

**Original Article**

**CORRELATION OF SERUM ALBUMIN AND CREATININE WITH OXIDATIVE STRESS MARKERS IN PATIENTS HAVING NEPHROTIC SYNDROME**

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**ABSTRACT**

**Objective:** Children with nephrotic syndrome (NS) have a stressful condition, and oxidative damage may impair their treatment response. This study aims to gain a better understanding of the relationship between oxidative stress and NS to lay the basis for further research into improved diagnostic options, treatment, and prevention of the disease.

**Methods:** We took a blood sample from 100 Indian patients aged 2-14 y. Each patient was tested for oxidative stress. The buege method was used to assess MDA levels in patients. The pyrogallol method was used to measure SOD activity in blood serum, and the jollow method was used to measure glutathione levels.

**Results:** The levels of oxidative stress markers (MDA, SOD, and GSH) were compared between NS patients and the control. SOD and GSH concentrations were significantly decreased in the NS group when compared to the control. In contrast, MDA level was significantly higher in the NS group than in the control. In the correlation analysis, we found that the serum SOD activity was significantly positively correlated with serum albumin and creatinine level in patients with NS. Thus, oxidative stress in children with NS is indicated by reduced antioxidant potential because of low albumin. Therefore, it is thought that oxidative stress is implicated in the development of NS in Indian children.

**Conclusion:** We concluded that oxidative stress was intensified in children with NS due to decreased antioxidant levels caused by hypoalbuminemia.

**Keywords:** Nephrotic Syndrome (NS), Oxidative stress, Malondialdehyde (MDA), Glutathione (GSH), Superoxide Dismutase (SOD), Indian children

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**INTRODUCTION**

Free radical-induced oxidative damage has been implicated in various clinical diseases [1], including kidney injury. Oxidative stress is described as an imbalance between the oxidation and antioxidation processes resulting in highly reactive molecules, primarily reactive oxygen species, being produced and cleared (ROS). According to studies, children with nephrotic syndrome experience oxidative stress (NS) [2]. The albumin protein mediates the majority of the antioxidant activity in plasma and serum. Human serum albumin was responsible for 70% of the free radical trapping activity (HSA) [3]. Renal perfusion decreases due to a reduction in intravascular volume. As a consequence, the glomerular filtration rate (GFR) is reduced. One of the investigations of renal failure in children with NS is a decrease in GFR [4]. Evaluation of GFR provides a clue for overall renal function, which is crucial in children having NS due to its rapid progression to acute renal failure. The feasible method to estimate GFR is to measure serum creatinine level [5]. For many decenniums, alteration between oxidants and antioxidants generates oxidative stress, which is intricate in developing several acquired/genetic diseases, including NS [6]. The pathogenesis of insufficient protein permeability and other NS difficulties is still unknown. The finding that reactive oxygen species (ROS) can act as mediators of glomerular injury advances our understanding of the disease's etiology significantly [7]. NS has also been related to increased oxidative stress in numerous studies [8, 9]. MDA (Malondialdehyde), GSH (Glutathione), and SOD (Superoxide Dismutase) are all readily quantifiable markers of oxidative stress [8]. MDA is the by-product of lipid peroxidation, which is used to check the status of ROS indirectly. SOD does damage to the superoxide radical by dismutating it into peroxide [10]. Kidneys rely on an adequate supply of GSH for their normal functioning [11]. Thus, serum albumin, creatinine, SOD, MDA, and blood GSH level

have a significant role in the vulnerability of these children to diseased conditions. This research aimed to highlight the role of oxidative stress in NS children. Excessive production of reactive oxygen species (ROS) is one of the possible causes of oxidative stress (ROS) associated with kidney injury.

**MATERIALS AND METHODS**

**Study Participants:** This research was carried out on nephrotic syndrome patients in India. The participants were split into two groups: (A) Children suffering from Nephrotic syndrome (B) Individuals who are healthy (Age: 2-14 y). Inclusion criteria: Renal insufficiency was defined as a glomerular filtration rate (GFR) less than 80 ml/min, a urine protein excretion larger than 0.05 g/kg per 24 h, and serum albumin less than 25 g/l. NS patients diagnosed with other systemic disorders were excluded from this study. Pediatric nephrologists made the diagnosis of NS at the authorized center of Muljibhai Patel Urological Hospital. The Institutional Ethics Committee of G. J. Patel Ayurvedic College, Vallabh Vidyanagar, Gujarat, approved this study (Approval No-IEC-4/GJPIASR/2017-18/08). Informed consent forms were signed before performing the experiments.

