European Journal of Biology and Medical Science Research

Vol.9, No.1, pp.22-34, 2021

Print ISSN: ISSN 2053-406X, Online ISSN: ISSN 2053-4078

DECODING THE ROLE OF OXIDATIVE STRESS AND ANTIOXIDATIVE PARAMETERS: IMPLICATIONS FOR DISEASE MANIFESTATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Ghizal Fatima[1], Puneet Kumar[2], Hemali Jha[3], Wajdy Al-Awaida[4], Hamzeh J. Al-Ameer[4], Najah Hadi[5], Ammar Mehdi[6], Hadeel AlTurk[7]

[1]Assistant Professor, Department of Biotechnology, Era's Medical College and Hospitals, Lucknow.
[2]Professor, Department of Rheumatology, King George's Medical University, Lucknow, India
[3]Professor, Department of Medicine, Hind Medical College, Lucknow, India
[4] Department of Biology and Biotechnology, American University of Madaba, Madaba, Jordan
[5]University of Kufa, Faculty of Medical Sciences, Kufa, Iraq
[6]Carrier Dental and Medical College, Lucknow, India
[7]Department of serology and immunology, Jordan Unilabs, Amman, Jordan.

ABSTRACT: *Systemic lupus erythematosus (SLE; lupus) is a autoimmune disease that mainly affects women of child bearing age. Lupus is characterized by antibodies produced against an individual's own proteins which are most commonly nuclear antigens. One of the proposed initiating factors include free radical-mediated oxidative stress, which play significant role in the pathogenesis of SLE. Previous studies reported evidence of elevated oxidative stress in the patients with lupus, although results between studies have been inconsistent. Several studies in lupus patients have indicated an imbalance between oxidant and anti-oxidant biomarkers. For example, the balance between the level of the oxidant, malondialdehyde and the antioxidant, superoxide dismutase, were skewed in SLE patients towards oxidant. In addition, excessive free radical levels may also be responsible for development of lupus and free radical-mediated oxidative stress including inflammatory cytokines may also play important roles in its pathogenesis. Further, oxidative stress was reported to be elevated in patients with SLE and also be related to its symptoms. Therefore, it is crucial to first understand, whether or not the parameters of oxidative stress are involved in SLE and second, what is the relationship between oxidant status, and antioxidants parameters in SLE patients. In this review we will systematically examine the relationship between oxidative stress as well as antioxidative parameters and there association to the pathogenesis and progression of SLE.*

KEYWORDS: oxidative stress, antioxidative parameters, systemic lupus erythematosus, autoimmune

INTRODUCTION

Systemic lupus erythematosus (SLE; lupus) affects mainly multiple organs of the body. Lupus is a systemic, autoimmune disorder that predominately affects females (female to male ratio is 9:1) during their reproductive age [1]. The incidence and the prevalence of SLE have been reported to vary across geographic regions of the world. However, examined at the pathophysiological level, SLE is distinguished by the production of autoantibodies, especially those antibodies that are produced opposite nuclear antigens. Even if it is accepted that the etiology of SLE stems from multiple factors, including hormonal and environmental, immune dysfunction and genetic susceptibility, the molecular systemic autoimmune reaction mechanisms are remain unknown. . The relevant question in the pathogenesis of the SLE is how the immune system in the body

exposes intracellular antigenes and targets it. [2]. In this account, excess production of reactive oxygen species (ROS), an altered redox state with defect in regulation of apoptosis (i.e. controlled cell death) are considered critical indicators involved in the creation and extensionof superoxide-dismutase (SOD) [3] and autoantibody-mediated flares as well as producing various clinical features in SLE and pro-inflammatory responses adjunctive to the failure to clear apoptotic cells in the presence of auto-antibodies [4].

Intracellular glutathione (GSH) depletion is an index of ROS and therefore is contributed in the dysfunction of apoptosis in SLE [5]. Oxidative damage mediated by ROS results in dysfunctional regulation of apoptosis that result in fault clearing of apoptotic cells leading to prolonged interaction between apoptotic macromolecules cells and ROS, therefore neoepitopes are produced that result in a wide range of production of autoantibody in SLE patients and leads to tissue damage[6-8]. Furthermore, elevated levels of MDA-modified proteins, anti-SOD and anti-catalase antibodies in the sera of SLE patients results in oxidative stress in development and progression of the disease [9].

Although there are some inflammatory clinical conditions found associated with increase in oxidative stress, there is not much information regarding oxidative stress in SLE. However, several inflammatory processes are related to oxidative stress which includes protein oxidation, lipid peroxidation and other oxidative stress biomarkers. There are very few studies that have reported the evidence regarding the role of adverse oxidative stress in the pathophysiology of SLE. In this review, we will try to explain how the complex network of oxidative imbalance occurs in SLE and in doing so also attempt to establish its relationship with disease manifestations.

Consequences of oxidative stress

Oxidative stress is an imbalance in between the systemic manifestation of reactive oxygen species and the potential of a biological system to remove the toxic substances from the reactive intermediates or to mend any resulting tissue or organ damage. However, disorders in the normal redox state of cells can lead to toxic effects via the peroxides and production of free radicals that harm all of the cellular components, including lipids, proteins, and DNA. Oxidative stress from over-active oxidative metabolism causes DNA base damage, and DNA strand breaks [10]. Base damage is usually indirect reason being that ROS is originated through OH (hydroxyl radical), O2- (superoxide radical) and H_2O_2 (hydrogen peroxide) production. Moreover, some ROS perform the role of cellular messengers in the process of redox signaling. Thus, in normal mechanism of cellular signaling, disruptions may occur due to oxidative stress. In a chemical reaction, oxidative stress is kindred with elevated production of oxidizing species or a significant reduction in the effectiveness of antioxidant defenses, such as GSH which therefore elevates oxidative stress parameters [11].

