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Original Article

Consequences of Nitric Oxide Metabolites in Leprosy: A Systematic Exploration

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ABSTRACT

Background: Leprosy, an ancient Disease remains a notable health concern in certain nations like India. It is an ongoing disease of infection brought on by *Mycobacterium leprae*. The production of Nitric Oxide by the action of inducible nitric oxide synthase serves as a crucial defense mechanism against bacterial activity, with its levels heightened in infectious diseases like leprosy. Nitric oxide exhibits potent antibacterial, antiviral and antitumor properties, yet it can be harmful to host cells, leading to tissue damage. Consequently, Nitrosative stress likely plays a pivotal role in leprosy progression. **Objectives:** This being the case, the study's objective was to evaluate the state of nitric oxide generation and its deleterious effects on proteins and lipids in leprosy. 50 healthy controls, 16 Paucibacillary (PB) leprosy patients and 34 Multibacillary (MB) leprosy patients were enrolled. In comparison to healthy controls, leprosy patients had considerably greater levels of Nitric Oxide metabolites (NOx), the lipid peroxidation marker Malondialdehyde (MDA), nitrothiol and Protein Carbonyl (PC), an indication of protein oxidation. Leprosy patients' serum total thiol concentration, which functions as a defense against NOx, was significantly decreased in comparison to controls. Moreover, there was a noteworthy distinction observed between individuals with Paucibacillary leprosy and Multibacillary leprosy in terms of NOx, Nitrothiol, Malondialdehyde and Protein Carbonyl contents. Nitrothiol, Protein carbonyl and nitric oxide all showed positive correlations in the illness group, but nitric oxide, Protein carbonyl and Nitrothiol all showed negative correlations with Thiol. Thus, the elevation of Nitric Oxide metabolites (NOx) leads to structural changes in lipids and proteins, potentially contributing to leprosy progression.

Keywords: Leprosy, Malondialdehyde (MDA), Multibacillary (MB), Nitric Oxide metabolites (NOx), Nitrothiol, Paucibacillary (PB) Thiol, Protein Carbonyl (PC).

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INTRODUCTION

Leprosy, among the oldest diseases known to humankind, persists as a significant public health challenge, particularly in countries like India, despite advancements in medical science. Although the National Leprosy Eradication Programme (NLEP) achieved elimination status at the national level, it continues to focus on initiatives aimed at early case detection to deter Grade 2 Disabilities and guarantee complimentary treatment for individuals afflicted with leprosy. While some regions within States/Union Territories remain endemic for leprosy, the implementation of different measures within the National Leprosy Eradication Program (NLEP) in recent years has led to a reduction in the count of new leprosy cases detected. Prevalence Rate (PR)/10000 populations in Maharashtra is about 1.2 (NSPRL, 2023). An obligate intracellular parasite, it exhibits an affinity for Schwann cells and the reticuloendothelial system, particularly macrophages. Macrophages, lymphocytes and their cytokines play a critical role in the defense mechanism by controlling the generation, release and moderation of several important cellular immune responses (Cressida *et al*., 2017). The ability of phagocytes to kill microorganisms via reactive nitrogen intermediates is a key defense process used by the human body's defense against microbial illnesses. One of the main defensive mechanisms of mammalian phagocytes is the synthesis of Nitric Oxide (NO•) synthesized from the amino acid L-arginine via the enzyme cytokine-responsive nitric oxide synthase. High quantities of NO• which are produced by macrophages, enhance their cytotoxicity against germs and tumor cells (Manchala and Ravirala, 2015). Strongly harmful Reactive Oxygen Species (ROS) are most often hosted by cells such as macrophages, which are able to produce both NO• and O•. ROS with a long half-life is peroxynitrite anion (ONOO), which is produced when O^- and NO^- anion react (Da *et al*., 2021). In patients with borderline leprosy, nerve injury has been linked to the production of peroxynitrite and NO• by macrophages in skin lesions (Namrata *et al*., 2015). In contrast to cytokines, nitric oxide interacts with other inorganic

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molecules and DNA structures, potentially causing a range of oxidative modifications in proteins such as proteolysis, decreased immunogenicity and inhibition of enzymatic activity (Jyothi *et al.*, 2008; Schalcher *et al.*, 2014). Protein oxidation can be detected by the presence of protein carbonyl. Targets encompass low molecular weight thiols such as glutathione and cysteine, as well as intracellular thiols and metal-containing proteins (Parul *et al.*, 2007).