**Sample collection**

Blood samples were collected in a vacutainer serum tube from Muljibhai Patel Urological Hospital Nadiad. After taking a blood sample, the serum was isolated from the blood and centrifuged for 10 min at 3200-3500 rpm; to obtain the red blood cells. From the fresh sample, oxidative stress markers like MDA, SOD, and GSH were estimated. Malondialdehyde (MDA) level in patients was checked using the buege method [12]. Superoxide dismutase (SOD) activity from blood serum was checked using the pyrogallol method [13]. Glutathione level in blood was measured using jollow's method [14].

**Estimation of GSH**

Jollow's methods were used to test blood glutathione. 200 µl of blood, 0.8 ml of D/W, and 0.5 ml of 10% Sulfosalicylic acid were mixed. The mixture was vortexed and centrifuged @ 3000rpm for 10 min; 0.5 ml of supernatant was added in 4.5 ml of 0.5M (pH 8.23) Tris phosphate buffer and 0.5 ml of 5,5-Dithiobis (2-nitro benzoic acid). The reaction mixture formed yellow color, which was read at 412 nm.

**Estimation of MDA**

1 ml serum was treated with 2 ml TCA-TBA-HCL and thoroughly mixed. The reaction solution was heated for 15 min and then centrifuged for 10 min at 1000g. The coloring complex developed in the supernatant was measured at 535 nm against a blank. Blank included all the reagents except the serum sample.

**Estimation of SOD**

The inhibition of pyrogallol autoxidation was used to determine SOD activity in serum samples, defined by Marklund [13]. 1 ml serum sample, 0.1 ml pyrogallol reagent, and 1.9 ml tris buffer were mixed. After a 90-second induction time, the inhibition of pyrogallol was calculated every 30 seconds for 3 min at a wavelength of 420 nm.

**Statistical analysis**

SPSS version 21.0 was used to conduct the statistical analysis. Comparison between control and nephrotic syndrome group was done by student t-test.

**RESULTS**

There is no noticeable difference in age between NS patients and controls. However, the NS group had considerably lower serum albumin and creatinine levels than the control group (p<0.05), the NS group had a higher UPCR ratio (p<0.05). On the other hand, the serum cholesterol level was normal in both groups (table 1).

MDA levels in the serum were substantially higher in NS patients than controls (P<0.05). The activity of SOD was markedly higher in control patients than in NS patients (p<0.05). GSH concentrations were substantially lower in NS patients than in the control group (p<0.05) (table 2). In patients with NS, a significant positive relationship between SOD activity and serum albumin and creatinine levels was observed (P<0.05). No significant association was seen when serum albumin and creatinine levels were compared to MDA and GSH levels (p>0.05) (fig. 1, 2, 3).

