Role of Oxidant-Antioxidant Imbalance in the Pathogenesis of Acute Post-Streptococcal Glomerulonephritis

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ABSTRACT
Background: A still-growing body of evidence has accumulated indicating that a disturbance of balance between oxidative stress and antioxidant defence mechanisms plays a major role in the pathomechanism of glomerular diseases.
Objectives: This study was carried out to evaluate the role of oxidant-antioxidant imbalance in the pathogenesis of acute post-streptococcal glomerulonephritis (APSGN).
Methods: Serum levels of some antioxidants (α-tocopherol, superoxide dismutase (SOD), selenium, zinc and copper) were estimated in 50 children, of ages ranging from 2 to 10 years (mean ± SD, 8.1 ± 2.5 years), diagnosed as APSGN, and compared with that of 25 healthy age- and sex-matched control children. Oxidant stress was evaluated as well, in all subjects by estimating levels of serum and urinary malondialdehyde (MDA).
Results: The levels of antioxidants were significantly decreased in children suffering from APSGN compared to control children. Meanwhile oxidative stress, measured by serum and urinary MDA was significantly increased in the patient group. In addition, a significant positive correlation between SOD and both copper and zinc was reported.
Conclusions: An oxidative stress, in the face of defective antioxidant defence, does exist and may play a particular role in the pathogenesis of acute post-streptococcal glomerulonephritis. So it is recommended that nutritional antioxidants, especially vitamin E, selenium, zinc, and copper should be added in the diet of children and all risky groups.

INTRODUCTION
The pathogenesis of APSGN is unknown. The disease is characterized by a history of preceding throat or skin infection with certain nephritogenic strains of group A beta-hemolytic streptococci, edema, tea- or cola-colored urine, and depending on the severity of renal involvement, patients may develop varying degrees of edema, hypertension, oliguria, congestive heart failure and hypertensive encephalopathy(1).

The existence and development of cells in an oxygen containing environment would not be possible without the presence of defense systems which protect them from oxidant induced cell damage. Thus detoxication of reactive oxygen species is one of the prerequisites of aerobic life and many defenses have evolved providing an important antioxidant defense system(2). Oxygen free radicals (OFR,) can break down proteins, lipids, carbohydrates and nucleic acids, and can easily produce injuries to cell membranes by initiation of polyunsaturated fatty acid peroxidation, inactivation of membrane enzymes and
receptors, depolymerization of polysaccharides and protein cross-linking and fragmentation\(^{(3)}\).

A disturbance of balance between oxidative stress and antioxidant defense mechanisms play a major role in the pathomechanism of glomerular diseases OFR, may be generated by activated neutrophils, monocytes, and mesangial cells during metabolic processes\(^{(4)}\).

The majority of research work has measured lipid peroxidation products using the thiobarbituric acid test, which measures only the potential products of lipid peroxidation (MDA)\(^{(5)}\).

**AIM OF THE WORK**

The study was designed to detect the association between serum levels of some antioxidants (vitamin E, SOD, zinc, copper and selenium), in 50 children, diagnosed as APSGN, and 25 normal counterparts, and to put a preventive strategy in a trial to avoid this catastrophe in our children afterwards.

**SUBJECTS AND METHODS**

This study was carried out at the Pediatrics Department of Zagazig University Hospitals, on 70 subjects, divided into two groups:

1. **Acute post-streptococcal glomerulonephritis (APSGN) group**: included 50 children diagnosed as having APSGN. Their ages ranged between 2 and 10 years, with a mean age ± SD of 8.1 ± 2.5 years. They were 30 males and 20 females.

2. **Control group**: included 25 age- and sex-matched apparently healthy children, of ages ranging from 2 to 10 years (mean age ± SD, 7.8 ± 2.4 years). They were 15 males and 10 females.

**Methodology**

The diagnosis of APSGN was reached by:

- History, 5 days to 3 weeks, of streptococcal pharyngitis, tonsillitis or dermatitis.
- Edema, tea-colored urine, oliguria with or without hypertension.
- Urinalysis revealing signs of glomerular inflammation with proteinuria, red blood cells, and red cell casts.
- A serum anti-streptolysin-O titre > 200 IU.

All subjects of the study were subjected to full history-taking, clinical examination, routine laboratory investigations including urinalysis, and complete blood picture, blood urea, serum and urine creatinine, determination of serum and urine malondialdehyde (MDA), determination of \(\alpha\)-tocopherol (vitamin E), intracellular superoxide dismutase (SOD)\(^{(5)}\), and serum zinc, copper, and selenium\(^{(6)}\).

The data were tabulated and statistically analysed for means, standard deviation (SD), and student "t" test\(^{(7)}\).
## RESULTS

### Table 1: Mean and standard deviation (SD) of serum level of antioxidants in both acute post-streptococcal glomerulonephritis (APSGN) cases and their controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APSGN group</th>
<th>Control group</th>
<th>“t” test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>α-Tocopherol (mg/L)</td>
<td>11.08 ± 1.1</td>
<td>2.5 – 21.3</td>
<td>15.1 ± 1.5</td>
<td>5.5 – 30.2</td>
</tr>
<tr>
<td>SOD (µ/ml)</td>
<td>40.09 ± 0.9</td>
<td>32.8 – 48.2</td>
<td>198.6 ± 5.7</td>
<td>160 – 250</td>
</tr>
<tr>
<td>Selenium (µg/dL)</td>
<td>8.5 ± 0.3</td>
<td>6.5 – 12.3</td>
<td>9.7 ± 0.4</td>
<td>6.5 – 13</td>
</tr>
<tr>
<td>Zinc (µg/dL)</td>
<td>85.3 ± 2.6</td>
<td>69.6 – 116</td>
<td>98.4 ± 45</td>
<td>72.2 – 140</td>
</tr>
<tr>
<td>Copper (µg/dL)</td>
<td>67.4 ± 2.0</td>
<td>62.1 – 95.3</td>
<td>76.9 ± 3.9</td>
<td>52.2 – 122.2</td>
</tr>
</tbody>
</table>

This table shows a significant decrease of serum levels of all antioxidants.

