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A review of nutrition in neuropathic pain of leprosy

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***Abstract*:** Leprosy is a neglected tropical disease (NTD) that continues to burden low- and middle-income countries (LMICs), despite being eliminated as a public health concern by the World Health Organization (WHO) in 2000. The causative agents, *Mycobacterium leprae* and *Mycobacterium lepromatosis*, affect nearly 200,000 individuals globally each year, with over 19,000 new cases detected in the Americas in 2020 alone. Canada has experienced an increasing incidence of leprosy, due to rising levels of travel and migration from endemic areas, reaching over 37,000 individuals with leprosy by the end of 2020. Patients experience a spectrum of signs and symptoms including hypopigmented cutaneous macules alongside peripheral neuropathy including peripheral neuropathic pain (PNP) and disabling sensory neuropathies. Despite the development of effective and curative therapeutics *via* multidrug therapy (MDT), many barriers to treatment adherence and effective immunological control of the pathogen challenge the care of patients with leprosy. Socioeconomic barriers, such as disability-related social stigma and often undiagnosed nutritional deficiencies, have resulted in heightened disease severity. PNP therapeutics are associated with significant side effects and remain ineffective as the majority of individuals will not experience a greater than 30% reduction of symptoms. Nutrient supplementation is known to be instrumental in reducing host oxidative stress, strengthening the immune system and mitigating comorbidities. Likewise, dietary lifestyle interventions known to be physiologically beneficial have recently emerged as powerful tools conferring neuroprotective effects, potentially mitigating PNP severity. However, a significant knowledge gap concerning the effect of adequate nutrition on host immunological control of leprosy and PNP severity exists. Further evaluation of this relationship will provide key insight into the pathogenesis of leprosy, strengthening the current body of literature.

Keywords: leprosy, *Mycobacterium leprae*, *Mycobacterium lepromatosis*, neglected tropical disease, nutrition, peripheral neuropathic pain, whole foods plant-based diet

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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.[1,2] 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.[3–5] Patients experience hypopigmented cutaneous lesions, disabling sensory neuropathies and debilitating peripheral neuropathic pain (PNP), often leading to stigma and social ostracization.[3,6–9] Standard pharmacological treatment of PNP using antidepressants, anticonvulsants and opioids results in a less than 30% reduction of pain at best.[10] In addition, a significant side-effect profile including anticholinergic effects, dizziness, confusion, hypertension and

weight fluctuation contribute to poor treatment adherence overall.[11] 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.

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.[12–14] Given these extensive barriers, patients with leprosy continue to experience a reduced quality of life even with adequate access to gold standard therapeutics.[9,15,16] In the absence of effective pharmaceuticals for PNP, alternative interventions must be explored to reduce overall morbidity.

Pathogen elimination is predicated upon a balanced immune response in which inflammatory mediators aid in host recovery while antioxidant substances protect the host environment.[12,13,17] 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.[12–14,17–20] Nutrient supplementation has been instrumental in reducing host oxidative stress, strengthening the immune system and mitigating potential adverse events in leprosy.[17,21–24] 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.[25–29] 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.

Peripheral neuropathic pain

Pathogenesis

Peripheral sensitization. The International Association for the Study of Pain defines PNP as 'pain caused by a lesion or disease of the peripheral somatosensory nervous system'. As such, PNP may arise as a consequence of many distinct and complex mechanisms. Mechanical, chemical and infectious etiologies result in peripheral nerve damage or injury to the nerves from the dorsal root to the sensory receptors, causing a shift in the cellular and molecular environment.[16] Following the initial injury, macrophages and molecular inflammatory mediators are recruited to simultaneously clear damaged tissue and modulate neurotrophin expression to aid in regeneration. Inflammatory mediators alongside injured Aβ afferent nerves produce a hyperexcitable state causing peripheral sensitization. During this process, several mechanisms promote ectopic discharge, in which axons spontaneously fire.[10,16,30,31] Typically, this phenomenon subsides over time; however, frequent injury due to a chronic disease can lead to perpetual sensitization, allodynia and hyperalgesia, typical of PNP.[10]

Mechanisms behind sensitization (local response). Several mechanisms can contribute to the hypersensitive state underlying PNP. Molecular inflammatory mediators are situated at the foundation of this response. Neuropeptides and neurotransmitters, such as calcitonin gene-related peptide, substance P, nitric oxide, glutamate, serotonin and histamine, work to activate pain receptors, known as nociceptors. By-products of injury such as cytokines, prostaglandins, leukotrienes, bradykinin and growth factors may then sensitize nociceptors. In addition to the neuroinflammatory response, altered expression of several ion channels play a significant role in neuropathic pain pathogenesis.[16,30] Following nerve damage, sodium, calcium and potassium channels are abundantly expressed, actively lowering the action potential threshold. The neuroinflammatory response and hyperexpression of these ion channels work to enhance and promote sensitization, allowing for ectopic discharge, contributing to neuropathic pain.[10,16,30]

Mechanisms behind sensitization (neighbouring response). In addition to local peripheral sensitization, mechanisms involving neighbouring intact nerves also contribute to PNP. Ephaptic crosstalk is the process by which adjacent connected nerve fibres propagate an action potential synchronously. During a PNP state, this process is hijacked as the spontaneous ectopic discharge of an injured nerve is propagated throughout connected intact nerve fibres.[16,30] As ectopic release continues, neurotransmitters begin to over-accumulate in the extracellular space and may diffuse to affect neighbouring unconnected nerves causing spontaneous excitation, in a process known as nonephaptic crosstalk. Consequently, ephaptic and nonephaptic crosstalk diffuses the hypersensitive state of injured nerves throughout a larger area, effectively altering one's response to stimuli, contributing to a final diagnosis of PNP.[16,30]

Diagnosis

History and physical examination. By definition, neuropathy manifests in the presence of a lesion or underlying disease. As such, a comprehensive history and physical examination are critical during assessment. Due to the subjective nature of pain, specific inquiry concerning pain onset, location, duration, intensity, quality, progression and known history of pathogen exposure or trauma are required.[10,16,32] Likewise, relevant literature suggests that specific patient pain descriptors, such as burning, electric shock and aching, have been associated with neuropathic pain *versus* non-neuropathic manifestations and therefore remain significant to a final diagnosis.[33] In addition to patient's history, characteristic signs could be assessed on physical examination *via* quantitative sensory testing. Sensitivity to pain is a critical component of PNP and may be ascertained by exposing the affected neuropathic area to stimuli. Mechanical (brush, pin prick) or thermal (cold, hot) stimuli to assess the presence of allodynia, hypoesthesia and hypo- or hyperalgesia have emerged as powerful diagnostic tools.[10,33–37] Finally, significant comorbidities can heighten the severity of PNP. As a result, a discussion of sleep patterns, stress levels, potential substance use, available social support and a psychological assessment for anxiety and depression are paramount to achieving a final diagnosis.[10,35]