The complete influences of oxidative stress rely full on the size of thesemodifications, with a cell having the ability to overcome the small perturbations and recover its original state. Further, extreme oxidative stress can lead to apoptosis and even average oxidation can trigger cell death. While other intense stresses may result in necrosis [12]. The generation of ROS is a uniquely catastrophic aspect of oxidative stress which involves the production of peroxides and Free Radicals. Few of the less effective but still more reactive of these species including superoxide can be transformed by oxidation reduction reaction with transition element or other redox cycling compounds, including quinones (1,4-benzoquinone) into more truculent radical species that can

cause boundless cellular damage [13]. Most importantly, long-term effects of oxidative stress may also cause damage to DNA. Therefore, DNA damage that is initiated by oxidative stress, have been implicated in aging and cancer [14]. Furthermore, such type of oxidative damage may cause cellular disruption, as well as it contributes to the pathophysiology of a large variety of diseases.

Oxidative Stress in SLE

Lipid peroxidation that occur in the membranes of mitochondria, lysosomes and is mediated by ROS, causes reactive aldehydes such as MDA and 4-hydroxy-2-nonenal (HNE), that can result in spreading oxidative damage throughout the peripheral circulation. Therefore, The blood circulation of SLE patients can be found in those cascade products formed by oxidative modifications[15]. For example, the HNE-mediated modification of serum albumin reflects oxidative stress [16] and the range of anti-MDA/anti-HNE protein adduct antibodies correlates with the activity of disease in SLE [17]. There is a complex role of ROS in autoimmunity. Oxidative stress can lead to the generation of novel autoantigens and therefore results in exacerbation of autoimmune response [18]. Throughout recent years, ROS has become significantly more active throughout pathogenesis of various human degenerotic diseases as potential causative agents [19]. The hydroxyl radical (·OH) is produced by high oxydative stress parameters in significant amounts during chronic inflammatory conditions. The isolated lymphocytes of SLE patients contain elevated level of 8-oxodG [20]. A study of isolated blood monocytes from SLE patients revealed that a defective repair system would lead to cell death and release of oxidized DNA impairment by removing 8-oxodG from the cellular DNA. ROS has already been known to cause damage to DNA and its function is well-reported in cancer production [21]. These radicals are also implicated in ageing, as well as other human diseases including multiple sclerosis, Parkinson's disease and autoimmune disorders [22-24]. Thus, it is believed that oxidative stress plays a significant role in initiating autoimmune disease through excess free radical formation.

Increased ROS production or decreased ROS-scavenging capacity resulting from endogenous metabolic alterations or exogenous stimuli can disturb redox homeostasis, which leads to an overall elevation in the levels of intracellular ROS, or oxidative stress [25, 26]. .OH is the most potent damaging free radical among the ROS, because of its capacity to react with all biological macromolecules, including, lipids, proteins, carbohydrates and nucleic acids while also leading to the formation of DNA-protein crosslinks, single and double-stranded DNA breaks, base damage in DNA, increased pro-inflammatory cytokine production (e.g. TNF-α), protein fragmentation and lipid peroxidation. This oxygen radical species may also cross cell membranes and then react with nuclear DNA [27, 28]. Further, an increase in serum nitrate and citrulline levels correlated with disease activity indices and, along with serum titers of anti-double-stranded (anti-dsDNA) antibodies, served as an indicators of the SLE pathology, including lupus nephritis [29, 30].

Production of free radicals and alteration in redox status has potential to modulate the expression of a range of immune and inflammatory molecules [31]. In some autoimmune diseases the aberrant immune responses also cause anemia. In a pathological condition like autoimmune hemolytic anemia antibodies attack RBCs preceding a diagnosis of SLE [32, 33]. ROS are elevated and appears to be the most underlying mechanism for SLE [34, 35]. The changes in ROS aggravate the inflammatory processes and ultimately results in tissue damage therefore, results in impairment, in the generation of superoxide, H2O2 and NO [36]. Oxidative stress appears to cause selective decreases in redox-sensitive proteins. The NADPH production is

elevated by activated G6PD in response to oxidative stress [37], and thus supports the reductive detoxification of ROS and oxidized molecules, although its activation mechanism is still unclear. Production of ROS also provides with the oxidant needed for thiol oxidation or peroxynitrite formation that may form modifications in antibodies [38]. The association between SLE and oxidative stress has been reported by the elevated levels of valid biomarkers of oxidative stress in SLE. Raised levels of 8-oxodG, an oxidative DNA damage marker in immune-complex-derived DNA, reported in serum and lymphocytes from SLE patients, reinforcing ROS as a disease etiology component and have also reported that oxygen radicals may cause SLE pathology by perpetuating the existence of an antigenic form of DNA in the blood circulation. [20, 39]. However, the levels of protein oxidation markers correlates with the disease severity in patients with SLE, which then supports the role played by protein oxidation in the pathogenesis and progression of SLE [40]. Elevated levels of F2 isoprostanes, are very similar to the prostaglandin like substances, they are derived from lipid peroxidation, and are found in the urine and serum of SLE patients [41]. It was also reported that ·OH, can result in the production of neo-antigens, like ·OH-mediated damage of human serum albumin (HSA), and in turn, this could exacerbate autoimmunity initiation in patients with SLE. Thus, these studies supported the role of oxidative stress in symptoms of SLE and in its progression [42]. However, the lipids in the cell membranes are the primary target of ROS, resulting in the impairment of cell structure and its function.

