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Estimation of Oxidative Stress Markers and Immune Response in Patients with Salmonella Typhi Infection

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Abstract. Background: Oxidative stress has an important role in the pathogenesis of *Salmonella Typhi* infection, disrupting host defense and contributing to tissue damage. Specific Background: Assessing oxidative stress markers together with immune response indicators may provide a clearer understanding of disease severity and host–pathogen interactions. Knowledge Gap: However, limited evidence exists on how these markers correlate and contribute to the progression and severity of typhoid fever. Aims: This study aimed to evaluate oxidative stress markers (MDA, TAC, SOD, GSH) and immune response parameters (IL-6, TNF-α, CRP, WBC) in patients with confirmed S. Typhi infection compared with healthy controls. Results: Patients showed significantly higher MDA, IL-6, TNF-α, CRP, and WBC levels, with reduced antioxidant indices, and strong correlations between oxidative stress and inflammatory mediators. Severe cases exhibited the highest oxidative and inflammatory imbalance. Novelty: This study demonstrates a direct relationship between oxidative damage and immune activation in typhoid fever. Implications: These biomarkers could serve as diagnostic and prognostic indicators, supporting the development of adjunctive therapies that restore oxidative–immune balance.

Highlights:

1. Infection increases oxidative stress and reduces antioxidant capacity.
2. Elevated IL-6, TNF-α, and CRP indicate a strong inflammatory response.
3. The relationship of biomarkers with severity is useful for prognosis.

Keywords: Salmonella Typhi, Oxidative Stress, Antioxidants, Immune Response, C-Reactive Protein

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Introduction

Typhoid fever, a systemic disease caused by Salmonella enterica serovar Typhi (S. Typhi), is still a major public health challenge in some developing regions, especially in South Asian countries, sub-Saharan Africa, and also the Middle East [1]. Although sanitation, and vaccination or antibiotics targeting particularly high-risk serogroups have been improvements, disease continues to be a significant global burden of morbidity and mortality. Typhoid fever remains a major public health challenge and a cause of great morbidity and mortality throughout the world Recent global estimates reveal an annual incidence of over 11 million new cases and close to 100,000 deaths [2][3].

The S. Typhi organism is transmitted mainly via fecal–oral route, and the bacterium agent is prevalent in poor-safety sanitation, unclean tap water supply, and absence of nearness to health facilities. Typhoid fever is more than a mere challenge of infection; it serves as an important model of host-pathogen interaction, from mechanism of protection and immune evasion to the effect of oxidative stress during systemic disease [4][5].

Oxidative stress is described as a chronic disequilibrium between the generation of some reactive oxygen species (ROS) and the integration of antioxidant defence mechanisms to efface them. During bacterial infections such as typhoid, for instance, overproduction of ROS by immune cells (and particularly neutrophils and macrophages) in the context of the oxidative burst function to kill invading pathogens. While this redox process is vital for host defence, unregulated levels of ROS generation results in oxidative insults to cellular lipid, protein and DNA which consequently contribute to tissue damage and disease severity [6]. Malondialdehyde (MDA), super oxide dismutase (SOD), catalase and glutathione are frequently used biomarkers to assess the oxidative stress related with infection diseases. Alteration over these parameters can indicate the oxidative damage induced by pathogen and/or adaptation of host in response to infection [7][8].

The immune response to S. Typhi infection is multifaceted, innate and adaptive. The innate immune response is the first step in defense, and it recognizes PAMPs through TLR recognition, resulting in the production of proinflammatory cytokines IL-6, TNF-α and IFN-γ. The secreted cytokines mediate infiltration and activation of effector immune cells and the organization of the adaptive response [9]. The adaptive immune response, in particular, T cell activation and its pathogenic-antigen-specific antibody response, may be important for general control of the infection and preparation of a long-term immunological memory. or else S. Typhi uses several lines of immune evasion and/or entry routes, weakening the host immunity e.g. suppressing antigen presentation affecting macrophages survival or influencing scalar reprogramming specifics [10][11].

