophylaxis, demonstrating the need for dietary variety in high-prevalence areas.<sup>13</sup> The disease's severity has increased due to socio-economic difficulties such as the social stigma associated with disabilities and increasing food intake inadequacies.<sup>14</sup> Inadequate food intake leads to reduced intake of carbohydrates, proteins, fats, vitamins and minerals, and nutritional deficiency impairs the immune system against infections.<sup>15</sup> Therefore, considering nutrition- and diet-related is essential to prevent and control spreading the diseases. The scoping review sought to synthesize the nutritional status, iron status, micronutrient supplementation, food and nutrition vulnerability and dietary behavior that have the strongest evidence related to leprosy disease.

## METHODS

### Data Sources and Search Strategy

Identifying peer-reviewed literature providing evidence that has not been thoroughly investigated or is complex and diverse in characteristics becomes more accessible using the scoping review process.<sup>16</sup> The evidence for diet and nutrition-based approaches for the supporting intervention and medical therapy of leprosy disease was investigated in any study of recent academic publications such as cross-sectional, case-control, randomized-controlled trial studies, etc. Due to the requirement that this study is not a systematic review, it was not submitted to the International Prospective Register of Systematic Reviews (PROSPERO).

Five academic databases were searched for published, peer-reviewed, literature, including PubMed, ScienceDirect, Wiley Online Library, EBSCO and Google Scholar. These databases are the most relevant in nutrition and public health research. Grey literature (thesis, proceeding, report, etc.) was not included as the intention of this review. Thus, a peer-reviewed process for publication was essential and hence required. The primary justification for using 10 years (from 2013 to 2023) for all databases was to ensure the most applicable and relevant practice.

### Methodological Approach

Tricco *et al.* (2018) stated that the scoping review was conducted using a structured approach presented and informed using preferred reporting of items for systematic reviews and meta-analyses (PRISMA). A standard approach was applied to map the literature related to the selected topic through

identifying relevant studies, selection of studies, data extraction and summarisation of results.<sup>17</sup>

### Eligibility Criteria

Studies requiring the following inclusion criteria were included: (1) Published between 2013–2023; (2) Full-text accessible for review; (3) Peer-reviewed published literature; (4) Following study design including cross-sectional, case-control, cohort, experimental, longitudinal studies or meta-analysis (related to human study); (5) Published in English or Bahasa Indonesia. Studies which met the following exclusion criteria were excluded: (1) The absence of a peer-review process; (2) Unpublished results or literature; (3) Animal or preclinical or in vitro studies, protocols, conference abstracts/presentations/posters, book chapters, editorials and commentary or opinions; (4) Did not include outcome(s) or measure(s) related to diet and nutrition for leprosy disease.

### Database Search Terms

In order to provide an in-depth review of all literature, punctuation and conventions-based keyword searches and criteria were applied. In comparison to using a single keyword, the use of multiple free-text keywords allowed for the recognition of the most relevant records feasible within a search. The inclusion of an asterisk (\*) expanded a search by recognizing phrases that share the same letters. Three Boolean operators—AND, OR, and NOT—provided a method for combining, focusing, refining, enlarging, or excluding keywords from the database search. All databases were searched using search terms: “leprosy”, “Hansen’s disease\*”, “nutrition”, “diet\*”, “vitamin\*”, “mineral\*”, “probiotic\*”, “dietary supplement\*”, “functional food\*”. The syntax generated using Boolean operators was nutrition OR diet OR vitamin OR mineral OR probiotic OR “dietary supplement” OR “functional food” AND leprosy OR “Hansen's disease”. All databases was performed filters to be applied regarding human population studies, article type, language and year of the publication.

### Selection Process and Filtering Data

Each particular database's collection of retrieved articles has been uploaded to Mendeley, de-duplicated and screened papers on Rayyan Intelligent Systematic Review®. For inclusion and exclusion criteria, all titles, abstracts and subsequently full-texts were reviewed and screened.