A complex machinery of antioxidant enzymes is possessed by all types of cells, including lymphocytes and other immune cells, [e.g. catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), superoxide dismutase (SOD), thioredoxin] and antioxidant molecules (e.g. reduced GSH and vitamins) for regulating the oxidizing reactions in cells by preventing free radical-mediated cytotoxicity [43]. For example, circulating red blood cells have the ability to scavenge $O_2 \cdot -$ and H_2O_2 by catalase, SOD and GPx-dependent mechanisms that may play a crucial role in regulating such reactions. SOD provides the first line of defense against ROS by catalyzing the dismutation of $O_2 \cdot -$ into H_2O_2. H_2O_2 gets transformed into H_2O and O_2 by the enzyme catalase. GPx is a selenoprotein which causes the reduction in lipidic or non-lipidic hydroperoxides as well as in H_2O_2 by utilizing GSH in cultured human fibroblasts. Furthermore, levels of lipid peroxidation were found significantly elevated, measured as malondialdehyde (MDA), in patients with SLE. The antioxidant enzymes such as SOD, CAT, GPx and antioxidant molecule GSH were reported to be significantly reduced in SLE patients as compared to controls. MDA levels were found positively correlated with SLE patients. Disease Activity Index (SLEDAI) score, IFN-gamma, IL-12 were negatively correlated with GSH in SLE patients. Strong positive correlations of IFN-gamma and MDA with SLEDAI score, suggested that the lipid peroxidation and proinflammatory cytokine, both are involved in the pathogenesis of SLE [44]. In addition, the decreased activity of cortisol and high percentage of CD8(+) T cells in the lymphocytes could also be involved in SLE pathogenesis [45]. Moreover, the reduced activity of SOD causes excessive deposition of $O_2 \cdot -$ that would otherwise have been converted enzymatically to H_2O_2. However, the elevated $O_2 \cdot -$ levels have retained the potential to initiate the lipid peroxidation chain reaction in SLE patients.

The relationship between the SLE and oxidative stress has also usually been determined by measuring the levels of DNA damage and the formation of anti-oxidants and free radicals. Both of them elevated the levels of ROS and reduced intracellular glutathione levels have been reported previously in conjunction with disease flare [9]. Possibly, a greater insight into the consortium between susceptibility of disease and oxidative stress might be obtained by the study of functional polymorphisms in genes that are intricated in guiding the levels of cellular

oxidative damage. Candidate pathways may include the anti-oxidant as well as DNA repair mechanisms that are controlled by individual genetic variation [9]. In this regard, polymorphisms in the genes, encoding CAT and SOD2 [46] have been identified, especially, CAT-330CC which may contribute to the clinical findings in SLE [47].

Both elevated as well as reduced activities of CAT from erythrocytes of patients with SLE have been documented by several groups [48]. However, GPx activity is controversial in SLE patients, whereas several studies have reported decreased activity of GPx in SLE patients [48]. Of note, the adequate concentrations of GSH are important and equally essential for regulating a variety of cell functions, including, protecting cells from oxidative damage, regulating lymphocyte activation, quenching oxidant species, activating natural killer cell and regulating lymphocyte-mediated cytotoxicity [49, 50]. In fact, the intracellular depletion of GSH has been related to several autoimmune mediated inflammatory diseases, including SLE [51].

Moreover, the decreased levels of GSH and the severity of SLE, were correlated with especially in lupus nephritis patients [44, 52]. The decreased level of intracellular GSH may be attributed to ROS-induced GSH export from cells or GSH oxidation [53]. Besides the significant role of GSH in maintaining the cellular redox state, GSH oxidation provides major contribution to lymphocyte apoptosis mediated by oxidants [54]. Thus, these studies confirmed that the level of oxidative stress found in SLE patient most likely results from faulty antioxidant system (e.g. SOD, CoQ10 etc) and elevated production of ROS that contributes to the disease activity. Therefore, finding the mode of origin of oxidative stress may help us in understanding the pathophysiology of SLE, and to put forth new therapeutic strategies for treating SLE.

Defense System of Antioxidants

Oxidation is a chemical reaction that involves an increase of oxidation state or the loss of electrons. Free radicals are produced by oxidation reactions and in turn, these free radicals can initiate chain reactions. Further, when the chain reaction starts in a cell, it causes the destruction, internal damage or death of the cell. An antioxidant is a molecule that prevents the oxidation of other molecules. By removing free radical intermediates and by inhibiting other oxidation reactions antioxidants terminate these chain reactions. Antioxidants perform this activity by getting themselves oxidized, and therefore antioxidants are often reducing agents such as ascorbic acid (i.e. vitamin C), thiols, or by the activity of polyphenols. Generally, these antioxidant systems either prevent the formation of these reactive species, or remove them before they can cause damage to the vital components of the cell. Nevertheless, the ROS also have useful cellular functions, such as signaling of the redox reaction. Therefore, the function of antioxidant systems is not the complete removal of the oxidants, but instead to maintain them at an optimum level [55]. Hence, an antioxidant can be defined as: “any substance when present in low concentrations compared to that of an oxidized substrate significantly inhibits or delays the oxidation of that substrate” [56]. Furthermore, the physiological role of antioxidants, as this definition implies, is to prevent cellular components damage emerging as a consequence of chemical reactions involving the free radicals.