Screening tools. Several comprehensive questionnaires have been established to guide physicians and patients in the diagnosis of PNP. These include the Neuropathic Pain Scale (NPS), Neuropathic Pain Questionnaire (NPQ), Neuropathic Pain Symptom Inventory (NPSI), Pain Quality Assessment Scale (PQAS), the Michigan Neuropathy Screening Instrument (MNSI), the McGill Pain Questionnaire (MPQ), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 questions (DN4), ID Pain and painDETECT.[10,16,33,35,37] The most common verbal descriptors utilized throughout these screening tools include tingling, needles, burning and shooting, which are often associated with PNP. Although many of these screening tools have been validated in over 90 languages, they cannot replace clinical judgement. These tools have a sensitivity of 74–85% and specificity of 76–90%, suggesting that 15–26% of patients with PNP remain undetected.[10,33,37]

Laboratory testing. Laboratory testing is required to confirm both the presence and underlying cause of PNP. Electrophysiological techniques have been essential in assessing nerve function and the presence of neuropathy. Specifically, nerve conduction studies, *via* somatosensory-evoked potentials (contact heat and laser-evoked potentials), and quantitative axon reflex measures, *via* the quantitative sudomotor axon reflex test, are utilized to measure nerve injury and activity.[10,32,33,35–38] Although these techniques are well established in the diagnosis of PNP, small, unmyelinated nerve fibres are often overlooked. As such, skin and nerve biopsy, in conjunction with electrophysiological techniques, must be carried out to assess intraepidermal nerve fib res.[10,32,33,35–39] Finally, to determine the presence of a neuronal lesion, basic imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) can be utilized.[32–34] If a lesion is not detected, the underlying disease mechanism responsible for PNP must be examined for. Standard biochemistry including complete blood count with white blood cell differential, sedimentation rate, thyroid function, basic metabolic panel and nutritional assessment should be completed. Specific testing to rule out underlying etiology, such as cancers, infection, rheumatologic syndromes and chemical intoxications, should be undertaken along with neuropathy-focused testing.[16,32,33,40] As such, the combination of a comprehensive history, screening tools and laboratory testing is required for a definitive diagnosis of PNP.

Symptoms

Overview. Due to the multivariate nature of the mechanisms underlying PNP, the clinical spectrum of disease varies immensely. Excessive ectopic discharge produces a heightened sensitivity to stimuli (positive sensory symptoms), while extensive nerve damage may simultaneously result in a loss of sensory function (negative sensory symptoms). Patients experiencing PNP present with a combination of both positive and negative symptoms, which do not necessarily correspond to the primary etiology.[10,16,32,33,37] PNP also often results in a reduced quality of life, as it has a significant negative impact on the physical and mental well-being of the patient.[16]

Positive sensory symptoms. Positive sensory symptoms include those that result in a heightened response to stimuli and may be categorized as spontaneous or evoked pain. Spontaneous positive sensory symptoms include paresthesia, paroxysmal pain and superficial pain, often described as an ongoing sensation of pins and needles, electric shock attacks and burning, respectively. Evoked positive sensory symptoms include allodynia, or pain brought on by nonpainful stimuli, and hyperalgesia, or pain brought on by painful stimuli. Hyperalgesia may be further categorized by the stimuli that elicits the response, including pressure and pin prick (mechanical), or cold and hot (thermal) subtypes. Finally, patients may also experience temporal summation in which repeated mechanical stimuli evokes increasing levels of pain.[10,16,32,33,37]

Negative sensory symptoms. Negative sensory symptoms include those that result in a diminished or absent response to stimuli due to a loss of sensory function. These include hypoesthesia and hypoalgesia, in which patients experience a reduced response to nonpainful and painful stimuli, respectively. Depending on the type of stimuli engaged, both negative sensory symptoms may be further subdivided as mechanical or thermal.[10,16,32,33,37] Symptoms of PNP may dictate the underlying mechanism to which they are being caused, resulting in mechanism-based therapeutics.

Treatment

Overview. Treatment of PNP may only be initiated after an adequate assessment of the underlying disease. If symptoms persist despite suitable or appropriate management, therapeutics for PNP may be considered. Prior to treatment it is crucial to establish comprehensive and realistic goals with the patient, as complete pain resolution is typically not feasible. A 30–50% reduction of pain is considered 'much improved' as 20–40% of individuals are unlikely to achieve a pain reduction greater than 30%.[10,37,41–43] Due to the additional psychosocial burden often associated with PNP, an interdisciplinary therapeutic approach is often utilized. Nonpharmacological management works to mitigate sleep disturbances, diminished quality of life, depression and anxiety which actively enhance the severity of PNP. In combination with first-, second- and third-line pharmaceuticals, a cumulative approach to PNP remains the gold standard of management.[10,37,41]

First-line therapeutics. First-line therapeutics include pharmaceuticals with the greatest efficacy, effectiveness and tolerance based on the literature. These include antidepressants and anticonvulsants. Antidepressants work to inhibit serotonin and norepinephrine reuptake while also blocking sodium channels that contribute to ectopic discharge. Specifically, the tricyclic antidepressants amitriptyline, nortriptyline and desipramine have been utilized for the treatment of PNP. In addition, selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) such as duloxetine and venlafaxine have also proven to be efficacious. Although side effects such as sedation, nausea, ataxia and anticholinergic effects are common with antidepressants, they also work to mitigate psychological comorbidities common in PNP.[10,11,16,32,35,37,41–45] Likewise, anticonvulsants that decrease the release of neuropeptides and neurotransmitters such as glutamate, norepinephrine and substance P, which significantly contribute to peripheral sensitization, are also considered first-line therapeutics. Calcium channel $\alpha 2$-δ ligands gabapentin and pregabalin, and sodium channel inhibitors, such as carbamazepine and oxcarbazepene, have been shown to be effective treatments for PNP. Common side effects include sedation, dizziness and peripheral oedema (Table 1).[10,11,16,32,35,37,41–45]

Second- and third-line therapeutics. Second- and third-line therapeutics include opioids and topical agents that are reserved for patients who did not respond well to first-line treatment. Similar to antidepressants, opioids inhibit norepinephrine

Table 1. Peripheral neuropathic pain therapeutics and side effects.

