INTRODUCTION

Systemic lupus erythematosus is a chronic autoimmune disease characterized by autoantibodies directed against nuclear antigens and causing a variety of clinical and laboratory abnormalities. SLE may involve multiple organs, causing significant morbidity and mortality in adults, adolescents, and children ***(Muscal and Brey, 2010)*.**

SLE in children is fundamentally the same disease as in adults with similar etiology, pathogenesis, clinical manifestations, and laboratory findings. However, the care of children and adolescents with SLE is very different from that of adults because of the impact of the disease and its therapy on physical and psychological growth and development ***(Lehman et al., 2011)*.**

Oxygen is an element indispensable for life. When cells use oxygen to generate energy, free radicals are created; these by-products are generally reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) that result from the cellular redox process. At high concentrations, they generate oxidative stress, a deleterious process that can damage all cell structures ***(Pham-Huy et al., 2008)*.**

Oxidative stress contributes to chronic inflammation of tissues, plays a central role in dyslipidemia and atherosclerosis ***(Rho et al., 2010)*** and causes immunomodulation, which may

lead to autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome and rheumatoid arthritis ***(Leitinger, 2008)*.**

Most clinical studies focus on the measurement of oxidative damage biomarkers – oxidants and antioxidants in blood samples to determine the presence of oxidative stress in systemic lupus erythematosus patients. Plasma Nitric oxide (NO) and Plasma Malondialdehyde (MDA) level have been used as a determinate of oxidative status in SLE ***(Pérez et al., 2012).***

AIM OF THE WORK

The aim of this study was to measure serum levels of Nitric oxide (NO) and Malondialdehyde (MDA) as indicators of oxidative stress in known children with pediatric systemic lupus erythematosus to study their relationship to the disease activity.

OXIDATIVE STRESS AND ITS RELATION TO VARIOUS DISEASES

1. Definition:

An imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage ***(Sies and Jones, 2007)*.**

Oxidative stress reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage of all components of the cell, including proteins, lipids, and DNA ***(Chandra et al., 2015)*.**

2. Antioxidant defence system:

The damaging effect of reactive oxygen species (ROS) is limited by the numerous cellular antioxidant defence mechanisms in the body including enzymes such as Superoxide dismutase (SOD) & Catalase (CAT), non- enzymes such as vitamins (A, C, E) & carotenoids and other antioxidants minerals (copper, ferritin, zinc, manganese, selenium etc.) ***(Lozovoy et al., 2013)*.**