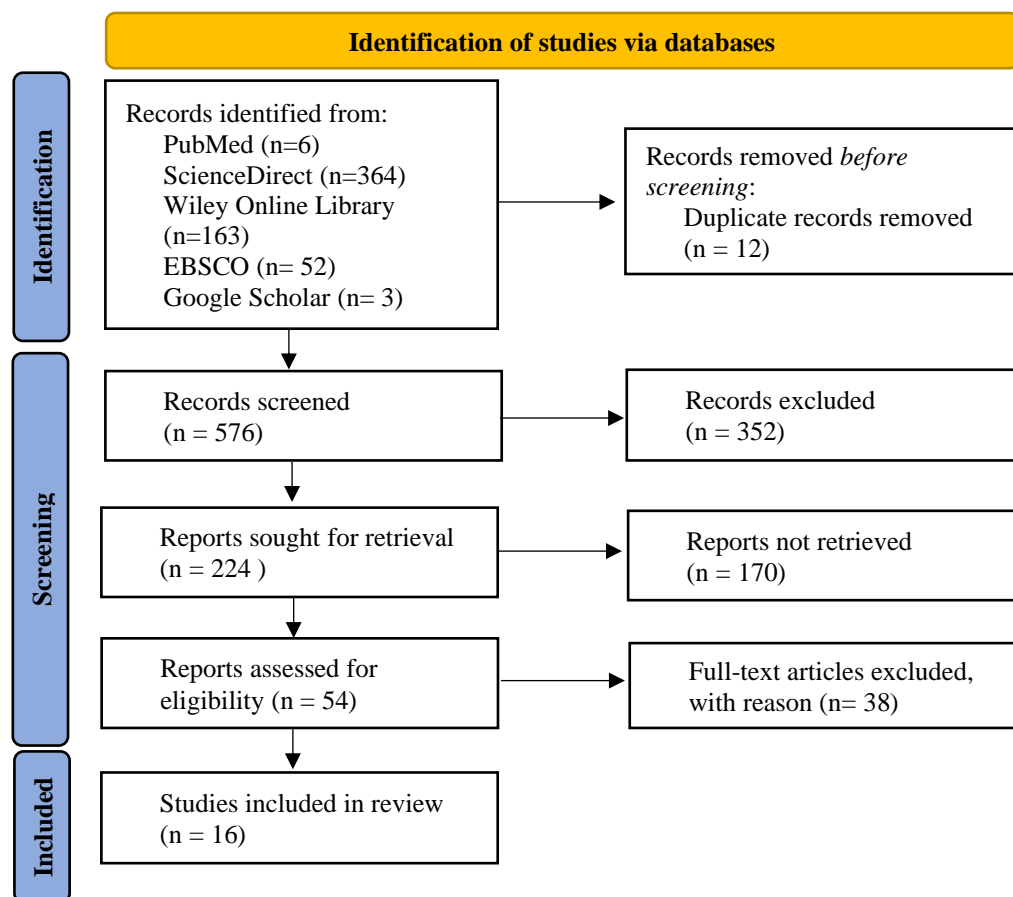
### Synthesis of Result

Extracted data was organized into tables to present general criteria of each included study. Results were organized by using the identification of dietary and nutritional intervention and/or factors related to leprosy disease.

**RESULT**

Total database searches of PubMed (6 articles), ScienceDirect (364 articles), Wiley Online Library (163 articles), EBSCO (52 articles) and Google Scholar (3 articles) identified 588 articles. The result articles were identified as 576 records after removing duplicates. Furthermore, 224 articles were identified for inclusion by title and abstract,

leading to the exclusion of 352 articles. After scanning the titles and abstracts, 170 citations were excluded, and 54 were assessed for full-text eligibility. Following examining the full-text, there were 16 eligible articles considered and included them in this study. The flow diagram of studies using PRISMA guidelines is provided in Figure 1.



**Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of review of reviews**

Table 1 summarizes the review of included nutritional and dietary factors related to leprosy disease. There are 16 eligible studies in this review. Each study was described by authors, publication year, objectives of study, study design, participants, location of the study, methods, intervention and/ or

exposure and key findings and/ or impacts/outputs. The examination was performed for 16 articles in case-control studies (n=9 articles), cross-sectional studies (n=4 articles), randomized-controlled trials (n=2 articles) and observational study (n=1 article).

Table 1. Description of included nutritional and dietary factors related to leprosy review

No	Author(s), Year	Objective(s)	Participants	Location(s)	Methods	Interventions or exposures	Key Findings, relating diet and/or nutrition
1.	Hilma <i>et al.</i> (2023) <sup>18</sup>	analyzed the serum level of 25-hydroxyvitamin D <sub>3</sub> (25(OH)D) and plasma level of VDR as association with BI in leprosy patients in Indonesia	28 patients (aged 18-59 years) diagnosed with leprosy	Cipto Mangunkusumo National Hospital, Indonesia	Cross-sectional study	<ul style="list-style-type: none"> <li>• Serum level of 25(OH)-vitamin D</li> <li>• Plasma level of VDR</li> </ul>	<ul style="list-style-type: none"> <li>• Low level of 25-hydroxy vitamin D in leprosy patients</li> <li>• No significant correlation between BI and serum levels of 25-hydroxy vitamin D, and plasma level</li> </ul>
2.	Jindal <i>et al.</i> (2022) <sup>19</sup>	Elucidated the nutritional status of leprosy patients and assess its effect on the type of leprosy, reaction states, and deformities	104 patients with leprosy disease	Uttarakhand, India	Prospective observational study	Nutritional status: BMI, hemoglobin level, iron serum level, serum cholesterol, and C-reactive protein	Low iron serum statistically significant associated to MB leprosy
3.	Oktaria <i>et al.</i> (2022) <sup>20</sup>	Investigated IL-6, IL-8, IL-10 and nutritional status as potential markers for the development of clinical leprosy among contacts	<p>Cases: 67 patients with MB, 65 household contacts of MB patients</p> <p>Control: 127 endemic controls</p>	Bangkalan, a district of Madura, East Java, Indonesia	Case-control study	Serum levels of IL-6, IL-8, IL-10, hemoglobin, ferritin, and transferrin saturation	<ul style="list-style-type: none"> <li>• Anemia was higher in MB group</li> <li>• ↑Underweight found in household contact</li> <li>• ↑IL-6, anemia, and iron deficiency can discriminate leprosy</li> </ul>
4.	Arifin <i>et al.</i> (2022) <sup>21</sup>	analyzed characteristics, BCG vaccine status, nutritional status and home environment, the correlated risk factors to child leprosy in Gresik District	<p>Cases: 18 respondents of cases group</p> <p>Control: 18 respondents (children from 3-14 years with positive leprosy)</p>	Gresik District, Indonesia	Case-control study	Characteristics (age, sex, and education) and BCG vaccine status (BCG scar and without BCG scar), nutritional status classified BMI and protein (albumin and hemoglobin serum), and home environment (wall, ceiling, floor, humidity, ventilation, and density of occupancy)	Underweight (low BMI) and low serum albumin had correlated with leprosy patients

Tabel 1. Description of included nutritional and dietary factors related to leprosy review (Cont...)