First-line therapeutics			**Dose (mg/day)**	**Side effects**
Antidepressants	Tricyclic antidepressants	Amitriptyline	10–150	Anticholinergic effects (blurred vision, constipation, dry mouth, urinary retention), cardiac conduction block, confusion, orthostatic hypotension, sedation, weight gain
		Nortriptyline	10–150	
		Desipramine	25–150	
	Serotonin-norepinephrine reuptake inhibitors	Duloxetine	30–120	Anxiety, appetite loss, constipation, dry mouth, hyperhidrosis, hypertension, insomnia, nausea, sedation
		Venlafaxine	150–225	
Anticonvulsants	Calcium channel ligands	Gabapentin	100–3600	Blurred vision, dizziness, lethargy, peripheral oedema, sedation, weight gain
		Pregabalin	150–600	
	Sodium channel inhibitors	Carbamazepine	200–400	Hepatotoxicity, hyponatraemia, sedation
		Oxcarbazepine	300–600	
Second/third-line therapeutics			**Dose (mg/day)**	**Side effects**
Opioids	Weak	Tramadol	25–400	Constipation, dizziness, nausea/vomiting
	Strong	Morphine	10–20	Addiction, ataxia, constipation, dizziness, lethargy, nausea/vomiting, seizures
		Oxycodone		
		Methadone		
		Levorphanol		
Topical		Lidocaine patch	1–4/3 months	Local erythema and rashes
		Capsaicin cream	1–3 uses/day	

Source: Adapted from Cavalli *et al.*[11]

and serotonin reuptake. The weak opioid tramadol and stronger opioids morphine, oxycodone, methadone and levorphanol are known to be sufficient pain-relieving pharmaceuticals. However, due to their propensity for addiction and possibility of significant side effects, including nausea, vomiting, constipation, lethargy, seizures, ataxia and potential respiratory depression, opioids are often avoided. Finally, topical agents that temporarily block sodium channels are also second-line therapeutic options utilized for PNP. Lidocaine patches and capsaicin cream and patches have been shown to alleviate PNP, although occasionally causing local erythema and rash (Table 1).[10,11,16,32,35,37,41–44]

Alternative and exploratory therapeutics. Non-pharmaceutical therapeutics have been essential

in alleviating the burden of PNP. Rather than a biochemical intervention, these treatments broadly target the gross anatomy, and psychological aspects of PNP, potentially mitigating side effects. Nerve stimulation techniques such as transcutaneous electrical or peripheral nerve stimulation, spinal cord, and deep brain stimulation, and direct current stimulation are being explored as potential therapeutic options, as well as surgical nerve decompression.[32,42,46,47] Likewise, nonpharmaceutical techniques that work to alleviate the psychological burden of PNP have been implicated as therapeutics. These include behavioural, cognitive and animal therapy; guided imagery; diaphragmatic breathing; mindfulness-based stress reduction; acupuncture; and exercise.[42] Many nonpharmaceutical therapeutics have been shown to mitigate pain at various levels; however, further research is required to validate efficacy.

Recent literature exploring the treatment of chronic pain has grown in specificity. Notably, research has been focusing on alternative pharmaceuticals that are biochemically similar to the current standard of care. Opioid antagonist, specific to the presynaptic *N*-methyl-d-aspartate receptor, which inhibits the neurotransmitter glutamate, has been explored with variable efficacy.[48] Likewise, drugs that act on PNP pathway targets such as sodium channel blockers (BIIB074 and Oxcarbazepine), angiotensin II type 2 receptor antagonists and nerve growth factor antagonists are being actively researched as potential therapeutics for pain reduction; however, more information is needed to determine effectiveness.[47,48] As the current standard of care for PNP is both ineffective and prone to side effects, additional research into novel pharmaceuticals and potential lifestyle interventions is direly needed.

Underlying etiologies

PNP may be the result of several distinct underlying health conditions. In the absence of a mechanical etiology, the underlying cause of PNP may be metabolic, nutritional, inflammatory, infectious or genetic in nature. Syndromes affecting metabolism are the most common cohort of PNP patients including painful diabetic neuropathy, alcohol abuse and treatment, amyloidosis and hypothyroidism. Although vitamin B and E deficiencies, and copper deficiency exacerbate PNP, many underlying etiologies arise from therapeutics rather than a disease mechanism itself. Common chemotherapeutics, infectious disease therapies (e.g. the antibiotics metronidazole and fluoroquinolone class drugs) and other drugs and toxins are often responsible for PNP. Inflammatory conditions such as vasculitis-associated neuropathy, and paraproteinemia, and genetic disorders such as Charcot-Marie-Tooth disease, and Fabry disease, may also cause PNP. Finally, infectious etiologies including leprosy and HIV significantly contribute to PNP prevalence. Up to 70% of individuals with leprosy will experience PNP to some degree following routine MDT. In addition, leprosy patients in reaction requiring corticosteroids are at an increased risk of developing biochemical diabetes, a significant and common comorbidity of leprosy. Biochemical diabetes may manifest in up to 50% of some leprosy cohorts and therefore remains a significant contributor to the incidence of PNP within leprosy patients. As nutritional interventions may modulate both leprosy and diabetes, a specific exploration of each mechanism remains relevant.[10,15,16,32,49,50]

PNP in diabetes and nutritional interventions evaluated to date

More than 425 million individuals have been diagnosed with diabetes mellitus worldwide. Neuropathy is found in roughly half of this population and up to 30% of individuals with diabetes have experienced PNP.[51] The microangiopathy and hyperglycaemia associated with diabetes can damage nerve fibres while simultaneously encouraging inflammation and oxidative stress resulting in the hyperexcitable state underlying PNP.[51,52] As such, patients within this cohort are more likely to experience adverse health events such as disruptions to sleep, mood and quality of life, as well as an increased mortality rate. Despite its prevalence, PNP in diabetes is often misdiagnosed and inadequately treated.[51] Duloxetine and pregabalin have emerged as first-line therapeutics; however, effectiveness is limited.[51,53] In addition, although pathogenic treatments targeting glycolysis by-products responsible for PNP have emerged, none have been officially approved. Research has suggested that glycaemic, cholesterol and triglyceride control *via* diet and exercise counselling is effective when treating PNP.[51,54] Consequently, the literature for nutritional interventions for painful diabetic neuropathy is more robust.

Several studies assessing the effectiveness of specific nutrients in the treatment of diabetic PNP have been conducted. Both vitamin B and D3 oral supplementation have been evaluated. Although positively trending, the use of vitamin B for diabetic PNP has seldom reached statistical significance.[55,56] However, in a study assessing weekly oral vitamin D3 (50,000 IU) in 58 adults for 12 weeks, statistical significance ($p < 0.001$) was met in both MNSI questionnaire and physical examination.[22] Likewise, studies assessing the use of omega-3 oral supplementation in diabetes have shown similar results. A statistically significant improvement in both corneal nerve fibre length ($p = 0.002$) and MPQ ($p < 0.01$) have been shown when taking daily oral omega-3 supplements for up to 1 year, in patients with type 1 and type 2 diabetes, respectively.[21,23] In addition, strategies such as lifestyle counselling have also resulted in statistically significant improvements in diabetic PNP. Patients receiving routine lifestyle counselling including diet and nutrition coaching have exhibited a 27% reduction in diabetic PNP, which remains statistically significant after a 15-year follow-up.[25,27] These findings have led recent research to focus on total dietary patterns rather than specific macro- or micronutrients and vitamins.