As a crucial intermediary for NO·-mediated biological activities, nitrothiol, the nitrosylated product of thiols, has been the subject of much research. As such, NO• metabolites might induce damage to proteins and lipids in individuals affected by leprosy. In light of this, the study sought to ascertain how NO• production was doing in leprosy patients as well as the harmful impacts it was having on biomolecules including proteins and lipids.

MATERIALS AND METHODS

The study was conducted at the Department of Biochemistry, KIMS Hospital in Karad, Maharashtra. Approval for the protocol was obtained from the institute's ethical committee and consent forms were acquired from all patients involved. Fifty clinically diagnosed leprosy patients and fifty healthy controls made up the total number of participants in the study. The study did not accept participants with illnesses affecting the heart, lungs, or kidneys.

All leprosy patients were between the ages of 21 and 60 years and diagnosed and classified by a dermatologist as per WHO guidelines. Required quantities of venous blood were collected from all subjects under sterile conditions using a 5 mL sterile syringe. Serum obtained from these samples was used for the estimation of various biomarkers including Malondialdehyde (MDA), Nitric oxide, Nitrothiol, Protein Carbonyl and thiol. The levels of serum NO•, serum Malondialdehyde (MDA), Protein Carbonyl (PC), Nitrothiol, Serum thiol were determined using a kinetic cadmium granule reduction method (Christian, 2001), the Kei Satoh method (Shailaza *et al.*, 2018), Levine method (NK *et al.*, 1990), Cook method (Kei, 1978) and the Habeeb method (Rodney, 1990) respectively. Biochemical parameters in leprosy patients and healthy controls were stated as mean±SD and were statistically compared using Z test and Tukey's test. The associations between variables were evaluated using Pearson's correlation coefficient, with statistical significance determined at $p<0.05$.

RESULTS

Table 1: Serum NOx, MDA, PC, Nitrothiol, thiol in control and PB and MB Leprosy patients.

Biochemical Parameters	Control	Paucibacillary Leprosy	Multibacillary Leprosy
Serum Nitric Oxide (NOx) (µmol/lit)	59.67±19.24	70.87±19.21	144.78±92.57
Serum Malondialdehyde (MDA) (µmol/lit)	1.30±2.96	1.36±6.20	8.27±1.60
Serum Protein Carbonyl (PC) (µmol/lit)	13.07±5.65	26.18±12.86	33.83±13.87
Serum Nitrothiol (µmol/lit)	2.4±0.91	5.12±2.95	9.68±5.76
Serum Thiol (µmol/lit)	16.37±2.91	13.24±2.63	10.52±3.65

Table 2: Relationship between Nitric oxide metabolites and Protein and Lipid alterations in Patients with MB Leprosy.

	NOx	MDA	Protein carbonyl	Thiol	Nitrothiol
NOx	--	+0.919	+0.935	-0.954	+0.845
MDA	+0.919	--	+0.946	-0.907	+0.698
Protein carbonyl	+0.935	+0.946	--	-0.907	+0.897
Thiol	-0.954	-0.907	-0.907	--	-0.842
Nitrothiol	+0.845	+0.698	+0.897	-0.842	--

Table 3: Relationship between Nitric oxide metabolites and Protein and Lipid alterations in Patients with PB Leprosy.