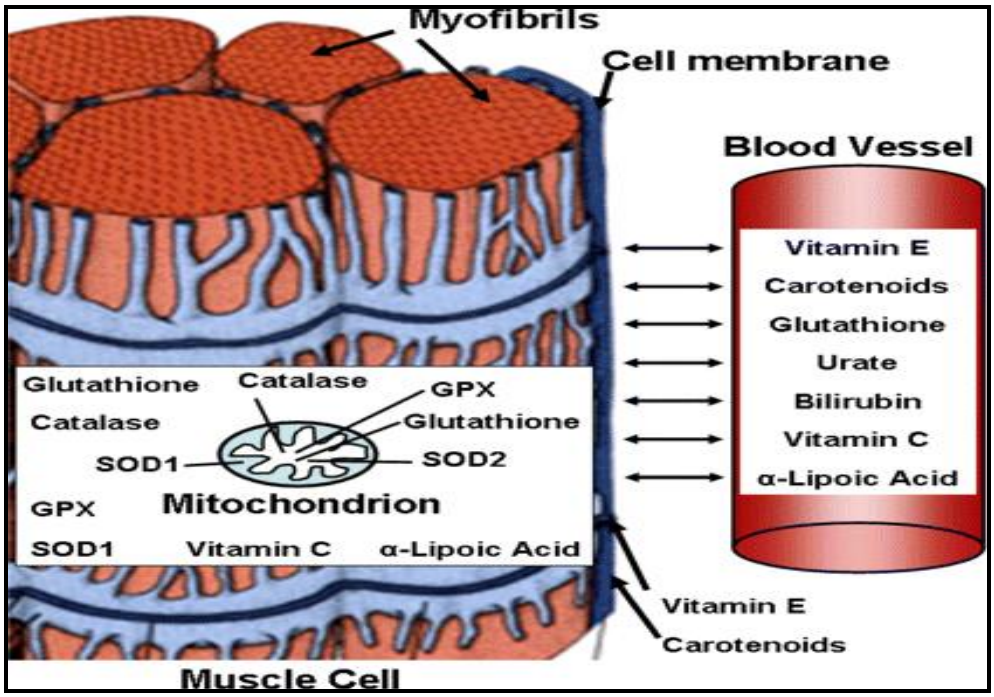

Figure (1): Antioxidant enzyme systems ***(Scott and Malcolm, 2008)***

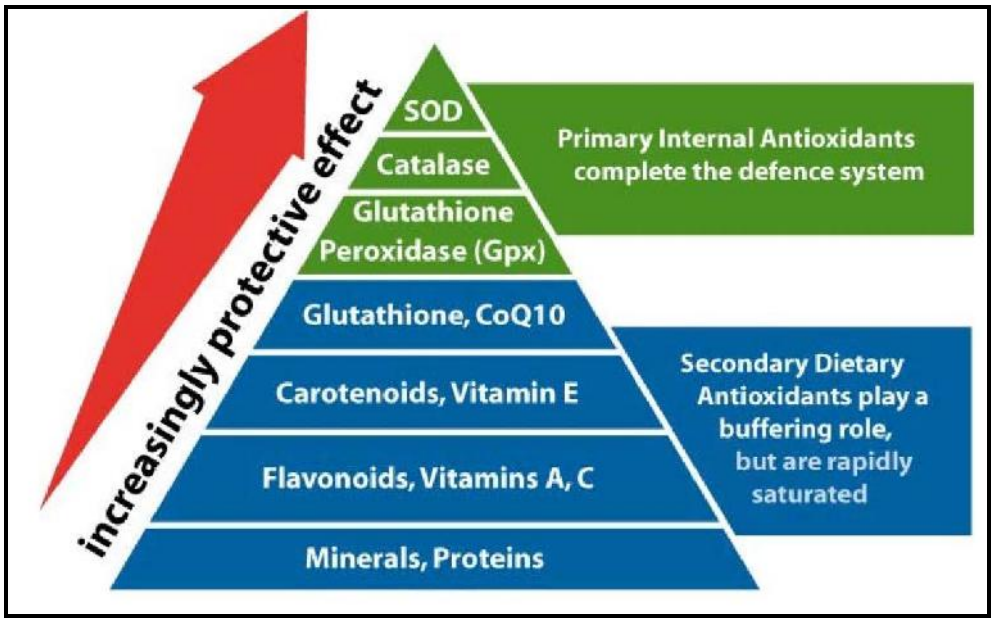

Figure (2): Antioxidant defence system ***(Wood et al., 2009)*.**

A-Glutathione:

Glutathione (L-γ-glutamyl-L-cysteinylglycine) is required for many critical cellular processes and plays a particularly important role in the maintenance and regulation of the thiol-redox status of the cell and in healthy cells and tissues, more than 90% of the total glutathione pool is in the reduced form (GSH) and less than 10% exists in the oxidized form (GSSG) ***(Schafer and Buettner, 2001).***

Diminished level of intracellular glutathione has been associated with immune dysfunction (T cell activation, imbalance Th1/Th2 cytokines and deregulation of apoptosis) and organ damage (nephritis, CNS) ***(Shah et al., 2009).***

The GSH/GSSG ratio is a valuable tool for defining oxidative stress ***(Shah et al., 2013).***

B-Superoxide dismutase:

Superoxide dismutase is a metalloprotein, considered to be the first line of defence against free radical formation and three forms of this enzyme found in human are: SOD1 located in cytoplasm, SOD2 in mitochondria and SOD3 in extracellular ***(Johnson and Giulivi, 2005).***

C-Catalase:

Catalase, located in peroxisomes (80%) and cytosol (20%), decomposes hydrogen peroxide to water and oxygen without the production of free radicals ***(Jones et al., 1981)*.** Concentration of CAT is highest in liver, kidney and erythrocyte and low in connective tissues ***(Aebi, 1984)*.**