Early research has shown that vegetarian/vegan diets are associated with a reduction of PNP in patients with diabetes. A cohort study assessing vegetarian/vegan diets in 21 participants with type 2 diabetes reported a statistically significant ($p < 0.01$) reduction of both serum triglycerides and total cholesterol, along with a noticeable decrease in subjective pain (17/21 patients endorsed complete pain relief in 4–16 days), weight (-4.9 ± 2.7 kg, 0 to -9.6 kg) and insulin requirements (5/19 patients no longer required insulin, while the remaining 14 experienced a 54% decrease in requirements overall, ranging from 25% to 75%).[29] A systematic review of vegetarian and vegan diets for the management of type 2 diabetes reports similar results. Data from over 110 observational and clinical trials suggest that these dietary patterns are associated with significant improvements in fasting glucose, insulin requirements, weight, cholesterol and lipid management. Specifically, in a 16-day trial assessing a near-vegetarian diet, insulin use was completely discontinued in 9/20 individuals and statistically significantly decreased from 26 to 11 units/day in the remaining participants ($p < 0.001$). Likewise in a 26-day trial assessing a similar intervention in conjunction with intensive exercise, mean fasting glucose concentrations decreased up to 24% ($p < 0.001$). Studies also reported a statistically significant decrease in weight alongside HbA1c levels ($p < 0.0001$), as well as a statistically significant reduction in lipid concentrations of up to 31% ($p = 0.01$), following a 22-week vegan dietary intervention. The prevalence of diabetes was up to two times lower among individuals with vegetarian and vegan diets, making these dietary patterns as effective as gold standard strategies for the management of diabetes.[28] Finally, a comprehensive randomized controlled trial (RCT) assessing a low-fat plant-based diet plus vitamin B12 supplementation *versus* vitamin B12 alone to manage the PNP of type 2 diabetes in 35 participants aged 18–65 corroborates previously reported data. Neuropathy was assessed using a Sudoscan device while pain was measured using various questionnaires including a visual analogue scale (VAS), MNSI, MPQ and NPSI. Dietary adherence was measured using 2-day dietary records, and participants were assessed twice within a 20-week follow-up period. A significant decline in mean weight [-7.0 ± 5.0 kg *versus* -0.6 ± 3.5 kg, 95% confidence interval (CI): -9.4 to -3.4, $p < 0.001$], and body mass index (BMI) (-2.4 ± 1.5 *versus* -0.2 ± 1.2, 95% CI: -3.2 to -1.2, $p < 0.001$), was observed alongside a statistically significant improvement in diabetes-associated PNP on MNSI (-2.2 ± 2.4 *versus* -0.6 ± 1.5, 95% CI: -3.0 to -0.2, $p = 0.03$) and MPQ (-9.1 ± 11.4 *versus* -0.9 ± 11.3, 95% CI: -16.1 to -0.3, $p = 0.04$) between the intervention and control groups, respectively. Quality of life also improved on the Norfolk Quality of Life Questionnaire, but did not reach statistical significance ($p = 0.43$).[26] Overall, vegetarian/vegan diets have proven to be effective in the management of the PNP of diabetes. Whole foods plant-based diets (WFPBDs) that avoid processed foods provide sufficient glycaemic control and lipid management, which, when uncontrolled, exacerbate PNP. As a result, this phenomenon may be translatable to the management of leprosy in which comorbidities of diabetes and PNP are keystone symptoms.

Leprosy

History/epidemiology

Leprosy, or Hansen's disease, is caused by acid-fast rod-shaped bacilli of the genus *Mycobacterium*.

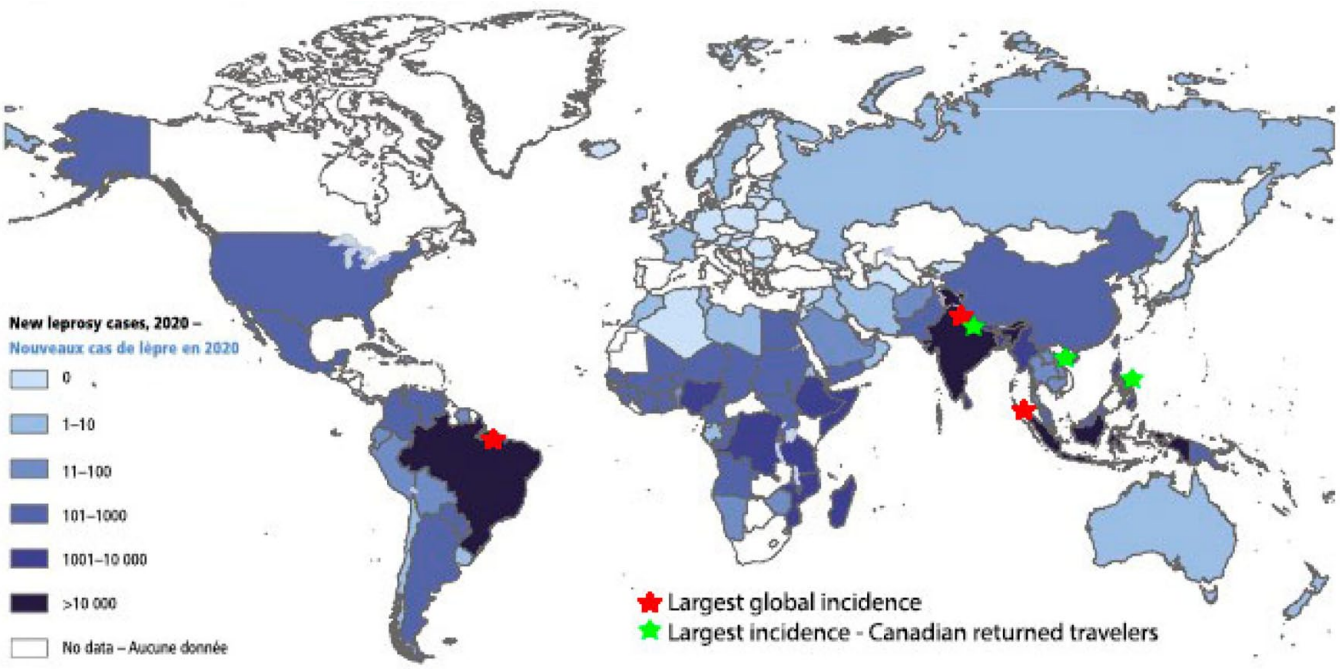

Figure 1. World Health Organization geographic distribution of new leprosy cases, 2020. Red star: India, Brazil and Indonesia. Green star: India, Vietnam and the Philippines.
Source: Adapted from World Health Organization.[61]