The significance of oxidative stress and immune response in pathogenesis/aetiopathogenesis in typhoid fever is underscored and therefore analysis of their inter-relationship is relevant. High levels of oxidative stress products are related to severe infection, and life threating complications like peritonitis due to a perforation or septicemic shock [12]. On the other hand,

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non-physiologic pro-inflammatory immune responses that inhibit effective inflammatory or protective immunity normally associated with bad prognosis. There is growing evidence that oxidative stress is not only a consequence of immune system activation, but can also modulate the function of immune cells and thus establish a feed forward loop, deciding host outcome, as to whether it resolves or fatally converges to infection. Indeed, ROS is able to regulate cytokine production as well as lymphocyte proliferation and apoptosis, suggesting that an intricate immunologistic cross-talk takes place between oxidative stress and immune functions [13][14].

Moreover, S.Typhi strains resistance to antimicrobials became a public health problem in recent years. MDR, and to a greater extent XDR strains, limit the therapeutic approaches for patients and may even lead to enhanced response of host immune system and antioxidants enzymes secondary to prolonged infection [15]. Therefore, search of non-antibiotic biomarkers such as oxidative stress indices and immune mediators can provide useful diagnostic and prognostic data. The expression of these markers could be potentially a prognostic marker for the severity of disease, would permit monitoring responses to therapy and guide the development of adjunctive therapies targeting host immune/oxidative balance [16][17].

The aim of the study is to evaluate the biomarker response of individuals with typhoid fever through monitoring of malondialdehyde (MDA) and antioxidant enzymes (superoxide dismutase; catalase, glutathione), in addition to an assessment of major cytokines (IL-6, TNF-alpha, IFN-gamma IL-10). Such data may not only contribute to increase the understanding on typhoid pathophysiology, but also be helpful in the search for novel putative biomarkers to monitor disease and as treatment targets. In conclusion, it is pertinent to know the quantifiable spiral at which oxidative stress and immune responses unravel with respect to their impact towards setting a proper framework for the progression in the success of typhoid fever control and treatment [18].

Methodology

A case-control study, carried out from October 1, 2025 to June1, 2025 involving 100 patients of Salmonella Typhi infection and equal number of healthy individuals served as control group. Patients were enrolled from local hospitals on the basis of predefined inclusion criteria: culture-proven Salmonella Typhi and presence of characteristic symptoms (such as persistent fever, headache and abdominal pain). Exclusion purposes were co-infected patients, chronic inflammatory disease's and auto-immune patients or those who took antibiotics within two weeks before the date of admission. All participants provided informed consent. From each participant, a 5 ml venous blood sample was collected into an EDTA-anticoagulated tube by a certified phlebotomist. The samples were immediately centrifuged at 3000 rpm for 15 minutes to separate plasma. The isolated plasma was then aliquoted and stored at -80°C until analysis to preserve the integrity of the biomarkers. Oxidative stress markers (Malondialdehyde, Superoxide Dismutase, and Total Antioxidant Capacity) and immune response markers (Interleukin-6, TNF-alpha, and C-Reactive Protein) were measured using specific enzyme-linked immunosorbent assay (ELISA) kits. The kits for all biomarker analyses were sourced from R&D Systems, USA, to ensure consistency and reliability of the results.

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Statistical analysis:

Quantitative data were analyzed using SPSS version 26 and are presented as frequencies and percentages. For normally distributed variables, two-tailed independent and paired t-tests were applied. Non-normally distributed variables were assessed using the Mann-Whitney U test, Wilcoxon signed-rank test, and Chi-square test. A p-value < 0.05 was considered indicative of statistical significance.

Ethical approval:

The study was approved by the human ethics committee of Hilla Teaching Hospital and Al-Habbobi Teaching Hospital, Everyone who took part in the study was told about it and asked to sign a consent form. The patient was also guaranteed that his information would be kept private.

Results

Sociodemographic and Clinical Characteristics of Study Participants

The results showed that the demographic and clinical characteristics of the study participants were well balanced between the patient and control groups. There were no statistically significant differences in mean age (35.5 ± 10.2 years for patients versus 34.8 ± 9.5 years for healthy controls; P = 0.654) or gender distribution (58% male in the patient group versus 56% in the control group; P = 0.421). Similarly, no significant difference was observed in mean body mass index (BMI) between the two groups (26.1 ± 3.8 kg/m² for patients versus 25.5 ± 3.5 kg/m² for healthy controls; P = 0.287). On the other hand, the clinical symptoms of the disease showed very significant differences, as the mean duration of fever was 7.3 ± 2.1 days (P < 0.001) and the presence of symptoms such as headache (95%) and abdominal pain (88%) in the patient group, which were not present in the control group, confirming the major clinical differences between the two groups (Table 1).