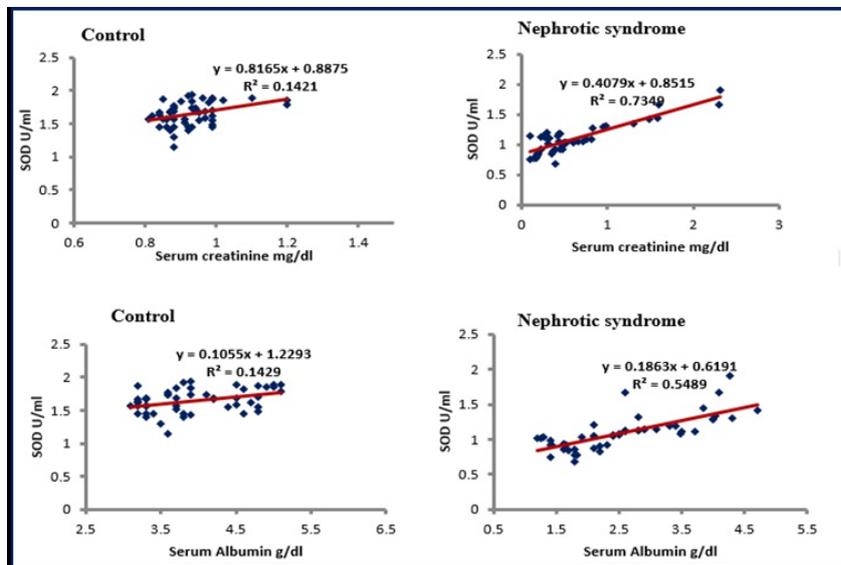


Fig. 1: Correlation of serum albumin, serum creatinine with SOD (superoxide dismutase) activity

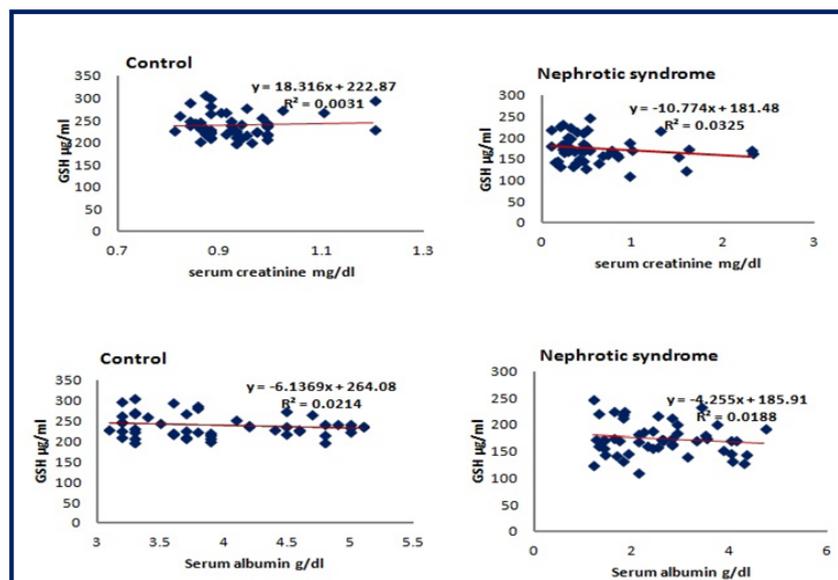


Fig. 2: Correlation of serum albumin, serum creatinine with GSH (glutathione) levels in the blood

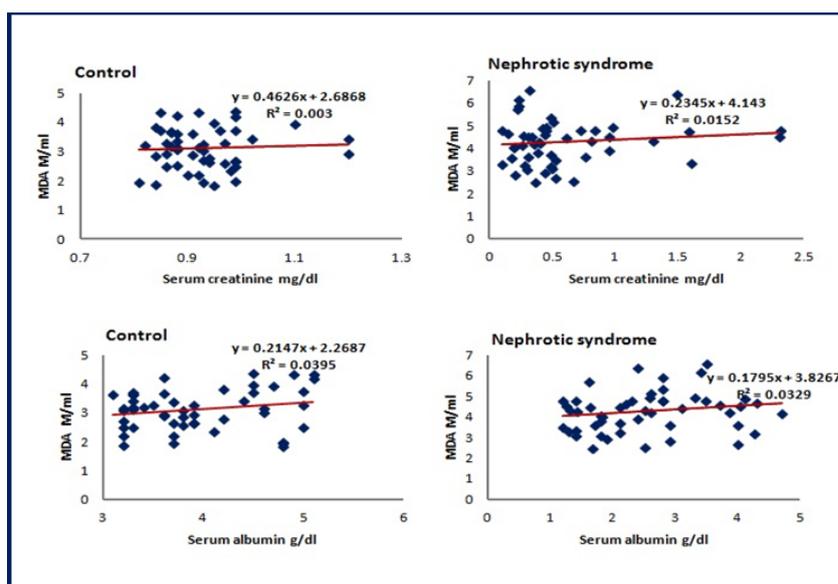


Fig. 3: Correlation of serum albumin, serum creatinine with MDA (Malondialdehyde) levels