Mycobacterium leprae was first described by Norwegian physician Dr Gerhard Henrik Armauer Hansen in 1874, while *Mycobacterium lepromatosis* was initially sequenced in 2008.[6,7,57–59] Both these bacteria have the functional capacity to cause leprosy, but are genetically dissimilar enough to be considered separate species.[6,59] Although leprosy was originally identified in the 19th century, historical records suggest that the pathogen has remained a global endemic disease for at least 3000 years. The pathogen rose to prominence in the 13th century as a consequence of urbanization and has since experienced a slow decline in prevalence.[7,57] In 2000, the WHO no longer considered leprosy a public health concern as its worldwide point prevalence fell below 1 in 1000. However, this milestone was not achieved within each individual country until 2005.[1,2,6,7] Despite this, more than 200,000 new leprosy diagnoses are still made each year as it remains endemic in 140 countries.[1,2,6]

Globally, Brazil, India and Indonesia account for 74% of the total new case burden of leprosy and in 2020 alone 127,396 new cases were reported from 127 countries (Figure 1).[60] Although the global incidence of leprosy has been steadily declining, a significant degree of transmission is still evident. This is especially concerning within Western populations, where the experience of leprosy is often underappreciated. In Canada, increasing levels of immigration from leprosy-endemic countries – particularly those form endemic areas of Asia – and poor migration detection programmes have resulted in a significant increase in leprosy incidence.[3–5] Migrants from India, the Philippines and Vietnam account for over 70% of the Canadian experience of leprosy (Figure 1).[3,5,8]

Transmission

Leprosy is primarily spread *via* aerosolized droplets and to a lesser extent by direct skin contact or vertical transmission.[1,3,6,7] Although humans are the principal reservoir, nine-banded armadillos, red squirrels and chimpanzees are also known hosts of *M. leprae* and *M. lepromatosis*, respectively.[1,6,7,58,62,63] Despite its known transmission routes, many patients do not have identifiable contacts due to an incredibly variable and typically prolonged incubation period.[3] Disease onset has been reported to

occur from 3 months to 40 years after exposure, with the tuberculoid and lepromatous forms of leprosy having a 3- to 5-year and 9- to 12-year incubation period, respectively.[1,3,6] This variability has led researchers to explore alternative routes of transmission, such as environmental proxies, vectors and other animal reservoirs; however, more research is needed.[58] Finally, transmission risk is predicated on several confounding factors. Duration and incidence of exposure, host infectivity, genetics, nutrition, hygiene and a compromised immune system may all modulate transmission risk.[3,6–8]

Pathogenesis

Phenolic glycolipid I antigen. A complete picture of leprosy pathogenesis has eluded researchers for decades due to its complex and multivariate relationship with host immunity, and its inability to be cultured in standard media. Unique animal models have allowed for some speculation despite these barriers. Following transmission routes, leprosy enters the host where it is able to survive and multiply within macrophages, monocytes, keratinocytes and Schwann cells.[64,65] The unique and specific *M. leprae* antigen, phenolic glycolipid I (PGL-I), preferentially binds to Schwann cells, initiating bacilli uptake. Pathogen replication is incredibly slow upon entry, eventually eliciting an inflammatory response.[7,64] During this response, specific pathogen recognition receptors (PRRs) and pathogen-associated molecular patterns (PAMPs) interact, engaging inflammatory responses characteristic of the polarized states of immunity in leprosy.

T helper cell response. In tuberculoid leprosy PRRs, toll-like receptors 1 and 2 and nucleotide oligomerization domains interact with *M. leprae* PAMPs, triacylated lipopeptides and muramyl dipeptide, respectively. These interactions upregulate Th1 cytokines interferon gamma (IFN-γ), tumour necrosis factor alpha (TNF-α), interleukin-12 (IL-12), IL-15, IL-18, IL-32 and IL-1β, resulting in macrophage and dendritic cell differentiation, and autophagy. This cell-mediated inflammatory response is highly effective, as the pathogen is eliminated or contained within granulomas, leaving few active organisms. In lepromatous leprosy, bacilli inhibit IFN-γ expression *via* the secretion of Th2 cytokines, IFN-β, IL-4, IL-5 and IL-10. In addition, leukocyte immunoglobulin-like receptors further inhibit Th1 cytokines, resulting in decreased cell-mediated immunity. Consequently, as a Th2 type humoral response predominates, bacilli are able to proliferate within and around foamy macrophages, resulting in poor pathogen control characteristic of lepromatous leprosy.[7,64,65] Recent literature has emerged suggesting a third cytokine profile, Th17, representative of a nonpolarized (Th0) disease state. Studies show that individuals experiencing borderline tuberculoid leprosy or leprosy reaction exhibit both the Th1 cytokine, IFN-γ, ad Th2 cytokines IL-4 and IL-5, simultaneously alongside Th17 cytokines IL-17, IL-21 and IL-22. It is hypothesized that the Th0/Th17 cytokine profile may be indicative of an alternative pathway for pathogen clearance; however, more research is necessary to elucidate its impact.[66,67]

Peripheral sensitization. Regardless, Th1, Th2 and Th0 type inflammatory responses are implicated in peripheral sensitization. Previous literature suggests that inflammation leads to irreversible damage to Schwann cells, resulting in fibrosis and eventual leprous neuropathy.[7] Cytokine elevation, including inflammatory mediators such as IFN-γ, TNF-α, IL-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10 and IL-17, produces reactive oxygen intermediates, which generate a toxic environment causing inflammatory demyelination and subsequent gross tissue damage.[66–70] It is also suspected that PGL-I induces nitric oxide synthase, effectively increasing oxidative stress within macrophages. Inadequate host control of the resulting reactive oxygen species (ROS) leads to mitochondrial damage, causing axon demyelination and leprous neuropathy. These by-products of injury including nitric oxide synthase, and cytokines, may then propagate peripheral sensitization throughout neighbouring tissues *via* mechanisms previously described. Interestingly, research has shown that effective control of ROS *via* nutritional supplementation may mitigate this phenomenon entirely (Figure 2).[64,71,72]

Diagnosis

Overview. Leprosy is diagnosed clinically based on an extensive history indicative of exposure and characteristic clinical manifestations. Presence of hypo- or anaesthetic hypopigmented lesions during assessment, and thickened peripheral nerves identified *via* palpation or ultrasonography, are key diagnostic features of leprosy.[73–75] Confirmatory laboratory testing to detect acid-fast bacilli in slit skin smears or biopsies using Fite staining and