Catalase does not show significant activity under physiological conditions due to its lower affinity than glutathione peroxidase for hydrogen peroxide, but becomes an important enzyme at disease state where concentration of H2O2 is elevated ***(Chance et al., 1979)*.**

D-Glutathione peroxidase and glutathione reductase:

Glutathione peroxidase and reductase are glutathione dependent enzymes located in the cytoplasm, mitochondria and nucleus ***(Gamble et al., 1999)*.**

It plays an important role in the defense mechanism in the erythrocytes against lipid peroxidation damage ***(Sen, 2000)*.**

3. Free radicals and Reactive oxygen species (ROS):

Origin:

Reactive oxygen species mostly originate from mitochondria, blood cells (lymphocytes, RBCs) and vascular endothelial cells in patients with Systemic Lupus Erythematosus (SLE). These ROS cause hyperpolarization of mitochondria, activated T lymphocytes, apoptosis and endothelial activation ***(Alam et al., 2007)*.**

It has been established that in eukaryotic cells over 90% of ROS are produced by mitochondria ***(Skulachev, 2012)*.**

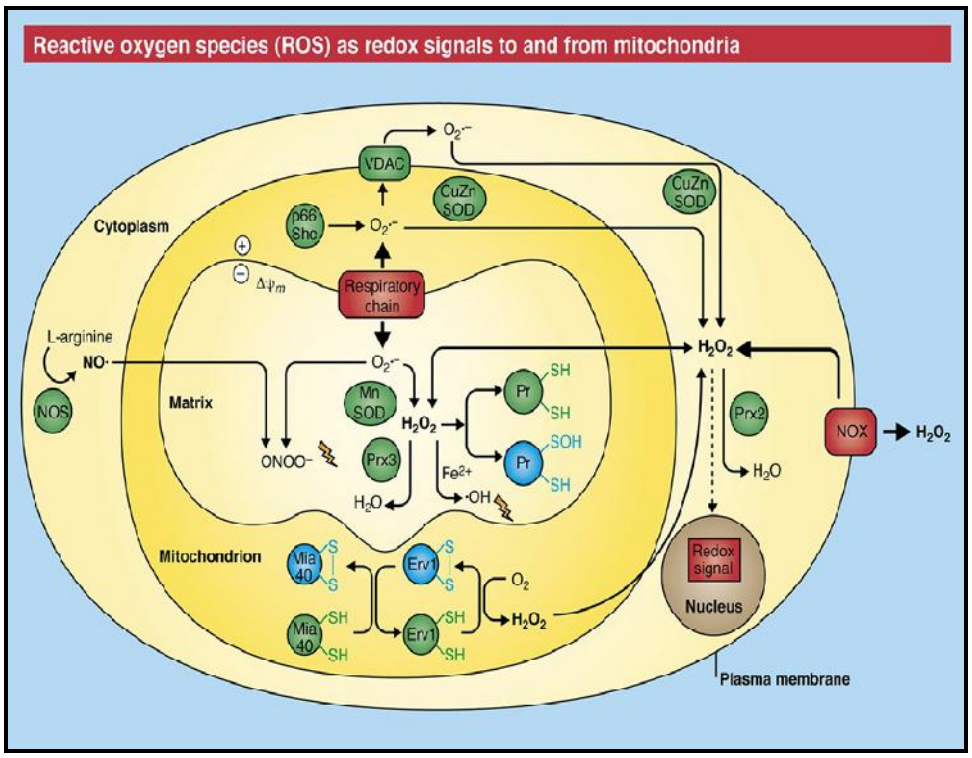

Figure (3): Mitochondrial redox signalling ***(Collins et al., 2012)*.**

Definition:

ROS is a collective term for the chemical species that are formed as a result of incomplete reduction of oxygen including peroxides (H2O2), superoxide (O2–.), hydroxyl radical (OH.), and singlet oxygen (O2) ***(Devasagayam et al., 2004)*.**

In living organisms under aerobic conditions more than 90% of oxygen consumed is reduced directly to water by cytochrome oxidase in electron-transport chain (ETC) via four-electron mechanisms without ROS release ***(Skulachev, 2012)*.**