No	Author(s), Year	Objective(s)	Participants	Location(s)	Methods	Interventions or exposures	Key Findings, relating diet and/or nutrition
5.	Dalimunthe <i>et al.</i> (2021) <sup>22</sup>	Determined the levels of vitamin A and its comparison in MB and PB leprosy patients, also the relationship between vitamin A levels with BI	34 leprosy patients	North Sumatera, Indonesia	Cross-sectional	<ul style="list-style-type: none"> <li>Levels of vitamin A</li> <li>Vitamin A levels with BI</li> </ul>	Vitamin A level in MB leprosy was lower than PB leprosy, negative correlation between vitamin A level and BI in leprosy
6.	Dennison <i>et al.</i> (2021) <sup>23</sup>	investigated the associations of helminth co-infection and select micronutrient deficiencies with leprosy using a case-control design	individuals aged $\geq 3$ years; 96 household contacts and 81 non-contact controls	Southeastern Brazil	Case-control study	Individual characteristics (age, sex, race/ethnicity, education, family income, leprosy classification and type, bacillary index, helminth infection, <i>Schistosoma mansoni</i> infection, IgG4 reaction, vitamin D deficiency, iron deficiency, and vitamin A deficiency	Vitamin D deficiency and <i>Schistosoma mansoni</i> infection may increase the risk of active leprosy
7.	Prakoewa <i>et al.</i> (2021) <sup>24</sup>	evaluated association between nutritional status and leprosy, especially in maternal and child leprosy	82 subjects, pair comprised of mother and child subjects; 41 subjects for each of the age group	Tuban, Indonesia	Case-control study	Age, BMI, hemoglobin level, white blood cells count, platelet count, hematocrit level, albumin level, and zinc level	<ul style="list-style-type: none"> <li>Low BMI in child subjects have no significant difference with control</li> <li>Children from mother with leprosy tend to have undernutrition (low BMI)</li> <li>Other group (child with leprosy) have overweight status</li> <li>Significant difference leprosy patients and contacted with control on hemoglobin level</li> </ul>

Tabel 1. Description of included nutritional and dietary factors related to leprosy review (Cont...)

No	Author(s), Year	Objective(s)	Participants	Location(s)	Methods	Interventions or exposures	Key Findings, relating diet and/or nutrition
8.	Anantharam <i>et al.</i> (2021) <sup>25</sup>	Investigated associations of leprosy and nutrition in the context of Ethiopia	Cases: 40 participants; leprosy (+) Control: 40 participants; healthy individual (leprosy (-))	North Gondar Zone, Ethiopia	Case-control study	Underweight (BMI<18.5 kg/m <sup>2</sup> ), low-MUAC ( $\leq 21$ cm), sex, age (year), education level, no utilization of institutional banking, <i>Schistosoma mansoni</i> infection, reducing or skipping meals, insufficient funds for meals, less of length time for market access, lack of food	<ul style="list-style-type: none"> <li>• Undernutrition and malnutrition (low MUAC) significantly associated with leprosy</li> <li>• Food insecurity was also associated with leprosy</li> <li>• Food habit (cutting the size of meals/skipping meals) associated with leprosy</li> </ul>
9.	Goswami <i>et al.</i> (2020) <sup>26</sup>	Evaluated an oxidative stress in leprosy patients	Cases: 116 lepomatous leprosy patients and 79 tuberculoid leprosy patients Control: 35 random age and sex matched healthy individuals	Darjeeling, West Bengal, India	Case-control study	Ascorbic acid (vitamin C), $\alpha$ -tocopherol (vitamin E), malondialdehyde (MD), superoxide dismutase (SOD), and MD/SOD	<ul style="list-style-type: none"> <li>• Ascorbic acid and <math>\alpha</math>-tocopherol significantly decreased in leprosy compared with control</li> <li>• MDA level and ratio of MDA/SOD increased in leprosy and a sharp decrease in SOD activity</li> </ul>
10.	Kurnianto <i>et al.</i> (2019) <sup>27</sup>	analyzed the effect of 40 mg/day dose of zinc sulphate supplementation for 12 weeks on the levels of proinflammatory cytokines levels TNF- $\alpha$ , IL-1 $\beta$ and IL-6 in type MB leprosy patients	36 patients as a supplementation group (treatment), and 36 patients as control group (randomly)	Tegal Regency, Indonesia	Randomized-controlled trial (pre and post-test)	Treatment group: MDT + 40 mg/ day for 12 weeks zinc sulphate supplements Control: MDT	The supplement can preserve to decreasing zinc serum level and reduce IL-1 $\beta$ levels

Tabel 1. Description of included nutritional and dietary factors related to leprosy review (Cont...)