However, in recent years, enough evidence has developed in support of free radicals occurring in many fundamental cellular reactions and therefore suggesting that oxidative stress might be very crucial in the pathophysiology and in the progression of many diseases, including, chronic renal failure, atherosclerosis, diabetes mellitus, etc [43]. Free radicals can react with indiscriminate effects damaging almost any cellular component, which means that they have a substantial array of antioxidant defenses, both endogenous and exogenous; to prevent free radical mediated

damage to the cellular components. However, the effect of damage mediated by the ROS is limited by the various number of cellular antioxidant defense mechanisms. As discussed earlier, common antioxidants like, enzymes such as catalase, SOD and glutathione-related enzymes like GR, GPx, GST and thioredoxin reductase and heme oxygenase [25] , as well as several non-enzymes such as carotenoids, flavonoids, GSH, vitamins (A, C, E) and other types of antioxidant minerals, like manganese, selenium, copper, ferritin, zinc, etc. A study reported that oxidative stress was found elevated in the SLE patients with insulin resistance, with increase in the ferritin levels, caused by the inflammatory process or by the hyperinsulinaemia, favours the redox process [57]. Study by Serban et al reported that administration of vitamin E with corticotherapy has a lower effect due to the metabolic disturbances by the autoimmune pathogenic processes [58]. All of the above mentioned antioxidants work in synergy with each other against various types of free radicals. For example, vitamin C together with vitamin E impedes hydroperoxidase formation and vitamin E suppresses the propagation of LPO [59].

Antioxidants in Experimental SLE

As discussed above, antioxidants are well known to shield against the tissue damage from ROS. Therefore, in autoimmune diseases, the ROS is likely to be generated by the activated macrophages, granulocytes and monocytes [60] and therefore, ROS functions to increase the activity of cytokines, such as TNF-α, which is a important inflammatory mediator in these diseases where TNF-α induces the proinflammatory cytokines such as MCP-1 and IL-8 expression, through production of reactive oxygen intermediates and subsequently results in activation of NF-kappa B in synovial cells, and then the antioxidants may impede, in part, the activation of NF-kappa B by TNF-α. Therefore, indicating that antioxidants such as N-acetyl-L-cysteine (NAC) may be helpful in treatment of diseases like rheumatoid arthritis and SLE [61]. In a murine model of SLE (i.e. female NZB x NZW F1 mouse) a dietary supplementation consisting of cysteamine (CYST) and N-acetylcysteine (NAC) as well as antioxidants, including α-tocopherol, β-carotene, selenium, ascorbic acid, lowered the level of autoantibody production hence leading to prolonged survival of the animal. Proving that reactive oxygen intermediates (ROI) play an important role in the lupus nephritis pathogenesis and that antioxidants reduces deterioration caused by renal insufficiency. Therefore, antioxidants may be a helpful adjunctive therapy in treatment of patients with SLE. In addition, vitamin E could also act to be beneficially effective in the progression of the SLE-like disease in MRL/lpr mice demonstrating a possible measure to combat SLE disease and other autoimmune diseases as well [62, 63].

Further, dietary supplements with vitamin E modulated inflammatory cytokines and delayed autoimmunity onset in the MRL/lpr mouse model [64]. Vitamin A derivative retinoic acid was also shown to inhibit the production of pro-inflammatory T-helper 17 cells (T_h17 cells) and, in addition, encouraged the production of the anti-inflammatory T-regulatory (T_{reg}) cells in murine models of autoimmunity [65]. However, relatively very little is known about the antioxidant influence intake through the diet on treatment or initiation of these diseases in humans [39, 66, 67]. Moreover, decreased antioxidant rates in SLE patients were reported, as well as decreased antioxidant intakes[68, 69]. In a case-control study within a Finnish cohort, 14 subjects with RA, an Average 20 years after diagnosis, blood antioxidant levels were decreased in comparison with healthy controls [70]. Similarly a study was conducted in Maryland, where 21 subjects who eventually developed RA and 6 who later developed SLE had provided their samples of serum to a serum bank, 2 to 15 years prior to the onset of a disease. Their blood samples reported lower levels of β-carotene, retinol and α-tocopherol, than those of their race, sex and age-matched controls [71].

SLE therapy by Antioxidants

Oxidative stress treatment requires interventions to avoid exogenous causes such as ultra violet (U.V) light and endogenous factors including mitochondrial function and, as well as stimulation of antioxidants. Some protective interventions are there other than antioxidant therapy to shield or to protect against oxidative damage like, application of sun-screen with a protection factor of slightly greater than 50 and photo-resistant clothing, which can be used to block the radiation of U.V light. Important antioxidant therapies include dietary nutrients such as vitamins as well as conjugated linoleic acid (CLA). In the MRL/lpr mouse model proof-of-principle in this area was already achieved where CLA (versus olive oil) elevated the levels of GSH, correlated with levels of oxidative stress and markers of SLE disease activity, and also enhanced the expression of glutamate cysteine ligase [72]. The effective treatment of inflammation using antioxidants might play an important role not only in the therapeutic reversal of redox-mediated signaling defects, but also in attenuating the toxicity of immunosuppressive therapies. For example, many epidemiological studies have reported the potential role of the prophylactic intake of antioxidant nutrients in the progression of SLE [35].