	NOx	MDA	Protein carbonyls	Thiol	Nitrothiol
NOx	--	+0.839	+0.817	-0.839	+0.914
MDA	+0.839	--	+0.957	-0.984	+0.845
Protein carbonyl	+0.817	+0.957	--	-0.950	+0.674
Thiol	-0.839	-0.984	-0.950	--	-0.884
Nitrothiol	+0.914	+0.845	+0.897	-0.884	--

DISCUSSION

Leprosy, which is induced by *Mycobacterium leprae*, is a persistent infectious condition. Activated macrophages play a significant role in host defense against clinical leprosy and limiting the proliferation of *Mycobacterium leprae*. When stimulated by bacterial agents, macrophages can release various cytokines, including TNFα, IFN-γ and IFN-β. Through iNOS, proinflammatory cytokines such as IFN-γ activate macrophages which in turn produce Nitric Oxide (NO). NO is involved in several physiological processes such as vasodilation, response to bacterial challenges, cytokine stimulation, platelet aggregation and neurotransmission. NO, however, can be harmful in pathological circumstances. iNOS is intimately linked to the pathophysiology characteristics of inflammatory illnesses. While NO is indispensable for various aspects of the immune system, excessive or uncontrolled NO production can result in tissue damage and contribute to pathological conditions (David, 1999; Sies *et al*., 2002). In certain instances, NO can combine with other molecules, such as superoxide (O_2-), to generate peroxynitrite (ONOO-), a highly reactive and potentially harmful molecule (David *et al*., 2011; Singh *et al*., 2012). Therefore, the regulation of NO production and its balance in the immune response is critical for maintaining immune function and overall health.

In our investigation, notable elevations in NOx metabolite levels were observed in both leprosy cohorts in comparison with control group (Table 1). The increase was particularly pronounced in Multibacillary (MB) leprosy patients compared to Paucibacillary (PB) patients (Table 1). Even while iNOS is normally triggered during inflammatory reactions, isolated TT skin lesions are the only places where it is shown to be more highly expressed. Additionally, the serum value is consistent with the body's overall nitric oxide metabolic strain, indicating that patients with many chronic lesions who are multibacillary may have increased NOx levels (Taysa *et al*., 2013). Peroxynitrite is a powerful reactive nitrogen species formed when Nitric Oxide (NO) and Superoxide (O_2^-) radicals react with each other. It can have various effects on lipids within biological systems (Bhagyawant *et al*., 2017; Fatma *et al*., 2015). Peroxynitrite contributes to oxidative stress, which can have a detrimental impact on cellular components, including lipids. Peroxynitrite can initiate lipid peroxidation, a chain reaction that damages lipids in cell membranes. It interacts with unsaturated fatty acids in lipids, causing the formation of lipid peroxides and other reactive lipid intermediates. This process disrupts the integrity and function of cell membranes. The lipid peroxidation products generated by peroxynitrite can lead to structural and functional changes in cell membranes (Sangeeta *et al*., 2020). These alterations can affect membrane fluidity and permeability, potentially leading to cell dysfunction and cell death. It can also lead to the depletion of endogenous antioxidants, further exacerbating oxidative damage to lipids and other biomolecules. Peroxynitrite can directly modify lipids by nitration and nitrosation. These post-translational modifications can change the structure and function of lipids, as well as their interactions with proteins. This can lead to structural and functional changes in cell membranes, contribute to oxidative stress and inflammation and play a role in various pathological conditions (Taysa *et al*., 2013). On statistical evaluation we found that positive correlation between NOx and MDA in PB and MB leprosy patient (Tables 2 and 3). This clearly suggests a correlation between elevated NOx levels and increased lipid peroxidation, indicating a close relationship between NOx and lipid peroxidation. The interaction between peroxynitrite and membrane lipids can result in the creation of diverse conditions, such as nitrated lipids, which could potentially exhibit biological properties as agents for signal transduction, both in physiological and pathological contexts. Furthermore, various intermediate products, such as isoprostanes and 4-hydroxynonenal, could additionally prompt secondary oxidative damage. The findings of this study align with those of V.R. Bhadwat *et al*., Reddy Y.N. *et al*., and P. Jyothi *et al.* In the current study, we observed a notable increase in serum Protein carbonyl levels in both groups compared to controls. Compared to Paucibacillary (PB) leprosy patients, the rise was more pronounced in MB leprosy patients (Table 1). Protein carbonyl compounds can arise from oxidative damage to the peptide backbone of proteins or to amino acids including arginine, histidine, proline and lysine. Proteins undergo physical changes as a result of this oxidative damage, which can be broadly divided into three categories: fragmentation, aggregation and proteolytic digestion susceptibility. Numerous studies have documented the fragmentation of proteins following oxidative degradation, including albumin, collagen and α-globulins.