## DISCUSSION

The glomerular basement membrane is degraded by superoxide-mediated oxidative damage, and de novo proteoglycans synthesis is reduced [15]. The Glomerular Filtration Barrier (GFB) is negatively charged by heparan sulfate, a proteoglycan, and thus repels the transport of negatively charged molecules. Oxidative damage to heparan sulfate may lead to increase glomerular permeability. Therefore, glomerular injury due to ROS may be responsible for the pathogenesis of glomerular diseases [16]. Clinical data of the participants suggest that creatinine clearance is helpful in clinical practice to measure glomerular filtration rate, and decline in serum albumin level indicates reduced antioxidant

level. Urine protein/Creatinine ratio and serum cholesterol level are significantly different in both groups. Many clinical disorders are caused due to oxidative damage by free radicals. Lipid peroxidation enhances protein permeability in the glomerulus and impairs the structural integrity of tubular epithelial cells due to the formation of reactive oxygen species (ROS). It is also reported that ROS is responsible for the pathogenesis of childhood nephrotic syndrome [17]. One of the possible factors which are responsible for damage in DNA is ROS. The rapid injury and damage to DNA caused by ROS result in proteinuria and subsequent glomerulosclerosis [18]. Many illnesses, including cancer, heart disease, diabetes, aging, liver, kidney, and lung disorders, are influenced by oxidative stress [19].

Table 1: Clinical characteristic of selected participants

Parameters	Control	Nephrotic syndrome	p-Value
Age	8.72±4.81	7.12±4.57	-
S/P Creatinine mg/dl	1.099±0.066	0.467±0.048	<0.05
S/P Serum Albumin g/dl	4.459±0.09	2.9168±0.133	<0.05
Urine protein/Creatinine ratio (UPCR):1	0.2518±0.028	3.1604±0.657	<0.05
S/P Cholesterol mg/dl	116.7225±6.954	91.733±1.726	<0.05

S, Serum; P, Protein; p-Value<0.05 considered as significant; Data were in mean±SD. Significant value for student *t*-test was considered<0.005 (p-value).

The assessment of lipid peroxidation status is an essential criterion in determining the degree of oxidative stress. Studies have indicated that free radical lipid peroxidation can harm the cell membrane and create enzymatic and receptor binding membrane activity abnormalities, resulting in damage to the organ [20]. The majority of phospholipids on the membrane are readily oxidized, resulting in lipid peroxide, which decomposes to aldehyde like MDA [21]. Our investigation discovered that the NS group had a significantly higher MDA level than the control group. Similarly, another study revealed a rise in the MDA level in NS compared to the control group [6-7, 9]. Turi *et al.* reported that eight children with post-streptococcal glomerulonephritis in the acute stage had significantly increased plasma MDA and decreased erythrocyte SOD activity compared to healthy controls [22]. Additionally, Templar *et al.* [23] demonstrated that patients with chronic renal failure due to chronic glomerulopathies had significantly higher plasma MDA levels than those with non-glomerular diseases, implicating a role for oxidative stress in the pathogenesis of glomerular injury [23]. Another study discovered a fourfold increase in the amount of MDA in the blood [24].

The superoxide radical produced by active neutrophils is required for the neutrophil-mediated acute inflammatory response, which results

in severe tissue damage [25]. Superoxide dismutase has been found as a molecule that acts as an anti-inflammatory and anti-superoxide scavenger [26]. Bulbul *et al.* discovered that the antioxidant enzyme SOD had a similar activity at disease start, during remission, and in control participants [27]. SOD is also expected to increase in response to excessive oxidative damage, compensating for and protecting tissue damage [28]. Thus, the absence of an increase in acute stage SOD activity could result from oxidative stress-induced depletion, as demonstrated by increasing MDA levels.