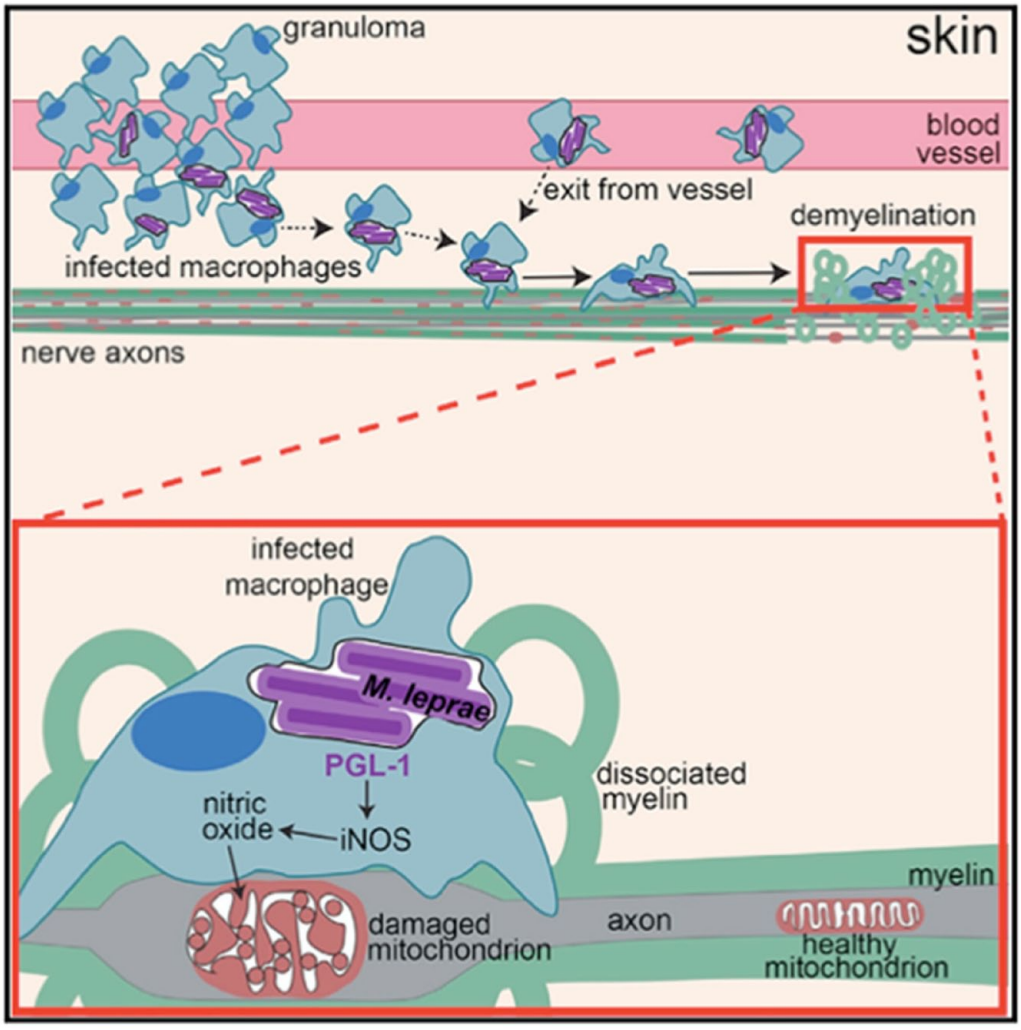

Figure 2. *Mycobacterium leprae* increases oxidative stress within infected macrophages and damages mitochondria, causing demyelination and subsequent peripheral neuropathic pain.
Source: Adapted from Madigan *et al.*[71]
iNOS, inducible nitric oxide synthase; PGL-1, phenolic glycolipid I.

light microscopy or polymerase chain reaction (PCR) amplification can also be completed. Diagnostic specimens are preferentially collected from persistent and active lesions typically located in cooler parts of the body.[1,3,6,7] Diagnostic specificity reaches 97% in the presence of hypopigmented lesions, thickened peripheral nerves and acid-fast bacilli in skin smear.[1,6] In paucibacillary leprosy, where acid-fast bacilli are scarce, skin biopsy can also be used.[3,7] Nucleic acid amplification testing has emerged as a powerful diagnostic tool in the identification of leprosy infection; however, implementation is limited in resource-constrained countries where leprosy is most prominent.[76–78]

Classification systems. The majority of the population is not susceptible to leprosy as only 1.25% of individuals exposed will enter the clinical spectrum of disease.[3] Clinical manifestations and classification of leprosy are dictated by two algorithms which are largely influenced by the host's immune response. The WHO and Ridley Jopling classification systems utilize clinical and histopathological features, bacteriological index and the number of skin lesions present to classify and treat patients along a spectrum (Figure 3).[1,3,6,7] Patients with a low bacterial load that endure a cell-mediated Th1 response are classified at the tuberculoid/paucibacillary pole. Clinically, lesions at this pole are limited (<6), asymmetrically distributed, well

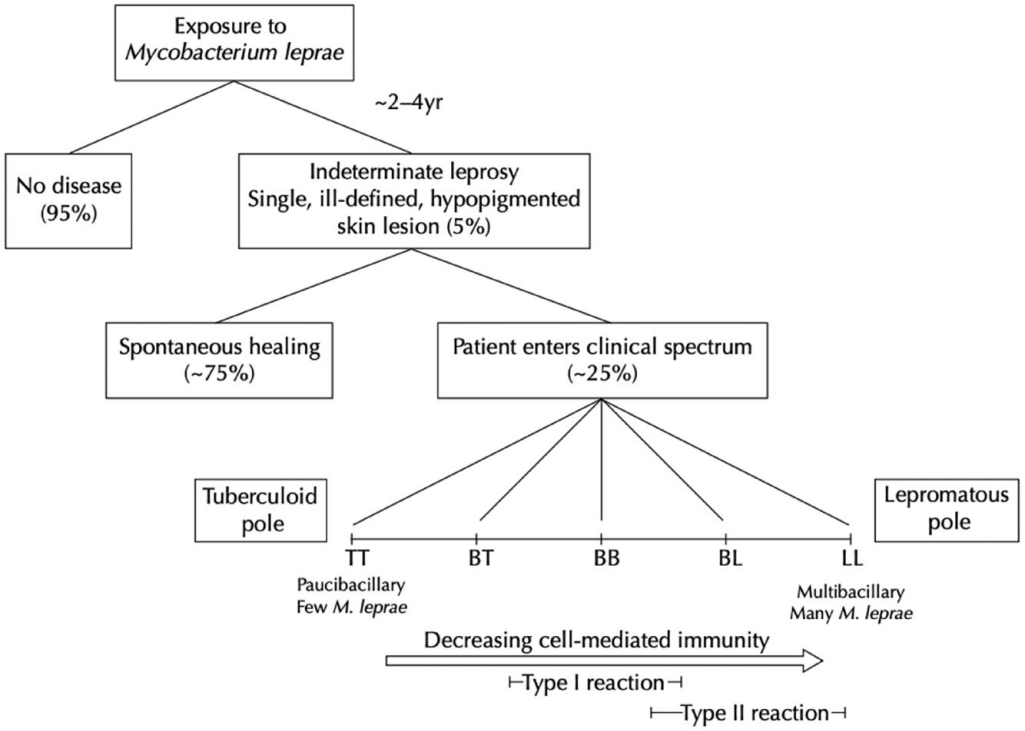

Figure 3. Transmission risk and clinical spectrum of leprosy.
Source: Adapted from Boggild *et al.*[8]
BB, borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; TT, tuberculoid leprosy.