Denaturation and Cu-binding ceruloplasmin cause protein to aggregate, resulting in native cross-linked protein aggregates as opposed to random protein fragment aggregation. Protein-protein cross-links, amino acid side chain modification to carbonyl or hydroxyl derivatives and polypeptide chain fragmentation are all possible outcomes of oxidation processes. Furthermore, it has been suggested that some unsaturated hydroxy aldehydes can react with proteins to produce compounds that can be found using the carbonyl assay. According to Stadman, the susceptibility of proteins to oxidation may be linked to the presence of metal ions capable of catalyzing a Fenton-type reaction. Furthermore, in addition to amino acids that are sensitive to oxidation, the protein's conformational and tertiary structure molecule can also have an impact on protein oxidation (Jyothi *et al*., 2008; Schalcher *et al*., 2014; Balasubrahmanya, 2008).

Protein carbonylation arises from secondary reactions of amino groups of lysine residues with reducing sugars and their oxidative products, as well as by reactions of lysine, cysteines, or histidine amino acids with α and β unsaturated aldehydes formed during the peroxidation of PUFA (Erythrocyte glutathione peroxidase, 2008). The existence of carbonyl groups in proteins has therefore

been utilized as an indicator of protein oxidation mediated by Reactive Oxygen Species (ROS). Proteins are negatively impacted by Reactive Nitrogen Intermediates (RNIs), which cause protein carbonyls to form. Proteolytic degradation is the only way to get rid of oxidatively damaged proteins because they cannot be restored. The cellular amount of oxidatively damaged proteins rises in response to a decrease in proteolysis efficiency, indicating an acceleration of the illness process (Sangeeta *et al*., 2013).

The possible methods via which RNIs such as the effects of Nitric Oxide (NO•) on antimicrobial activity are varied, encompassing modifications of bacterial proteins and lipids on microbial surfaces, deamination of bacterial DNA and direct interactions with accessory protein targets. These interactions can result in enzymatic inactivation or other protein malfunctions, consequently initiating intracellular mycobacterial eradication.

In our current investigation, we detected a substantial elevation in serum Nitrothiol levels in both leprosy groups when compared to controls, with a more prominent increase observed in Multibacillary (MB) leprosy patients compared to Paucibacillary (PB) patients (Table 1).

Furthermore, we found that in both leprosy groups, there was a positive connection between serum Nitrothiol and NO metabolites (Tables 2 and 3). Nitric Oxide (NO•) has the ability to target DNA, lipids, transition metals and thiols. Under typical circumstances, NO• can combine with thiol-containing compounds, such as Glutathione (GSH), to form S-nitrosothiols, which have been found in a variety of body fluids and are known to have antibacterial properties. It is also suggested that these substances aid in the transfer of NO• to bacterial outer membrane thiols, hence preventing spore development. Nitrosonium equivalents (NO+) are added to amines and thiols, respectively, to generate N-nitrosamines and S-nitrosothiols. Target molecules in the culture media are nitrosed and iNOS is expressed when rodent macrophages are activated with LPS and IFN-γ (da *et al*., 2021; Amit *et al*., 2011; Namrata *et al*., 2015).

Furthermore, NOx, MDA, protein carbonyl and nitrothiol were found to positively correlate with one another in leprosy patients with MB and PB (Tables 2 and 3), indicating that increased nitric oxide levels are involved in the synthesis of nitrothiols, protein carbonyls and lipid peroxides. Furthermore, when comparing the leprosy groups to the controls, we discovered a significant decrease in serum Thiol levels, with the MB leprosy patients showing a more pronounced decline than the PB group (Table 1). Furthermore, we found that in both leprosy groups, there was a negative association between Thiols and MDA, Nitrothiol, Protein Carbonyl and NO metabolites (Tables 2 and 3). Thiols, which contain a sulphydryl group, constitute a major portion of the body's antioxidants and play a crucial role in defense against Reactive Oxygen Species (ROS) (Chauhan *et al*., 2021). A variety of disease conditions can be diagnosed using the redox status of plasma thiols. A greater concentration of nitrothiol is produced when more peroxynitrite (ONOO-) is produced, which in turn converts more thiols to nitrothiols (Carlos *et al*., 2019).