Glutathione is the most potent antioxidant that is found in every cell [29]. It is a thiol-containing tripeptide found in high concentrations in live cells in its reduced form (GSH). When it comes into contact with reactive oxygen species (ROS), it is oxidized to glutathione radical, regenerated to its reduced form via glutathione reductase activity. We noticed a significant decrease in GSH concentrations in the patients' group, ascribed to increased reactive oxygen species generation, converting the reduced form to the oxidized form (GSSH). Glutathione peroxidase (GPx), glutathione-S-transferase (GST), and glutathione reductase all use GSH as a substrate (GRx). The decrease in concentrations may be due to the increased turnover of GSH required to prevent oxidative damage under these

conditions [30]. Previously, similar discoveries of lower GSH concentrations in nephrotic syndrome were documented [31], implying that nephrotic syndrome is related to increased oxidative stress. In contrast, nephrotic syndrome has been associated with unchanged erythrocyte GSH concentrations [6].

Our antioxidant and oxidant status results were well supported by a study done by the reddy's group in 2016. They found a significantly increased level of MDA and decreased the level of SOD activity and GSH in NS patients [8]. In contrast, another study found unaltered GSH concentrations and increased SOD concentration in children

with NS [6, 17]. We observed a statistically significant positive association between serum creatinine and SOD activity and serum albumin and SOD activity (fig. 1). Similarly, Mistry *et al.* also reported a positive correlation of SOD activity in Diabetic nephropathy [32]. The earlier study found that SOD is a responsible and significant mediator of the podocyte damage, causing glomerular injury influenced by puromycin and involved in many other diseases [33]. As a result, SOD activity is one of the most potent stress markers in diagnosing renal disease, including NS. No significant correlations were found in MDA and GSH levels compared with serum albumin and serum creatinine (fig. 2,3).

**Table 2: Oxidative stress markers in the control and patients**

Parameters	Control	Nephrotic syndrome	% change	p-Value
MDA ( $\mu\text{M/ml}$ )	3.116 $\pm$ 0.03	4.2814 $\pm$ 0.03	+137.38	<0.05
GSH ( $\mu\text{g/ml}$ )	239.86 $\pm$ 0.01	175.12 $\pm$ 0.02	-73	<0.05
SOD (U/ml)	1.64 $\pm$ 0.17	1.092 $\pm$ 0.24	-66.58	<0.05

Data were presented in mean $\pm$ SD

In this investigation, the lack of association of MDA and GSH with serum albumin and creatinine levels indicated that these oxidative stress markers were not predominantly generated by renal insufficiency in NS. The antioxidative defense mechanism of superoxide dismutase regulates reactive oxygen species (ROS) (O<sub>2</sub>). It is one of the most effective antioxidant defenses in all cells exposed to oxygen and plays a critical role in the body's antioxidant defenses [34]. Thus, elevated levels of oxidative stress and decreased antioxidant defense may be related to the development of NS. Numerous studies have established that oxidative stress plays a role in developing various diseases, including NS. As a result, excessive ROS production may contribute to the progression of renal disease [31]. Thus, determining the amount of oxidative stress produced is critical for NS prediction. *In vitro* investigations have revealed a crucial role in oxidative stress in the development of NS [35]. The oxidation-reduction reaction of ROS can generate protein carboxylation, DNA damage and cytoskeleton disruption. The cell injury influence by ROS hampers the glomerular permeability to proteins and disorganizes the tubular epithelial cells' integrity, eventually results in NS [17]. The limitation of this study is the sample size, so additional research with larger sample size is required to properly analyze the findings reported here. This study requires a larger sample size to determine the etiology of NS in children.

## CONCLUSION

The current study's findings state that the NS group has significantly greater MDA levels and lower SOD and GSH levels, and as a result, they have higher oxidative stress. Furthermore, a positive correlation was identified in SOD activity compared with serum albumin and serum creatinine level, implying that oxidative stress defined by diminished antioxidant potentials due to hypoalbuminemia exists in children with NS. Thus, oxidative stress has a role in the development of NS in children. However, the antioxidant defense mechanisms of the body, such as SOD, GSH, and serum albumin, may attempt to alleviate this damage. Additional research involving a greater number of patients is necessary to explore the findings presented here.

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Nil

## AUTHORS CONTRIBUTIONS

**Conceptualization:** Kinnari N. Mistry, Sishir Gang

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**Formal analysis and investigation:** Glory S. Parmar, Kinnari N. Mistry, Sishir Gang

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**Supervision:** Kinnari N. Mistry.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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