However, in a large prospective health survey of 184,643 women in the U.S. the data reported that the intake of antioxidant nutrients such as vitamins C, A, E, β-carotene, α-carotene, lutein, lycopene, and cryptoxanthin from foods and supplements was not found connected with a reduced risk of SLE and RA [73]. Therefore, these findings suggested that although in general antioxidants are secure, no protection against SLE disease are provided by antioxidants, probably due to their impotency to monitor the intracellular signaling within the immune system. Thus, the conclusion from this study was braced by the results of a double-blind, 3-months placebo-controlled pilot study of vitamin C, (500 mg) and vitamin E (800 IU) supplemented daily in 39 SLE patients, a regimen that decreased the blood plasma levels of MDA without affecting disease activity and endothelial function [74]. Furthermore, this view was also supported by the results of study performed on mice that concluded that vitamin C decreased the levels of IgG and anti-dsDNA, but that inadequate consumption of vitamin C could induce inflammation in the active phase of SLE which maintained oxidative stress [75]. In a study carried out by Minami et al, on a total number of 279 patients with SLE, that the vitamin C intake has been found to be reversed with the relative risk of inflammatory activity progression in SLE. The antioxidant vitamin C properties can therefore modulate immune functions and result in the release of inflammatory mediators [75]. Moreover, day-to-day vitamin C, (500 mg dose) and vitamin E combinations (800 IU dose) were strongly associated with reduced levels of lipid peroxidation for 3 months without affecting other oxidative stress markings or endothelial function of SLE patients. [74].

However, other experimental results showed that retinoids, personified by Vitamin-A inhibited the development of T_h17 cells and hence promoted the formation of T_{reg} cells in autoimmune diseases [73]. Furthermore, in an extension of those findings to human studies, Kinoshita et al. [76] reported that patients with SLE treated with retinoids, had decreased levels of anti-dsDNA, and reduced levels of proteinuria with no side-effects reporting that treatment of lupus nephritis with retinoids might be a promising adjunctive therapy.

Supplementations with Vitamin A and vitamin D in patients with SLE have also been tested. Therefore, a 2-weeks supplemented dose of 100,000 IU of vitamin A was beneficial to show high antibody-dependent cell cytotoxicity and an increased natural kill cell activity and a positive IL-2 response.[77]. However, high levels of consumption of vitamin A (> 10 000 IU) may also

lead to adverse events such as dry skin, nausea, pseudo-hydrocephalus, anemia, headache, anorexia and ultimately death. Vitamin A deficiency has shown major symptoms severity in experimental animal model SLE. . In that regard, a study carried out by Varghese et al. [78] in a mice model of SLE concluded that immunotherapy in combination with folate minimized SLE symptoms and prolonged the life span. In addition a study reported by Minami et al [79] showed an association between high doses of vitamin B6 and folate in Japanese SLE patients with decreased disease frequency.

Vitamin D is another antioxidant which is developed in the skin and derived from food and is a significant nutrient because of its many immunomodulatory effects. Several studies have clearly shown low serum levels of 25(OH) D (i.e. ~25.5 ± 12.1 nmol/L; mean±SD) in SLE patients which is significant in comparison to the recommended minimum serum concentration range of 25(OH) D (i.e. 50–80 nmol/L) [80, 81]. Thus vitamin D supplementation is sufficient as its more precise predictor (1, 25(OH)2 D3) also plays a role in the controlling immune system and in calcium homeostasis. Abe et al [82] reported that supplementation with vitamin D_3 to the MRL/lpr spontaneous developing lupus mouse model significantly improved longevity and reduced proteinuria. The impact of the active form of Vitamin D, 1, 25(OH) 2 D3, on the immune response take place as a result of the inhibition of the T_h1 lymphocyte proliferation [83]. However, no link was found between the intake of vitamin D and the relative risk of progression of SLE in a recent prospective study carried out among 18,000 women for 22 years.. Therefore, supplements with micronutrient are not amalgamated In SLE patients with disease incidence and enhanced quality of life[84]. The inverse relation between proportionate consumption of vitamins A and E and SLE activity has been discussed previously, In particular, patients with SLE have multiple risk factors due to vitamin D deficiency and severity of disease that seems associated with decreased vitamin D levels. Therefore, treatment of SLE with vitamin D could be particularly pertinent in patients with SLE due to associated insults on their tissue and bone, and its immunomodulatory effect that is exerted by vitamin D [85, 86]. Importantly, a study by Costenbader et al [87] There is no link between eating antioxidants or supplements or risk of developing RA or SLE in women has been supported. This approach is therefore unlikely to succeed due to the lack of therapeutic efficacy associated with inadequate dosing or vitamin C's failure to increase the intracellular levels of GSH in T cells.

CONCLUSIONS

The association between antioxidants, free radicals and the functions of numerous organs is highly complex; the unearthing of ‘signaling of redox’ is a milestone in initiating this pivotal relationship. Advances in the research have focused on different strategies to shield the critical organs and tissues against oxidative damage that is induced by free radicals Countless new approaches were established and in recent decades several substantial and vital results have been published. There is sufficient evidence to confirm that in cells oxidative stress prevails as an effect of normal physiological processes and environmental interactions, as well as that the complicated web of antioxidants defense systems plays a crucial role in the control of oxidative stress damages. Decrypting the character of compartmentalized oxidative stress in phagocytic cells and T-cells in patients with SLE can be anticipated to provide further insights into the pathogenesis of SLE. In addition, a better characterization of oxidation-related cell and molecular causes of stress that contribute to SLE will promote the development of therapeutic approaches to reverse and mitigate the exposure effects and may even lead to useful bio-markers and a positive clinical response to therapy. Meanwhile, clinical studies must appraise the dietary intake of antioxidants in studies consisting of large sample size by evaluating the effect of increasing intake of antioxidants. Therefore, a complete elucidation of the biochemical events

occurring at the cellular level to effectively inhibit oxidative damage is required to usher in future therapeutic advances. Finally, using favorable oxidative stress processes and eliminating the harmful pathways can improve immunotherapy's effects by reducing disease activities, thus improving the quality of life for SLE patients.