Based on statistical analysis, it was discovered that leprosy patients with PB and MB had negative correlations between thiol and NOx, Protein carbonyl, MDA and nitrothiol (Tables 2 and 3). This suggests that as oxidants rise, leprosy patients' thiol levels fall. According to these findings, nitrosative stress rises in proportion to the severity of the disease and the decline in thiol levels in leprosy suggests that these compounds are being depleted to mitigate nitrosative stress. Furthermore, numerous detoxifying enzymes utilize thiols as their reducing equivalents to help eliminate the products of lipid peroxidation (Boga *et al*., 2010; De *et al*., 2022).

Therefore, Thiols constitute a versatile and resilient defense system against biochemical disruptions induced by oxidative stress. Overall, our findings indicate a successive increase in nitrosative stress in PB and MB leprosy, with thiols showing alleviating effects, albeit insufficiently. In present study we found that statistically significant fall in thiol levels in PB and MB leprosy patients when compared with controls. Further thiol levels in PB were significantly higher than MB leprosy patients.

To our current understanding, no research has been conducted on thiol in leprosy. When NO attacks thiol groups, it forms s-nitrosothiol, which is its favorite target. More thiols will be transformed into nitrothiol as more ONOO- is produced. Thus, the concentration of nitrothiol is higher. Out of all the antioxidants available in the body, thiols constitute the majority of the body's overall antioxidant content and are important for protecting the organism against reactive nitrogen and oxygen species (Chauhan *et al*., 2021). S-NO•, the link that forms between thiol and NO•, is weak. Reactive nitrogen intermediates are released by homolytic or heterolytic cleavage. Disulphides are created when the residual free thiols combine with other free thiol groups in the same protein. The production of disulfides may cause a decrease in the thiol level.

On statistical evaluation negative correlations were found between thiol and NOx, PC, MDA and nitrothiol in both PB and MB leprosy patients (Tables 2 and 3). All these correlations shows that as NOx MDA, PC and nitrothiols were increased, the thiol level decreased in leprosy patients. The aforementioned findings suggest that when stress intensity rises, so does nitrosative stress. The reduction in thiol levels suggests that thiols are used up to lessen the nitrosative stress caused by leprosy. Furthermore, the elimination of lipid peroxidation products that use thiols as reducing equivalent is aided by a number of detoxifying enzymes. Thus, the consumption of intracellular thiols is frequently caused by the oxidation of proteins as well as by both enzymatic and nonenzymatic reactions of the lipid peroxidation product. As a result, thiols serve as a flexible and strong defensive mechanism

against the biochemical excitement brought on by oxidative stress, as they are the most vulnerable targets of ROS and associated free radicals (Carlos *et al*., 2019). Thus; we deduce that nitrosative stress increases in PB and MB leprosy in a sequential manner. The inadequate relieving effects of thiols are indicated by the negative association seen between oxidants and thiols.

CONCLUSION

In Leprosy as disease progress, for defending against *Mycobacterium leprae* nitric oxide level increases which causes nitrosative stress. Nitrosative stress affects lipid and protein biomolecules leads to consumption of antioxidants like thiol. This observation prompted us to consider the potential usefulness of supplementing antioxidants alongside anti-leprosy drug therapy to enhance treatment outcomes. Consequently, such therapy may effectively prevent lipid and protein nitrosative modifications in leprosy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PB: Paucibacillary; **MB:** Multibacillary; **MDA:** Malondialdehyde; **PC:** Protein Carbonyl; **NO:** Nitric Oxide; **NOx:** Nitric Oxide metabolites.

ETHICAL APPROVAL

Ethical Approval was given by the Institutional Ethical Committee of Krishna Institute of Medical Sciences, Karad, Maharashtra.

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