No	Author(s), Year	Objective(s)	Participants	Location(s)	Methods	Interventions or exposures	Key Findings, relating diet and/or nutrition
11.	Teixeira <i>et al.</i> (2019) <sup>28</sup>	characterize food insecurity, nutritional status, and eating habits of people affected by leprosy.	276 cases (based on consensus data)	Vitoria da Conquista and Tremedal, Bahia State, Brazil	Cross-sectional study	weight and height measurements, meal frequency, and household, socioeconomic, psychosocial and clinical variables	Leprosy was influenced by nutritional vulnerability (high food insecurity prevalence, inadequate eating habits and nutritional status)
12.	Partogi <i>et al.</i> (2018) <sup>29</sup>	Analyzed correlation selenium serum levels with bacteriological index in leprosy	30 leprosy patients; 19 PB patients, 11 MB patients	Adam Malik Hospital, Pirngadi Hospital, and Lau Simomo Hospital, (Indonesia)	Cross-sectional study	Selenium serum level	<ul style="list-style-type: none"> <li>• Selenium serum levels PB &gt; MB leprosy</li> <li>• High BI was correlated with low selenium serum levels</li> </ul>
13.	Oktaria <i>et al.</i> (2018) <sup>13</sup>	investigated the association between poverty-related diet and nutrition with leprosy	100 recently diagnosed leprosy patients and 200 controls, matched for age and gender	Bangkalan, Madura, East Java, Indonesia	Case-control study	Demographics, socioeconomic situation, health, and diet, BMI, dietary diversity score, anemia and iron micronutrient profiles	<ul style="list-style-type: none"> <li>• Unstable income, anemia, and food insecurity were significantly associated with leprosy</li> <li>• Higher education and land freeholder have significant protective factors for leprosy</li> <li>• Low dietary diversity, lack food stock, low serum iron, and high ferritin were found commonly</li> </ul>
14.	Zuhdan <i>et al.</i> (2017) <sup>30</sup>	Determined the factors related to leprosy disease post-chemoprophylaxis	284 subjects (1:1 case and control subjects)  Control group was subject without leprosy disease	Sampang, Indonesia	Case-control study	Duration contacts with patient, BCG vaccination status, nutritional status (under), open wound history, low economic status, poor personal hygiene	Undernutrition (poor nutritional status) and poor personal hygiene have correlated with leprosy post-chemoprophylaxis



Tabel 1. Description of included nutritional and dietary factors related to leprosy review (Cont...)

No	Author(s), Year	Objective(s)	Participants	Location(s)	Methods	Interventions or exposures	Key Findings, relating diet and/or nutrition
15.	Rahfiludin <i>et al.</i> (2016) <sup>31</sup>	Analyzed the effect of vitamin A, zinc and vitamin E supplementation on the immune response in seropositive leprosy patients	30% of 100 subjects with seropositive for IgM and PGL-1 (anti-phenolic glycolipid) for detecting <i>M. leprae</i> infection	Indonesia	Randomized-controlled trial	Intervention: high dosage vitamin A (200,000 IU), daily dose Zn (10 mg) and vitamin E (40 mg) were given in daily for 45 days  Control: identical appearance pills but lacked supplements	<ul style="list-style-type: none"> <li>• ↑ Retinol and tocopherol (intervention group)</li> <li>• ↓ Zinc (both group)</li> <li>• ↓IFN-<math>\gamma</math> (control group)</li> <li>• ↓IL-2 (both group)</li> </ul> Zinc supplementation combined vitamin A and vitamin E could be useful for preserving immune responses in leprosy
16.	Wagenaar <i>et al.</i> (2015) <sup>32</sup>	identified possible differences in dietary intake between recently diagnosed leprosy patients and control subjects	newly diagnosed leprosy patients and control subjects (52:100)	Nilphamari and Rangpur district, Bangladesh	Case-control study	Socioeconomic situation, health and diet status	Food shortage, low dietary diversity, and household food insecurity was higher in leprosy patients