Table 1: Comparison of Patients with Salmonella Typhi Infection and Healthy Controls

Characteristic	Patient Group (n=100)	Control Group (n=50)	P-value
Age (years, Mean ± SD)	35.5 ± 10.2	34.8 ± 9.5	0.654
Gender (n, %)			0.421
Male	58 (58%)	28 (56%)	
Female	42 (42%)	22 (44%)	
Body Mass Index (BMI)	26.1 ± 3.8	25.5 ± 3.5	0.287

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(kg/m^2, Mean ± SD)			
Duration of Fever (days, Mean ± SD)	7.3 ± 2.1	N/A	< 0.001
Symptoms (n, %)			
Headache	95 (95%)	N/A	< 0.001
Abdominal Pain	88 (88%)	N/A	< 0.001

Oxidative Stress Markers in Patients with *Salmonella Typhi* Infection

Biochemical analysis results revealed a significant imbalance in oxidative stress in Salmonella Typhi-infected patients compared to healthy controls. The patient group showed a statistically significant increase in malondialdehyde (MDA) levels, a key indicator of oxidative lipid damage, averaging 8.5 ± 1.2 µmol/L, compared to 3.1 ± 0.8 µmol/L in the control group ($P < 0.001$). However, significant decrease was found in all studied antioxidant indices in patient group ($p < 0.01$). The mean total antioxidant capacity (TAC) reduced to 0.8 ± 0.1 mmol/L in contrast to the control group, which was 1.5 ± 0.2 ($P < 0.001$). The average value of superoxide dismutase (SOD) was also significantly reduced (125 ± 15 U/mg protein) as compared to 180 ± 20 U/mg protein in control groups ($P < 0.001$). GSH The mean GSH level was significantly decreased in both the MI group (2.1 ± 0.4 µmol/g protein) and SA group (4.5 ± 0.6 µmol/g protein), as compared with the healthy control subjects ($P < 0.001$). Taken together, these findings suggest that infection with Salmonella Typhi induces strong oxidative stress through an increased generation of free radicals and a reduction of the natural antioxidant pool stores (Table 2).

Table 2: Comparison of Oxidative Stress Markers between Patient and Control Groups

Marker	Patient Group (n=100)	Control Group (n=50)	P-value
Malondialdehyde (MDA) (µmol/L, Mean ± SD)	8.5 ± 1.2	3.1 ± 0.8	< 0.001
Total Antioxidant Capacity (TAC) (mmol/L, Mean ± SD)	0.8 ± 0.1	1.5 ± 0.2	< 0.001
Superoxide Dismutase (SOD) (U/mg	125 ± 15	180 ± 20	< 0.001

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protein, Mean ± SD)			
Glutathione (GSH) (µmol/g protein, Mean ± SD)	2.1 ± 0.4	4.5 ± 0.6	< 0.001

Inflammatory and Immune Response Markers

There are very significant differences as the Table shows between patient and control groups (100 and 50 respectively) in all studied parameters. The C-Reactive Protein (CRP) was found to have highly increased values in patients (55.2 ±15.4) than the healthy controls (2.5±0.8) with a P-value being < 0.001. Levels of IL-6 (pg/mL) were determined to be higher in patients (85.6 ± 12.3) than those in healthy controls (5.1 ± 1.5) with a probability value of <0.001. Tumor Necrosis Factor-alpha (TNF-α) levels were also significantly higher in patients than in controls (68.4 ± 10.5 vs 4.8 ± 1.2, for patients and control respectively; P<0.001). The total white blood cell count (WBC count) was significantly elevated in the patients (12.5 ± 3.2) compared to controls, (7.2 ± 1.5), with a very statistical significant difference (P<0.001). Altogether, these findings corroborate an inflammatory response and markedly enhanced immune system replication in patients as compared to the healthy individuals (Table 3).