Acknowledgment: We would like to acknowledge Dr. Charles J. Malemud, faculty at Case Western Reserve University School of Medicine for his substantial contribution in the study.

References:

1. D'Cruz, D., *Khamashta M a, Hughes GR V. Systemic lupus erythematosus.* Lancet, 2007. **369**(9561): p. 587-596.
2. Graham, K.L. and P.J. Utz, *Sources of autoantigens in systemic lupus erythematosus.* Current opinion in rheumatology, 2005. **17**(5): p. 513-517.
3. Kurien, B.T. and R.H. Scofield, *Free radical mediated peroxidative damage in systemic lupus erythematosus.* Life sciences, 2003. **73**(13): p. 1655-1666.
4. Munoz, L.E., et al., *Apoptosis in the pathogenesis of systemic lupus erythematosus.* Lupus, 2008. **17**(5): p. 371-375.
5. Franco, R. and J. Cidlowski, *Apoptosis and glutathione: beyond an antioxidant.* Cell Death & Differentiation, 2009. **16**(10): p. 1303-1314.
6. Griffiths, H.R., *Is the generation of neo-antigenic determinants by free radicals central to the development of autoimmune rheumatoid disease?* Autoimmunity reviews, 2008. **7**(7): p. 544-549.
7. Ahsan, H., A. Ali, and R. Ali, *Oxygen free radicals and systemic autoimmunity.* Clinical & Experimental Immunology, 2003. **131**(3): p. 398-404.
8. Malemud, C.J. and H.J. Gillespie, *The role of apoptosis in arthritis.* Current Rheumatology Reviews, 2005. **1**(2): p. 131-142.
9. Mansour, R.B., et al., *Increased levels of autoantibodies against catalase and superoxide dismutase associated with oxidative stress in patients with rheumatoid arthritis and systemic lupus erythematosus.* Scandinavian journal of rheumatology, 2008. **37**(2): p. 103-108.
10. Maynard, S., et al., *Base excision repair of oxidative DNA damage and association with cancer and aging.* Carcinogenesis, 2009. **30**(1): p. 2-10.
11. Fatima, G., S.K. Das, and A.A. Mahdi, *Some oxidative and antioxidative parameters and their relationship with clinical symptoms in women with fibromyalgia syndrome.* International journal of rheumatic diseases, 2017. **20**(1): p. 39-45.
12. Lennon, S., S. Martin, and T. Cotter, *Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli.* Cell proliferation, 1991. **24**(2): p. 203-214.
13. Valko, M., H. Morris, and M. Cronin, *Metals, toxicity and oxidative stress.* Current medicinal chemistry, 2005. **12**(10): p. 1161-1208.
14. Evans, M.D. and M.S. Cooke, *Factors contributing to the outcome of oxidative damage to nucleic acids.* Bioessays, 2004. **26**(5): p. 533-542.
15. Skaggs, B.J., B.H. Hahn, and M. McMahon, *Accelerated atherosclerosis in patients with SLE—mechanisms and management.* Nature Reviews Rheumatology, 2012. **8**(4): p. 214.
16. Khatoon, F., K. Alam, and A. Ali, *Physicochemical and immunological studies on 4-hydroxynonenal modified HSA: Implications of protein damage by lipid peroxidation products in the etiopathogenesis of SLE.* Human immunology, 2012. **73**(11): p. 1132-1139.
17. Wang, G., et al., *Markers of oxidative and nitrosative stress in systemic lupus erythematosus: correlation with disease activity.* Arthritis & Rheumatism, 2010. **62**(7): p. 2064-2072.