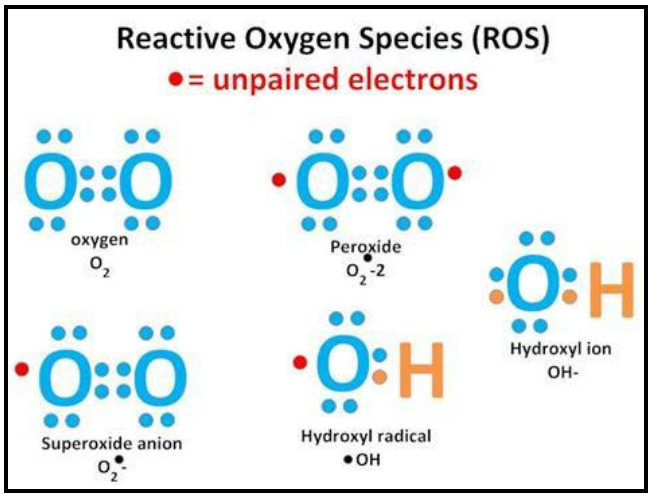

Figure (4): Reactive oxygen species **(Devasagayam, et al 2004).**

Source:

In eukaryotes, the system is represented by ETC, located in internal mitochondrial membrane, whereas in prokaryotes ETC components are located in plasmatic membrane ***(Lushchak, 2014)*.**

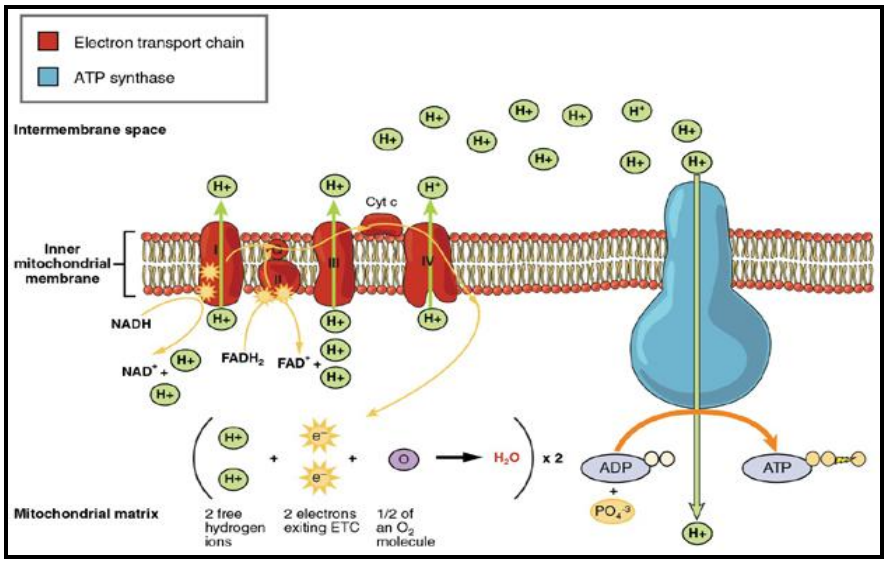

Figure (5): Electron transport chain ***(Betts et al., 2013).***

Operation of ETC is coupled with oxidative phosphorylation to produce energy in ATP form and less than 10% of oxygen consumed is reduced via one-electron successive pathways resulting in conversion of molecular oxygen to superoxide anion radical (O2-) followed by one-electron reduction with concomitant accepting of two protons to yield hydrogen peroxide (H2O2); this compound is not a free radical, but is chemically more active than molecular oxygen due to which is included in the ROS group ***(Semchyshyn and Lozinska, 2012).***

Hydrogen peroxide molecule accepting one more electron is split up to hydroxyl radical (HO-) and hydroxyl anion (OH-). Finally, HO- interacts with one more electron and proton resulting in formation of water molecule ***(Lushchak, 2014).***