circumscribed, hypopigmented, dry, scaly and anaesthetic. Patients with a high bacterial load and a predominantly humoral or Th2 response are classified at the lepromatous/multibacillary pole. Lesions are abundant (6+), symmetrically disseminated, smooth, shiny and slightly hypopigmented or erythematous.[1,3,6–8] Individuals may also present anywhere along this spectrum with borderline tuberculoid, mid-borderline or borderline lepromatous leprosy. Skin lesions are highly variable in quantity and appearance as a result of an unstable balance between cell-mediated immunity and pathogen abundance and will typically progress towards a distinct pole.[3,6]

Symptoms

Overview. Leprosy primarily presents as hypopigmented cutaneous macules and debilitating sensory and motor dysfunction in patients. Neuropathy is a hallmark symptom of leprosy and can vary depending on the host immune response.[3,6–8] Extensive nerve damage in paucibacillary leprosy typically presents early and can result in wrist drop, foot drop and clawing of the hand. Patients with multibacillary leprosy endure slow yet progressive nerve damage, often beginning as hypoesthesia and distal weakness of the hands and feet.[3,6,8] In both cases, peripheral neuropathies often lead to repetitive trauma, infection and necrosis, resulting in amputation.[3] Leprosy patients may also experience extensive nasal and oral mucosal involvement which can cause nasal obstruction, epistaxis, septal perforation and saddle nose deformity. Ulcerative erythematous lesions present in 11.5–57% of leprosy patients involving the hard and soft palates, posterior tongue and gingivae.[3,6] Finally, blindness can occur in up to 5% of patients due to extensive damage to cranial nerves innervating the cornea, orbicularis oculae musculature and the optic nerve itself. These additional symptoms are more common in patients with lepromatous leprosy due to poor cell-mediated immunity and management of infection.[3,6]

Reactions. Sudden acute inflammatory responses, known as leprosy reactions, can exacerbate neuritis, further impairing function of sensory, autonomic and motor nerves leading to limb deformity

and a reduced quality of life. Reactions are considered medical emergencies and can occur in up to one-third of leprosy patients at initial presentation.[3,8] There are two common types of reactions: type 1 (upgrading or downgrading/reversal) reactions and type 2 erythema nodosum leprosum (ENL) reactions. Type 1 reactions are most often characterized by cellular hypersensitivity, altered expression of IFN-γ, TNF-α and IL-10, causing a shift towards the tuberculoid pole. Symptoms such as fever, malaise, oedema, enhanced neuritis and worsening of pre-existing leprous skin lesions are characteristic of a type 1 reaction. Type 1 reactions can occur spontaneously or may be induced by MDT, illness, psychological stressors, puberty, pregnancy or parturition.[63,79] Conversely, type 2 ENL reactions are characterized by humoral hypersensitivity, antigen–antibody deposition and an increased release of inflammatory cytokines such as TNF-α, typically occurring at the lepromatous pole. Multisystemic inflammation including the eyes, joints, digits, lymph nodes, testicles and nerves alongside crops of tender erythematous skin lesions that wax and wane in areas of previously unaffected skin are characteristic of ENL. Type 2 reactions can be triggered by treatment or immune stimulants such as viral infections, vaccination or tuberculin skin test.[3,7,8,64,80,81]

Treatment

Therapeutics. Dapsone emerged as a first-line leprosy therapeutic in the 1940s; however, in the 1960s, due to antibiotic resistance, MDT was established as the gold standard and officially approved for the treatment of leprosy in 1981.[1,3,7] The current WHO recommendations for the treatment of multibacillary leprosy include 1–2 years of triple therapy consisting of rifampicin 600 mg/month, clofazimine 300 mg/month or 50 mg/day and dapsone 100 mg/day. Dosing remains the same for paucibacillary leprosy; however, only 6 months of therapy is required due to enhanced control of pathogen replication.[1,3,7] Single-lesion paucibacillary leprosy can also be treated with a single course of ROM (rifampin, ofloxacin, minocycline) therapy, which includes 600 mg rifampin, 400 mg ofloxacin and 100 mg minocycline (Table 2).[3] Likewise, ofloxacin-containing MDT has recently emerged as a well-tolerated and effective therapeutic alternative to standard dapsone- and clofazimine-containing MDT which is often associated with significant side effects.[82] Following MDT, lesions typically resolve within 1 year, but may persist for up to 5 years in multibacillary leprosy. Up to 1.4% of patients will relapse within the first 10 years after treatment, requiring a follow-up period of at least 5–10 years.[3] Likewise, after 1 year of MDT, 5–10% of patients undergo a type 1 reaction, requiring 40–60 mg of prednisone daily, tapered as reaction begins to subside. Patients undergoing a type 2 ENL reaction also require prednisone for neuritis; however; this may be substituted for 300–400 mg of daily thalidomide, tapered to 50 mg/day for as long as necessary. Clofazimine can also be used as a steroid-sparing agent in cases of chronic ENL (Table 2).[3,7] Corticosteroid therapy for 3–6 months may be required to treat resultant neuritis in both cases, and patients must be followed every 3 months for the first year after treatment for acute reactions.[3] Although patients may be considered cured, research has shown significant progression of physical disability up to 15 years after treatment cessation.[83] Likewise, standard polychemotherapy is associated with significant side effects such as hemolytic anaemia, sulfonic syndrome, hepatitis, gastrointestinal alterations and photosensitivity.[84] Given a complex clinical course often requiring the engagement of several allied health services such as occupational therapy, physical therapy, nutrition and dietician services, wound care, ophthalmology and endocrinology, as well as the propensity for reaction, relapse and prolonged disability, the burden of leprosy remains significant both physically and economically.[4]

Stigma. Despite adequate leprosy therapeutics, the psychological toll endured by patients remains a substantial burden. Patients suffering from debilitating PNP experience significant activity limitations and social participation restrictions, leading to stigma and social ostracization. These disabilities can perpetuate a vicious cycle in which negative emotions and behaviours further promote poor treatment adherence, enhancing physical disability.[9,85–87] As such, leprosy patients are significantly more likely to encounter psychiatric morbidity. A comprehensive systematic review assessing mental health in leprosy patients suggests that determinants of health such as stigma, discrimination, visible impairments, therapeutic side effects and poor lifestyle choices significantly impact psychiatric morbidity.[9] Leprosy patients are more likely than the general population to experience depression, mental distress, reduced quality of life, suicidal tendencies and anxiety disorders, contributing to an estimated disability-adjusted life year (DALY) of

Table 2. Leprosy therapeutics, dosage and duration.