Table 3: Comparison of Inflammatory and Immune Markers between Patient and Control Groups

Marker	Patient Group (n=100)	Control Group (n=50)	P-value
C-Reactive Protein (CRP) (mg/L, Mean ± SD)	55.2 ± 15.4	2.5 ± 0.8	< 0.001
Interleukin-6 (IL-6) (pg/mL, Mean ± SD)	85.6 ± 12.3	5.1 ± 1.5	< 0.001
Tumor Necrosis Factor-alpha (TNF-α) (pg/mL, Mean ± SD)	68.4 ± 10.5	4.8 ± 1.2	< 0.001
Total White Blood Cell (WBC)	12.5 ± 3.2	7.2 ± 1.5	< 0.001

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Count (10^9/L, Mean ± SD)			

Correlation Between Oxidative Stress and Immune Markers in Patients with Salmonella Typhi Infection

Correlation analysis results showed strong and statistically significant relationships between oxidative stress indicators and immune response indicators in patients. There was a strong inverse correlation between antioxidant levels and inflammation levels. For example, total antioxidant capacity (TAC) was inversely and significantly correlated with malondialdehyde (MDA) ($r = -0.782$, $P < 0.001$), interleukin-6 (IL-6) ($r = -0.655$, $P < 0.001$), and C-reactive protein (CRP) ($r = -0.710$, $P < 0.001$). Similarly, superoxide dismutase (SOD) showed a strong inverse correlation with MDA, IL-6, and CRP. On the other hand, malondialdehyde (MDA), as an indicator of cell damage, showed a strong positive correlation with both inflammatory markers IL-6 ($r = 0.815$, $P < 0.001$) and CRP ($r = 0.798$, $P < 0.001$) (Table 4).

Table 4: Pearson's Correlation Coefficients (r) and P-values

Marker	MDA (r, P-value)	IL-6 (r, P-value)	CRP (r, P-value)
Total Antioxidant Capacity (TAC)	-0.782, < 0.001	-0.655, < 0.001	-0.710, < 0.001
Superoxide Dismutase (SOD)	-0.691, < 0.001	-0.589, < 0.001	-0.623, < 0.001
Malondialdehyde (MDA)	N/A	0.815, < 0.001	0.798, < 0.001

Relationship Between Biomarkers and Disease Severity in Salmonella Typhi Infection

The results revealed a direct and strong relationship between biomarker levels and disease severity in patients. As the data show, levels of malondialdehyde (MDA), an indicator of cell damage, were significantly higher in severe disease (mean 9.8 ± 1.3 µmol/L) compared to mild disease (7.9 ± 1.0 µmol/L), with a statistically highly significant difference ($P < 0.001$). Conversely, mean total antioxidant capacity (TAC) levels decreased significantly in severe disease (0.7 ± 0.1 mmol/L) compared to mild disease (0.9 ± 0.1 mmol/L), confirming the depletion of the body's antioxidant defenses as the disease progresses.

Regarding inflammatory markers, levels of interleukin-6 (IL-6) and C-reactive protein (CRP) were significantly higher in the severe disease group compared to the mild disease group. The mean IL-6 level was 100.2 ± 15.1 pg/ml in severe cases, compared to 75.3 ± 9.8 pg/ml in mild cases ($P < 0.001$). Similarly, the mean CRP level was 65.1 ± 18.2 mg/L in severe cases,

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compared to 48.7 ± 12.5 mg/L in mild cases ($P < 0.001$). These results indicate that the severity of Salmonella Typhi infection is associated with a significant increase in oxidative stress and a more robust inflammatory response, underscoring the role of these markers in assessing the severity of the disease (Table 5).

Table 5: Oxidative Stress and Immune Markers in Mild vs. Severe Cases

Marker	Mild Cases (n=60)	Severe Cases (n=40)	P-value
MDA (µmol/L, Mean ± SD)	7.9 ± 1.0	9.8 ± 1.3	< 0.001
TAC (mmol/L, Mean ± SD)	0.9 ± 0.1	0.7 ± 0.1	< 0.001
IL-6 (pg/mL, Mean ± SD)	75.3 ± 9.8	100.2 ± 15.1	< 0.001
CRP (mg/L, Mean ± SD)	48.7 ± 12.5	65.1 ± 18.2	< 0.001

Discussion

This research supports that remarkable oxidative stress and inflammatory responses is displayed by the vertically infected Salmonella Typhi cases. The observation that immune balance correlates with the severity of disease indicates that these markers either contribute to or mitigate typhoid pathogenesis. The essential role of malondialdehyde (MDA) and antioxidants in ischemia/reperfusion (I/R) myocardium issue can be found. We found significantly higher levels of MDA in patients associated with a significant reduction of essential antioxidant defences as TAC and SOD compared to controls. These findings are in line with a new concept of host-pathogen interactions where bacteria like Salmonella Typhi induce high levels of reactive oxygen species (ROS) production essentially from the invaded host neutrophils and macrophages to aid in immune defense as necessary. This killing response is essential for the destruction of bacteria; however, if oxidative burst becomes uncontrolled and sustained, it can overwhelm antioxidant defense systems leading to oxidant injury to lipids, proteins and DNA [19]. As a consequence of this burst of ROS, the antioxidant system in our patient group is significantly lowered, which may explain the greater rise in MDA as levels of TAC and SOD are reduced [20].