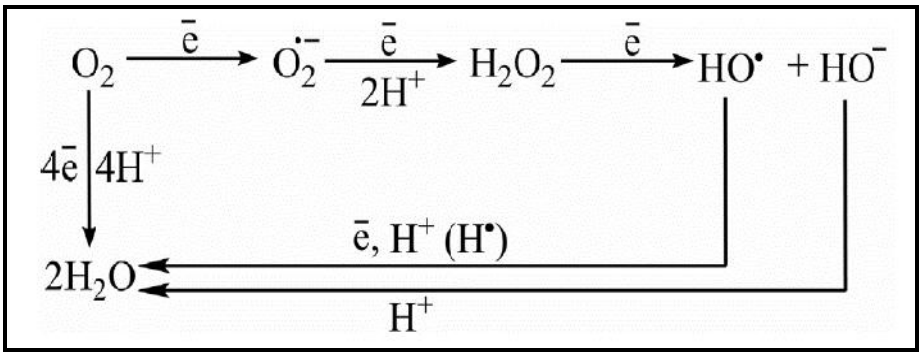

Figure: (6): Catabolism of hydrogen peroxide ***(Shah et al., 2014).***

Summarizing described above, O2 -, H2O2, and HO- collectively are called reactive oxygen species, but only O2- and HO- are free radicals, whereas H2O2 is not and reactive oxygen species include not only mentioned above O2-, H2O2, and HO-, but also diverse peroxides, like lipid peroxides, and peroxides of proteins, and nucleic acids ***(Semchyshyn and Lozinska, 2012).***

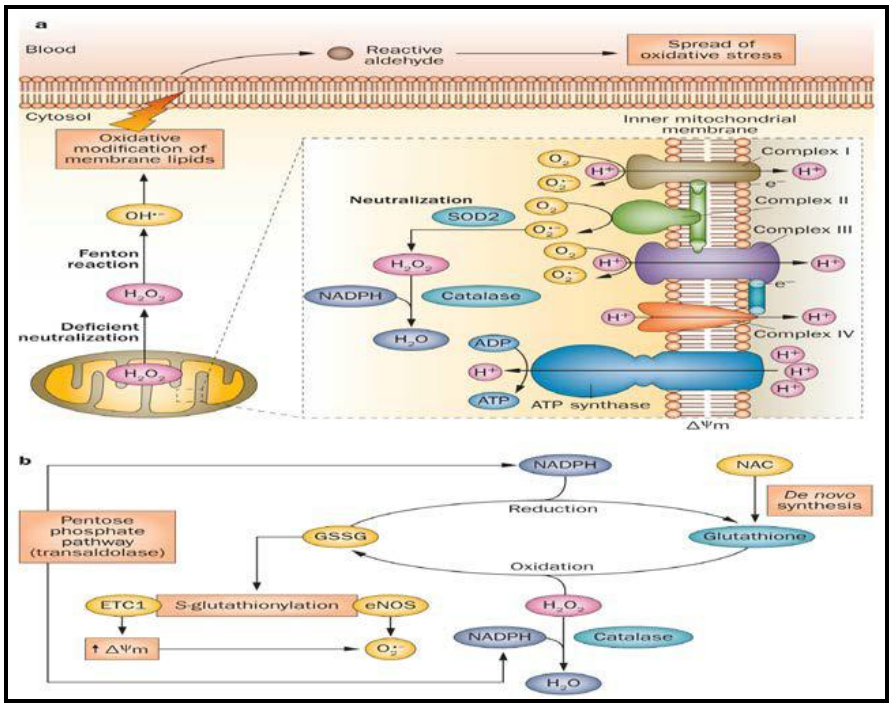

Figure (7): Mitochondrial generation and systemic propagation of oxidative stress and overview of redox balance mechanisms ***(Perl, 2013)***

Function:

ROS are short-lived molecules produced by normal cellular metabolism that are well recognized for playing a dual role; they are both deleterious and beneficial species ***(Kim-Howard et al., 2014).***

At low or moderate concentrations, ROS is required for the regulation of many cellular processes, including cell signalling, differentiation, proliferation, growth, apoptosis, and cytoskeletal regulation, and can act as lethal weapons for the host defence system ***(Shah et al., 2014).***

The harmful effect of free radicals occurs when there is an over-production of Reactive oxygen species (ROS)/ Reactive Nitrogen Species (RNS) or a deficiency of enzymatic and non-enzymatic antioxidants ***(Kim-Howard et al., 2014).***