18. Xie, H., et al., *Vitiligo: how do oxidative stress-induced autoantigens trigger autoimmunity?* Journal of dermatological science, 2016. **81**(1): p. 3-9.
19. Imlay, J.A. and S. Linn, *DNA damage and oxygen radical toxicity.* Science, 1988. **240**(4857): p. 1302-1309.
20. Lunec, J., et al., *8-Hydroxydeoxyguanosine: A marker of oxidative DNA damage in systemic lupus erythematosus.* Febs Letters, 1994. **348**(2): p. 131-138.
21. Ashok, B.T. and R. Ali, *Binding of human anti-DNA autoantibodies to reactive oxygen species modified-DNA and probing oxidative DNA damage in cancer using monoclonal antibody.* International journal of cancer, 1998. **78**(4): p. 404-409.
22. Ames, B.N., *Endogenous oxidative DNA damage, aging, and cancer.* Free radical research communications, 1989. **7**(3-6): p. 121-128.
23. Marx, J.L., *Oxygen free radicals linked to many diseases; the oxygen free radicals, although made as by-products of normal oxygen-using reactions, nevertheless have a wide potential for causing cell injury.* Science, 1987. **235**: p. 529-532.
24. Halliwell, B. and M. Grootveld, *The measurement of free radical reactions in humans: some thoughts for future experimentation.* FEBS letters, 1987. **213**(1): p. 9-14.
25. Halliwell, B., *Reactive oxygen species in living systems: source, biochemistry, and role in human disease.* The American journal of medicine, 1991. **91**(3): p. S14-S22.
26. Wiseman, H. and B. Halliwell, *Damage to DNA by reactive oxygen and nitrogen species: role in inflammatory disease and progression to cancer.* Biochemical Journal, 1996. **313**(Pt 1): p. 17.
27. Stohs, S.J. and D. Bagchi, *Oxidative mechanisms in the toxicity of metal ions.* Free radical biology and medicine, 1995. **18**(2): p. 321-336.
28. Lloyd, R.V., P.M. Hanna, and R.P. Mason, *The origin of the hydroxyl radical oxygen in the Fenton reaction.* Free radical biology and medicine, 1997. **22**(5): p. 885-888.
29. Wanchu, A., et al., *Nitric oxide synthesis is increased in patients with systemic lupus erythematosus.* Rheumatology international, 1998. **18**(2): p. 41-43.
30. Gilkeson, G., et al., *Correlation of serum measures of nitric oxide production with lupus disease activity.* The Journal of rheumatology, 1999. **26**(2): p. 318-324.
31. Sundaresan, M., et al., *Requirement for generation of H2O2 for platelet-derived growth factor signal transduction.* Science, 1995. **270**(5234): p. 296-299.
32. Fujii, J., et al., *Oxidative stress as a potential causal factor for autoimmune hemolytic anemia and systemic lupus erythematosus.* World journal of nephrology, 2015. **4**(2): p. 213.
33. Scatizzi, J.C., et al., *The Lbw2 locus promotes autoimmune hemolytic anemia.* The Journal of Immunology, 2012. **188**(7): p. 3307-3314.
34. Gordon, C., et al., *Abnormal sulphur oxidation in systemic lupus erythematosus.* The Lancet, 1992. **339**(8784): p. 25-26.
35. Perl, A., *Oxidative stress in the pathology and treatment of systemic lupus erythematosus.* Nature Reviews Rheumatology, 2013. **9**(11): p. 674.
36. Tsai, K.-J., et al., *Impaired production of nitric oxide, superoxide, and hydrogen peroxide in glucose 6-phosphate-dehydrogenase-deficient granulocytes.* FEBS letters, 1998. **436**(3): p. 411-414.
37. Iuchi, Y., et al., *Rescue of anaemia and autoimmune responses in SOD1-deficient mice by transgenic expression of human SOD1 in erythrocytes.* Biochemical Journal, 2009. **422**(2): p. 313-320.
38. Crane, F. and H. Low, *Reactive oxygen species generation at the plasma membrane for antibody control.* Autoimmunity reviews, 2008. **7**(7): p. 518-522.

39. Evans, M., et al., *Aberrant processing of oxidative DNA damage in systemic lupus erythematosus.* Biochemical and biophysical research communications, 2000. **273**(3): p. 894-898.
40. Morgan, P.E., A.D. Sturgess, and M.J. Davies, *Evidence for chronically elevated serum protein oxidation in systemic lupus erythematosus patients.* Free radical research, 2009. **43**(2): p. 117-127.
41. Abou-Raya, A., D. El Hallous, and H. Fayed, *8-Isoprostaglandin F2 alpha: a potential index of lipid peroxidation in systemic lupus erythematosus.* Clinical and investigative medicine, 2004. **27**(6): p. 306.
42. Avalos, I., et al., *Oxidative stress in systemic lupus erythematosus: relationship to disease activity and symptoms.* Lupus, 2007. **16**(3): p. 195-200.
43. Is, Y. and J. Woodside, *Antioxidant in health and disease.* J Clin Pathol, 2001. **54**(3): p. 176-186.
44. Shah, D., et al., *Oxidative stress in systemic lupus erythematosus: relationship to Th1 cytokine and disease activity.* Immunology letters, 2010. **129**(1): p. 7-12.
45. Shah, D., et al., *Relationship between T lymphocyte subsets and cortisol in systemic lupus erythematosus.* Kathmandu University Medical Journal, 2009. **7**(3): p. 213-219.
46. Stoimenov, T.J., et al., *Polymorphic variants of antioxidative defense enzymes and their gene-gene epistatic interactions in systemic lupus erythematode patients.* Clinical rheumatology, 2017. **36**(9): p. 2019-2026.
47. Warchoł, T., et al., *Catalase− 262C> T polymorphism in systemic lupus erythematosus in Poland.* Rheumatology international, 2008. **28**(10): p. 1035-1039.
48. Shah, D., A. Wanchu, and A. Bhatnagar, *Interaction between oxidative stress and chemokines: possible pathogenic role in systemic lupus erythematosus and rheumatoid arthritis.* Immunobiology, 2011. **216**(9): p. 1010-1017.
49. Franco, R., M.I. Panayiotidis, and J.A. Cidlowski, *Glutathione depletion is necessary for apoptosis in lymphoid cells independent of reactive oxygen species formation.* Journal of Biological Chemistry, 2007. **282**(42): p. 30452-30465.
50. Ballatori, N., et al., *Glutathione dysregulation and the etiology and progression of human diseases.* Biological chemistry, 2009. **390**(3): p. 191-214.
51. PERL, A., P. GERGELY JR, and K. BANKI, *Mitochondrial dysfunction in T cells of patients with systemic lupus erythematosus.* International reviews of immunology, 2004. **23**(3-4): p. 293-313.
52. Túri, S., et al., *Oxidative stress and antioxidant defense mechanism in glomerular diseases.* Free radical biology and medicine, 1997. **22**(1-2): p. 161-168.
53. ML, C., *Aw TY. Glutathione and apoptosis.* Free Radic Res, 2008. **42**: p. 689-706.
54. Rhee, S.G., *H2O2, a necessary evil for cell signaling.* Science, 2006. **312**(5782): p. 1882-1883.
55. Halliwell, B. and J. Gutteridge, *The definition and measurement of antioxidants in biological systems.* Free radical biology & medicine, 1995. **18**(1): p. 125-126.
56. Sies, H., *Role of reactive oxygen species in biological processes.* Klinische Wochenschrift, 1991. **69**(21-23): p. 965-968.
57. Lozovoy, M., et al., *Relationship between iron metabolism, oxidative stress, and insulin resistance in patients with systemic lupus erythematosus.* Scandinavian journal of rheumatology, 2013. **42**(4): p. 303-310.
58. Serban, M., E. Bălănescu, and V. Niţă, *Lipid peroxidase and erythrocyte redox system in systemic vasculitides treated with corticoids. Effect of vitamin E administration.* Romanian journal of internal medicine= Revue roumaine de medecine interne, 1994. **32**(4): p. 283-289.