Abbreviations: BI=bacterial index, BCG=bacilli Calmette-Guerin (vaccine for tuberculosis disease), BMI=body mass index, IFN=interferon, IL=interleukin, MB=multibacillary, MUAC=mid-upper arm circumference, PB=paucibacillary

## DISCUSSION

### Malnutrition and Immunity Impairment in Leprosy Disease

This review analyzed that leprosy patients in any investigations have malnutrition instead of deficiencies or excesses in nutrient intake, imbalance of essential nutrients, or impaired nutrient utilization. In this review, undernutrition was identified by low BMI. On the other hand, one study also found that being overweight (in that group of the study) correlates with leprosy disease. Arifin *et al.* (2022) stated that being underweight implies insufficient food intake and nutritional adequacy. Malnutrition causes an alteration in protein-energy intake, which severely decreases immunity.<sup>21</sup> Inadequate dietary intake suppresses immunity, which increases the risk of contracting infections.<sup>32</sup> The cause of the leprosy reactions' low immunity was an inadequate diet. Therefore, underweight patients cannot improve immune responses, making it easier for the leprosy reaction to invade the body.<sup>33</sup> Since nutrients are necessary to control immune response, lower BMI indicates poor nutritional status, which may compromise immunity.<sup>34</sup>

One study identified that low BMI index in leprosy patients did not have significantly different controls (without leprosy diagnosed). The Ministry of Health in Indonesia stated that leprosy patients received logistic assistance from the government, including ferrous sulfate, antioxidants and other vitamins. This may lead to the case group in the study having a better nutritional status.<sup>24</sup> Overweight leprosy patients can be explained by a sedentary lifestyle and activity or work limitation among leprosy patients, as well as unhealthy dietary intake that resulted in excessive calorie intake.<sup>28</sup> It might be a multifactorial correlation to assess.

MUAC measures the sum of the muscle and subcutaneous fat in the upper arm. MUAC is an easy-to-obtain anthropometric measure and has been used to monitor patients' nutritional status in acute malnutrition.<sup>35</sup> Malnutrition frequently compromises the immune system and, in some situations, increases an individual's susceptibility to clinically manifest infection.<sup>36</sup> The risk of infection rises with malnutrition. Malnutrition frequently causes secondary immunological deficiencies and susceptibility to infection in humans.<sup>37</sup> The profound effects of several pathogens on nutrition complicate the link between malnutrition and immunological suppression and infection. Infections that trigger an immunological response raise the requirement for metabolically produced anabolic energy and related substrates, generating a vicious cycle that impairs nutritional status and increases infection susceptibility.<sup>38</sup> Additionally, the altered gut mucosa

structure, which includes flattened hypertrophic microvilli, decreased lymphocyte numbers in Peyer's patches and decreased Ig A (immunoglobulin A) secretion, compromises the immunological defense at the epithelial barrier of the undernourished host. Malnutrition restricts the complement availability, inhibiting phagocytes' ability to engulf and destroy the pathogens.<sup>39</sup>

Albumin examination could be used as a biomarker for malnutrition. Three studies evaluated albumin serum levels in leprosy patients. According to Arifin *et al.* (2022), subjects with low albumin serum levels have a 9.10 times greater risk of leprosy. Depleting albumin serum levels correlates with inadequate daily food intake, inflammatory conditions and protein catabolism in infectious diseases.<sup>40,41</sup>