Control of ROS by antioxidant defence mechanism:

Under normal conditions, ROS level fluctuates in certain range defined by concerted operation of systems of their generation and elimination ***(Lushchak, 2011).***

The control of ROS steady-state level is provided not only via their production, but also via elimination as living organisms possess multilevel and complicated antioxidant system operating either to eliminate ROS, or minimize their negative effects ***(Lushchak, 2014).***

There are several approaches to classify these systems and here we will use the mostly appreciated one based on molecular masses, placed in two groups:

1- **Low molecular mass antioxidants:** (usually with molecular masses below one kilo Dalton)

The group of low molecular mass antioxidants includes chemically different compounds usually well known to readers such as vitamins C (ascorbic acid) and E (tocopherol), carotenoids, anthocyanins, polyphenols, and uric acid, most of them are received by human organism as food or supplement components ***(Lushchak, 2012).***

2- **High molecular mass antioxidants:** (with molecular mass higher than one or actually higher than ten kilo Daltons).

One very important antioxidant glutathione (tripeptide c-glutamyl- cysteinyl-glycine, GSH) is synthesized by most living organisms and used to control ROS level either via direct interaction with them, or serving as a cofactor for ROS-detoxifying enzymes ***(Lushchak, 2012)*.**

Glutathione level is finely adjusted by organisms to specific conditions via several regulatory pathways ***(Uys et al., 2014)*.**

GSH as other thiols may interact with nitric oxide (NO) to neutralize it and at the same time providing additional regulatory mechanism for ROS-related processes like s-nitrosylation ***(Ownsend et al., 2014)*.**

This pathway not only decreases NO- level, but also creates buffer for this gaseous signal transmitter and provides its transportation on relatively long distances and protects thiol groups from irreversible oxidation during oxidative boots ***(Lushchak, 2012)*.**

Melatonin:

Antioxidant role of melatonin (N-acetyl-5-methoxytryptamine) should be highlighted here also certainly,

its health benefits like optimization of blood pressure and antioxidant activity ***(Tain et al., 2014)***. Melatonin can improve glucose metabolism via correction of insulin production protecting pancreatic b-cells against ROS induced damage ***(Lardone et al., 2014)*.**

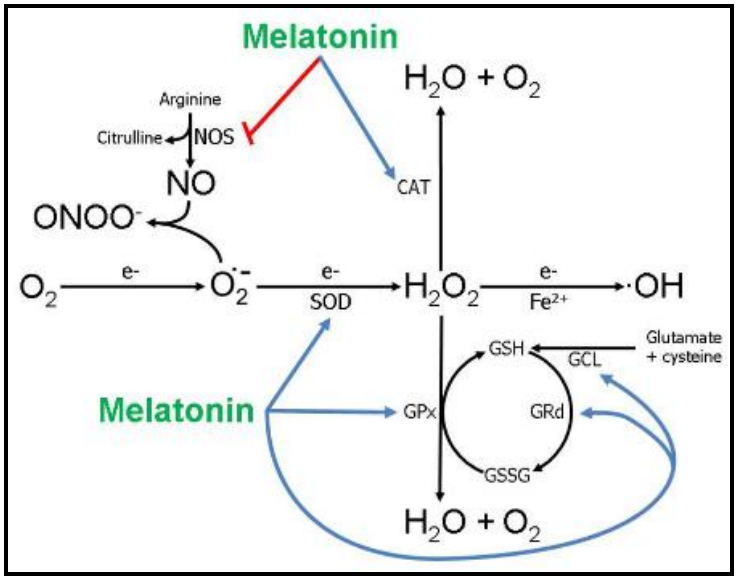

Figure (8): Antioxidant role of melatonin ***(Reiter et al., 2013)***

Prevention of hydroxyl radical production is the best way to protect living organisms from its deleterious effects ***(Sies, 2015)*.**

<u>Hydrogen peroxide is reduced by three general mechanisms:</u>

- It is the substrate for two enzymes, catalase and glutathione peroxidase, which catalyze the conversion of H2O2 to H2O+O2; this presumably is a detoxification mechanism ***(Morgan et al., 2009)*.**