### Table 2: Mean and standard deviation (SD) of oxidant parameter (MDA) in both acute post-streptococcal glomerulonephritis (APSGN) cases and their controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>APSGN group</th>
<th>Control group</th>
<th>“t” test</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Range</td>
<td>Mean ± SD</td>
<td>Range</td>
</tr>
<tr>
<td>Serum MDA (µ mol/L)</td>
<td>8.1 ± 0.5</td>
<td>2.9 – 13.0</td>
<td>2.7 ± 0.2</td>
<td>1.2 – 5.1</td>
</tr>
<tr>
<td>Urine MDA (nmol/mg creatinine)</td>
<td>0.07 ± 0.002</td>
<td>0.05 – 0.1</td>
<td>0.01 ± 0.001</td>
<td>0.007 – 0.03</td>
</tr>
</tbody>
</table>

This table shows a significant increase of MDA in APSGN, in comparison to healthy children.
Fig. 1: Scatter gram indicates significant positive correlation between superoxide dismutase and copper in glomerulonephritis group.

Fig. 2: Scatter gram indicates significant positive correlation between superoxide dismutase and zinc in glomerulonephritis group.
DISCUSSION

Reactive oxygen molecules participate in the pathogenesis of various renal diseases including inflammatory lesions, such as glomerulonephritis. These reactive oxygen species including superoxide anions, hydrogen peroxide and hydroxyl radical may be generated by activated neutrophils, monocytes and mesangial cells during metabolic processes.

Cytokines and oxygen radicals released in the inflammatory process appear to decrease glomerular blood flow and change basement membrane permeability.

Among the various blood and cellular defense mechanisms against the effect of oxidative stress, a prominent role is usually played by vitamin E, which forms the first line of defense against peroxidation of polyunsaturated fatty acids contained in cellular and subcellular membrane phospholipids.

Our study showed a significant decrease (p < 0.01) of serum vitamin E in children suffering acute post-streptococcal glomerulonephritis (APSGN) compared to the control group. This is in agreement with Turi et al. and Fdryk et al., who attributed their results to decreased vitamin E intake, decreased absorption or increased consumption during antioxidant activity.

This study revealed a statistically highly significant decrease of serum superoxide dismutase (SOD) compared to controls. This is in accordance with that reported by Ichikawa et al. and Turi et al.

Superoxide radical plays a major role in the neutrophil-mediated acute inflammatory response. Neutrophils produce superoxide for the primary purpose of aiding in killing of microbes. The superoxide released from actively phagocytosing neutrophils serves to attract more neutrophils by reacting with and activating a latent chemotactic factor present in the plasma and results in extensive tissue damage. This study revealed a decreased SOD levels in APSGN versus control group.

The decreased level of SOD can be attributed to increased oxidative stress, as well as its consumption in the process of antioxidant activity.

Selenium is an essential trace element for humans and it is an integral component of the membrane - protecting enzyme glutathione peroxidase which utilizes glutathione for breakdown of peroxides. Reduced glutathione peroxidase activity reflects an increased oxidative stress.

This study revealed a significant decrease of serum selenium level in APSGN, as compared to the control group. This is similar to that reported by Yu (1993), who attributed this drop to decreased intake and decreased intestinal absorption.

Our study revealed a statistically significant decrease of serum zinc in APSGN, than that of control children. This can be explained by increased urinary zinc excretion due to increase in serum amino acids, polypeptides and other low molecular weight metabolites which competitively complex with zinc and make it ultrafilterable rather than protein-bound.

A significant hypocupremia was noted in children with APSGN, as compared to control children. This is similar to that obtained by Yu, who attributed hypocupremia, in these patients, to decreased dietary
intake, decreased intestinal absorption, and/or increased oxidative stress\(^{(15)}\).

Superoxide dismutase is a cupro-zinc enzyme; it has copper atoms at each of its two catalytic sites and additionally contains two zinc atoms which have a structural function. The decreased activity of the enzymatic mechanisms of defense against OFR, can be explained by a disturbance in the status of copper and zinc\(^{(15)}\). Our results detected a significant positive correlation between SOD and serum levels of both copper and zinc, in APSGN patients (Fig. 1 & 2). This is agreement with that reported by Richard et al. (1991)\(^{(17)}\).

In view of our gained data, we conclude that:

1. Oxidative stress may have a role in the pathogenesis of acute post-streptococcal glomerulonephritis. This was evident in the increased levels of serum and urinary malondialdehyde, in children suffering APSGN.

2. There was a correlational decrease of antioxidants as vitamin E, SOD, selenium, zinc, copper in APSGN cases in comparison to their healthy controls.

3. So, it is recommended that nutritional antioxidants specially vitamin E, selenium, zinc and copper must supplement the diet of children and all risky age groups.

4. Antioxidant therapy may be suggested in the management of children with APSGN.

REFERENCES