### Anemia and Iron Deficiency towards Leprosy Disease

According to Oktaria *et al.*, (2022), low BMI subjects in the MB leprosy group had a significantly lower hemoglobin, iron serum and transferrin level than contracted and endemic groups. Another finding, Jindal *et al.* (2022), low iron serum levels were significantly associated with MB in leprosy disease. Anemic lepromatous leprosy in individuals has been shown to have a blunted erythropoietin response and its inflammatory-related mechanism. Serum IL-6, underweight and iron deficiency are potential markers to diagnose leprosy disease in individuals in contact with index cases or lively closeness in endemic areas. IL-6 is a soluble mediator with a pleiotropic effect on inflammation, immune response and hematopoiesis.<sup>42</sup> In the initial stage of inflammation, IL-6 circulates and induces synthesis of acute phase proteins and declines fibronectin, albumin and transferrin production.<sup>43</sup> IL-6 modulates cellular iron to plasma and extracellular fluid through ferroportin, which should be used for dietary iron absorption, erythropoiesis and iron storage. Inflammation mediator will block ferroportin-mediated iron export from the gut and macrophage, which leads to iron-restricted erythropoiesis and anemia. Beyond iron deposit in macrophages, it is fully available for *M. leprae* intracellular growth.<sup>44</sup>

### Vitamin D Antimicrobial Pathway in Leprosy Disease

A few pieces of evidence investigated vitamin D deficiency as a potential risk of leprosy cases. Hilma *et al.* (2023) stated that low serum 25-hydroxy vitamin D was found in leprosy patients, whereas 25-hydroxy vitamin D had no significant correlation with BI. The study also indicated lower VDR (vitamin D receptor) plasma levels in the higher BI patients. Vitamin D is an

immunomodulator that can accelerate natural immune response and trigger antimicrobial activity through binding to VDR. VDR targeted cathelicidin, which encodes protein to eliminate intracellular bacteria. 25-hydroxy vitamin D is metabolized rapidly in leprosy infection to decrease the serum level.<sup>18,45,46</sup> According to Lu'ong *et al.*, (2012), VDR polymorphism drives susceptibility to leprosy because it generates the host immune response and determines the type of leprosy.<sup>47</sup>

A case control study in southeastern Brazil also found vitamin D deficiency significantly associated with leprosy, compared to non-contact controls.<sup>23</sup> The sufficiency of vitamin D prior to declining the infection viability. Skin lesions from patients with different forms of leprosy suggested a correlation between vitamin D activation through gene expression profiling. The second is vitamin D, which activates the antimicrobial pathway as an innate immune response since *M. leprosy* infection via induction.<sup>48</sup>

### Nutritional Vulnerability and Dietary Behaviors among Patients with Leprosy

Assessing food security and dietary behaviors among patients with leprosy could add value to investigating nutritional deficiency as a risk factor or consequence of leprosy. Four of the 16 studies in this review stated that nutrition vulnerability, food insecurity, inadequate eating habits, low dietary diversity, lack of food stock and food shortage had been associated with leprosy. Most leprosy patients were conceived and grew up in impoverished situations, and the stigma and obstacles associated with the disease continue to reinforce them further into poverty.<sup>49</sup>

Low-income households need more resources to spend on food. Therefore, they eat less nutritious, non-staple foods, including meat, fish, milk, eggs, fruits and vegetables. Anantharam *et al.*, (2021) studied infection risk variables regarding poverty and discovered that reducing the size of meals/skipping meals, or not having enough money for food (making food less accessible) were associated with leprosy. Another case-control study also stated that leprosy patients have less money to spend on food, have fewer household food stocks and have a less diverse diet. The case group had lower consumption of highly nutritious foods such as meat, fish, eggs, milk, fruits and vegetables. Long-term nutritional deficits result from an insufficient diet. The body's immune system requires proteins, vitamins, and minerals to combat infections efficiently. The study concluded that those who live in poverty and are unable to obtain a sufficient, varied diet are more likely to develop leprosy.<sup>25,32</sup>