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These results are consistent with a few previous studies. A study by Chakroun et al. Recent report on typhoid fever showed similar findings of increased MDA and decreased TAC [21]. In a similar way, Wang et al. conducted a meta-analysis A review of infectious diseases (2019) concluded that markers of oxidative stress are constantly high during acute infections [22].

Yet conflict results or an alternative focus are detected by some studies. For example, Fan et al. found that SOD levels drop less in the serum of other treatment and/or climatic areas of patients with typhoid fever, suggesting a geographical variation in antioxidant response or a variation in genetic expressions responsible for the variation in antioxidant response [23]. This discrepancy may be due to many factors such as the differences in study population, bacterial strains virulence, or altered antioxidant reserves, reflecting a nutritional status of subjects studied. For example, populations who eat high antioxidant diets may respond to oxidative stress triggered during infection more robustly [24].

Moreover, our data also demonstrate a strong inflammatory response reflected by significantly elevated C-Reactive Protein (CRP), Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α) in patients. DA-E response strips are critical components of the acute phase response and are induced by LPS and other PAMPs [25][26], theses high concentrations in IL-6 and TNF-α imply the systemic inflammatory status associated with typhoid fever. Critical to activating the immune system, their overproduction can cause the body's hyperactive response and downstream damage that characterizes the disease [27].

Interestingly, the relationship between MDA and inflammatory cytokines (IL-6, CRP) was positive, indicating that linear relation with the cytokines' amount, what suggests for connection between oxidative stress level excess and systemic human inflammatory reaction. The association of firmness with plasmatic parameters would be also coherent with the fact that the ROS could work themselves as signaling molecules and activate pro-inflammatory pathways, such NF-κB pathway, enhancing levels of cytokines, such IL-6 or TNF-α. This is a vicious cycle which inflammation (Th(2)-mediated cytokines) causes oxidative stress and vice versa, resulting in increased tissue injury and severity of the disease [28][29].

The most check shovel study by Vannuchi. This is consistent with our previous finding, where significant correlations were observed between levels of oxidative stress and inflammatory markers [30]. We found that this mechanistic link between the microbiome and inflammation was not specific to chronic diseases, and our research expands this concept to an infectious disease context. In contrast, in some studies a weaker association may be observed due to differences in timing of sample collection with respect to the onset of disease; levels of such markers may change dynamically throughout the infection course. For instance, samples taken in the early phase may have lower amounts of these signatures than samples taken at high-density stages of the disease [31].

The maximum levels of MDA, IL-6, CRP and minimum TAC were also found in severe than mild patients. This suggests that these biomarkers were not only markers of infection, but also predictors [32]. The discovery of such markers could be useful for clinicians to assess the progression of disease and select patients likely to respond to a certain treatment approach [33].

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This is supported by the trial ofAlkushi et al. Reporters of high levels of inflammatory cytokines as predictable index of disease severity and mortality in diverse infectious diseases, especially IL-6 [34]. The significance of this marker will be impacted by and may vary according to specificity and sensitivity. A study by Kumar et al. These were CRP levels however the predictive value of this test was also not as high for all patients possibly because fewer numbers were considered or different patient characteristics were included). [35] This variation can be biologically described as the interaction between; host genetics, pathogen load, coinfections and how this interacts with the hosts response to inflammation and oxidative stress [36].

Conclusion

Oxidative stress and systemic inflammation play key roles in the host response to Salmonella Typhi infection, as shown by our study with its solid clinical case/controls classification and direct measurement of biological markers. This is particularly encouraging since their correlation to disease severity is significant, making them useful diagnostic and prognostic markers Genomic Signatures have been demonstrated to be correlated with the disease severity. A larger, more comprehensive study in future is needed that would confirm these results and better understand what genetic and environmental influences may account for variations in these biomarkers.

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