Disease state	Drug	Dosage (mg)	Duration (months)
Paucibacillary (I, TT, BT)	Rifampin	600/month, supervised	6
	Dapsone	100/day, self-administered	
	Clofazimine	300/month, supervised or 50/day, self-administered	
Single lesion, Paucibacillary	Rifampin	600	One time
	Ofloxacin	400	
	Minocycline	100	
Multibacillary (BB, BL, LL)	Rifampin	600/month, supervised	12
	Dapsone	100/day, self-administered	
	Clofazimine	300/month, supervised or 50/day, self-administered	
Type 1 reversal reaction	Prednisone	40–60/day	Tapered
Type 2 erythema nodosum leprosum	Prednisone	40–60/day	Tapered
	or		
	Thalidomide	300–400/day	Tapered to 50 mg

Source: Adapted from World Health Organization.[1]
BB, borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; I, Indeterminate disease; LL, lepromatous leprosy; TT, tuberculoid leprosy.

over 21,000.[9,88–92] It is especially important to note that patients actively receiving treatment are significantly more likely to experience adverse psychiatric morbidity. Psychological factors may be exacerbated by the side effects of gold standard therapeutics such as MDT and steroids, including the highly stigmatizing hyperpigmentation of clofazimine, increasing DALYs and perpetuating this vicious cycle.[9] Consequently, social stigma is deeply entrenched in the modern experience of leprosy, and a need for novel therapeutics that may mitigate the influence leprosy has on psychiatric comorbidities is desperately required.

Nutritional interventions

Overview. Proper elimination of bacilli requires an adequate immune response for which clinical manifestations are characterized. Although inflammatory mediators aid in host recovery, ROS and nitric oxide signalling molecules promote oxidative stress, resulting in significant injury to surrounding tissues.[12,13,17] Antioxidant substances are required to maintain a balanced immune response that eliminates pathogens while protecting the host environment. However, inflammatory mediators, therapeutics and dietetic limitations can significantly reduce antioxidant availability, resulting in a more significant pathogenesis and disease severity. Further to this, both economic status and inadequate access to nutritional knowledge can significantly enhance leprosy transmission (in that leprosy is a disease of poverty) and pathogenesis.[18,87] Nutritional deficiencies of vitamins and minerals with powerful antioxidant and immune regulatory properties are common. Specifically, it has been shown that vitamins A, C, D, E and B12 and minerals zinc, magnesium and selenium are significantly lower in leprosy patients when compared with healthy controls.[12–14,19,20] As such, research has explored supplementing specific nutrient deficiencies in leprosy to enhance the antioxidant response and decrease morbidity overall.

Vitamin A, C and D. Vitamin A and its precursors, retinoic acid and beta carotene, have been shown to decrease oxidative stress by inhibiting lipid peroxidation and capturing free radicals. Research has also demonstrated that they can modulate the Th1 immune response, as low vitamin A levels result in reduced IFN-γ and weak cell-mediated immunity. Vitamin A consumption within leprosy cohorts is routinely below the recommended level, possibly directing disease progression.[12,13] Similarly, vitamin C also exhibited a protective role against bacterial infections. It acts as a powerful enzymatic co-factor that can eradicate free radicals and a nonenzymatic antioxidant, controlling ROS-induced inflammation. Research has shown that supplementation with vitamin C has resulted in enhanced pathogen control in non-leprosy mycobacterial infections. Vitamin D shares similar immune-modulatory properties; however, research has focused on genetics as specific polymorphisms in the vitamin D receptor gene yield explicit immune responses that characterize leprosy.[12,13] Although vitamins A, C and D have been significantly implicated in the immune response of bacterial infections, the relative impact on leprosy has been seldom reported.

Vitamin E and zinc. In contrast, evidence to support nutrient supplementation in leprosy treatment has been accrued for with vitamin E and zinc. Vitamin E has been shown to protect lipid membranes against peroxidation in high oxidative environments. In a comprehensive trial assessing the co-administration of daily oral vitamin E (400 IU) with MDT *versus* MDT alone for 12 months, a significant reduction of oxidative stress indices, as measured by the presence of enzymatic and nonenzymatic antioxidants in whole blood samples, was described in the vitamin E plus MDT group.[12,13,17] Zinc is also a powerful antioxidant that has the capacity to mitigate the effects of lipid peroxidation, as well as control the Th1 inflammatory response. Supplementation with daily oral zinc (220–400 mg) for 3–8 months has been shown to improve therapeutic requirements and tolerance and decrease the incidence of leprosy symptoms and reactions. Specifically, up to 80% of patients receiving zinc supplementation showed increased tolerance to conventional therapeutics, and an almost 30% reduction in the incidence of leprosy reactions was observed when compared with the control group.[12,13,24] Although becoming increasingly relevant, research assessing the role of micronutrient supplementation in leprosy is limited due to its status as a NTD. In addition, within the field of nutrition, a shift towards total dietary intake, as opposed to specific nutrient deficiencies, is occurring due to the multivariate nature of nutrition and pathogen control. As a result, a demonstrable need for robust dietary assessments and interventions that coopt previous nutrient-specific literature is evident.

Conclusion

Current therapeutics are limited in preventive efficacy against leprosy reactions, which are common following a complete course of MDT. Moreover, the global COVID-19 pandemic has led to a greater burden of reactions among leprosy patients due to the ubiquitous presence of the trigger, SARS-Cov-2 and vaccines against it.[93–95] PNP therapeutics also remain relatively ineffective as the majority of individuals will not experience a greater than 30% reduction of symptoms.[10] Likewise, these therapeutics are also associated with significant side effects (Table 1), increasing the incidence of adverse events. In fact, leprosy patients in reaction requiring corticosteroids are at an increased risk of developing biochemical diabetes, a significant and common comorbidity of leprosy.[50] Nutrient supplementation has been instrumental in reducing host oxidative stress, strengthening immune responsiveness and mitigating potential adverse events in both leprosy and diabetes. Research assessing the implications of vitamin and mineral supplementation in leprosy has demonstrated a significant reduction in symptoms and therapeutic requirements.[12–14,17,24] Likewise, trials assessing the implications of WFPBD in diabetic PNP patients exhibited a statistically significant reduction of overall symptomatology and improvement in quality of life.[21–23,25,27–29] As such, WFPBD may have beneficial effects on PNP in leprosy by mitigating adverse events related to nutrient deficiency. Thus, by examining this relationship, one may be able to develop effective lifestyle interventions thereby reducing pharmacological requirements and PNP severity in leprosy.

Glossary

Allodynia = pain brought on by nonpainful stimuli

Ephaptic = conduction of a nerve impulse across parallel neurons without the mediation of a neurotransmitter

Sudomotor = nerve fibres that control the activity of sweat glands

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N/A

Consent for publication
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Author contribution(s)
Michael Klowak: Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Andrea K. Boggild: Conceptualization; Funding acquisition; Investigation; Project administration; Resources; Supervision; Validation; Writing – review & editing.

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