Inadequate consumption of fruit and vegetables tends to increase the chance of infectious diseases, particularly leprosy. In one randomized controlled trial, researchers compared the effect of low (2 servings per day) fruit intake and high ( $\geq$  five servings per day) vegetable intake in subjects that can boost immune outcomes.<sup>50</sup> After 12 weeks of the dietary intervention, the antibody response was higher in the group consuming the higher intake of fruits and vegetables. This is essential evidence that a diet varying in fruits and vegetables supports a more robust immune response, most likely because of the nutrients and bioactives that fruits and vegetables can deliver to the body.<sup>51</sup>

### Complying Micronutrient Adequacy in Tackling Leprosy Disease

Considering to supplementation of vitamins A, C, D, E, and zinc and selenium, has been proved to enhance the antioxidant response and reduce incidence in leprosy in cohort study. Nutrient supplementation has been shown to reduce oxidative stress, improve the immune system and reduce the risk of adverse outcomes in leprosy. Furthermore, nutritional supplementation has explicitly been proven to lower overall indicators and improve the quality of life of leprosy patients.<sup>52,53</sup> Declined levels of ascorbic acid and  $\alpha$ -tocopherol in leprosy patients may be improved by supplementation of ascorbic acid and  $\alpha$ -tocopherol and prevent tissue injury.<sup>26</sup> According to Rahfiludin *et al.*, (2016), combining zinc (10 mg), vitamin A (200,000 IU) and vitamin E (40 mg) supplementation is recommended as an important alternative treatment to prevent leprosy and inhibit transmission in contacted individuals.

Other studies also examined the higher BI values of lower vitamin A and Selenium.<sup>22,29</sup> Several clinical trials examined the effect of vitamin A supplementation on indicators of immunity in humans. The impact of vitamin A (200,000 IU) on circulating effectors of innate immunity, including acute-phase response proteins and the complement system, was studied in trials from Ghana, Indonesia, and South Africa.<sup>54</sup>

Selenium is an essential trace dietary element that can act as an antioxidant and has been shown to slow the progression of certain diseases and strengthen the immune response. Individuals with low selenium levels have also been more susceptible to multiple infections, particularly in leprosy disease. With a low selenium level, supplementation may assist the vulnerable individual in obtaining the selenium requirements.<sup>55</sup> Selenium also drives the chemotactic and microbicidal actions of phagocytic cells, which are

components of the innate immune response. Selenium modulates leukotriene production and peroxide control in the microenvironment of immunologically competent cells. However, a natural (fit) balance of selenium must be maintained because high selenium supplementation can enhance phagocytosis and lymphocyte activity; higher dosages are inhibitory.<sup>56,57</sup>

Serum ascorbic acid levels have been reported to be lower in leprosy patients.<sup>26</sup> Non-enzymatic antioxidants, such as ascorbic acid, play an essential role in controlling the inflammation induced by ROS (reactive oxygen species). Although it is well known that ROS has a significant impact on the eradication of intracellular bacteria such as *M. leprae* and other intracellular pathogens, the immune system can also react to these oxidative attacks.<sup>57</sup>

Kurnianto et al. (2019) found that a zinc sulfate supplementation (40 mg/day) for 12 weeks maintained a decrease in zinc levels and reduced levels of IL-1 in type MB leprosy patients. Low zinc levels in leprosy patients can promote the growth of *M. leprae* bacteria due to a lack of cellular immunity, resulting in difficulty in bacteria elimination. In patients, zinc sulfate supplementation will positively affect serum zinc levels, which are vital for the development of cellular immunity.

## CONCLUSION

Malnutrition is a nutritional aspect correlated with leprosy. Low indicators of micronutrients and protein were also reported in leprosy patients. Food insecurity and low diet quality have been associated with leprosy. Multiple micronutrient supplementation can enhance healing and prevent the spread of leprosy. Exploring the interconnectedness of nutrition and leprosy further is worthwhile to improve leprosy control, prevention and intervention (treatment). This review is expected to provide an essential embark for the government to formulate a policy/ regulation towards neglected tropical diseases control.

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