59. Shah, D., et al., *Oxidative stress and its biomarkers in systemic lupus erythematosus.* Journal of biomedical science, 2014. **21**(1): p. 23.
60. Choy, E.H. and G.S. Panayi, *Cytokine pathways and joint inflammation in rheumatoid arthritis.* New England Journal of Medicine, 2001. **344**(12): p. 907-916.
61. Sato, M., et al., *Antioxidants inhibit tumor necrosis factor-alpha mediated stimulation of interleukin-8, monocyte chemoattractant protein-1, and collagenase expression in cultured human synovial cells.* The Journal of Rheumatology, 1996. **23**(3): p. 432-438.
62. Suwannaroj, S., et al., *Antioxidants suppress mortality in the female NZB× NZW F1 mouse model of systemic lupus erythematosus (SLE).* Lupus, 2001. **10**(4): p. 258-265.
63. Weimann and Hermann, *Inhibition of autoimmune deterioration in MRL/lpr mice by vitamin E.* International journal for vitamin and nutrition research, 1999. **69**(4): p. 255-261.
64. Klack, K., E. Bonfa, and E.F. Borba Neto, *Diet and nutritional aspects in systemic lupus erythematosus.* Revista brasileira de reumatologia, 2012.
65. Elias, K.M., et al., *Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway.* Blood, The Journal of the American Society of Hematology, 2008. **111**(3): p. 1013-1020.
66. Pattison, D.J., R.A. Harrison, and D.P. Symmons, *The role of diet in susceptibility to rheumatoid arthritis: a systematic review.* The Journal of rheumatology, 2004. **31**(7): p. 1310-1319.
67. Fatima, G., S. Das, and A. Mahdi, *Oxidative stress and antioxidative parameters and metal ion content in patients with fibromyalgia syndrome: implications in the pathogenesis of the disease.* Clin Exp Rheumatol, 2013. **31**(6 Suppl 79): p. S128-S133.
68. Bae, S.-C., S.-J. Kim, and M.-K. Sung, *Impaired antioxidant status and decreased dietary intake of antioxidants in patients with systemic lupus erythematosus.* Rheumatology international, 2002. **22**(6): p. 238-243.
69. Paredes, S., et al., *Antioxidant vitamins and lipid peroxidation in patients with rheumatoid arthritis: association with inflammatory markers.* The Journal of Rheumatology, 2002. **29**(11): p. 2271-2277.
70. Heliövaara, M., et al., *Serum antioxidants and risk of rheumatoid arthritis.* Annals of the rheumatic diseases, 1994. **53**(1): p. 51-53.
71. Comstock, G., et al., *Serum concentrations of α tocopherol, β carotene, and retinol preceding the diagnosis of rheumatoid arthritis and systemic lupus erythematosus.* Annals of the rheumatic diseases, 1997. **56**(5): p. 323-325.
72. Bergamo, P., F. Maurano, and M. Rossi, *Phase 2 enzyme induction by conjugated linoleic acid improves lupus-associated oxidative stress.* Free Radical Biology and Medicine, 2007. **43**(1): p. 71-79.
73. Costenbader, K.H., J.H. Kang, and E.W. Karlson, *Antioxidant intake and risks of rheumatoid arthritis and systemic lupus erythematosus in women.* American journal of epidemiology, 2010. **172**(2): p. 205-216.
74. Tam, L.S., et al., *Effects of vitamins C and E on oxidative stress markers and endothelial function in patients with systemic lupus erythematosus: a double blind, placebo controlled pilot study.* The Journal of Rheumatology, 2005. **32**(2): p. 275-282.
75. Minami, Y., et al., *Diet and systemic lupus erythematosus: a 4 year prospective study of Japanese patients.* The Journal of rheumatology, 2003. **30**(4): p. 747-754.
76. Kinoshita, K., et al., *Successful treatment with retinoids in patients with lupus nephritis.* American journal of kidney diseases, 2010. **55**(2): p. 344-347.
77. Patavino, T. and D.M. Brady, *Natural medicine and nutritional therapy as an alternative treatment in systemic lupus erythematosus.* Alternative Medicine Review, 2001. **6**(5): p. 460-472.

78. Varghese, B., N. Haase, and P.S. Low, *Depletion of folate-receptor-positive macrophages leads to alleviation of symptoms and prolonged survival in two murine models of systemic lupus erythematosus.* Molecular pharmaceutics, 2007. **4**(5): p. 679-685.
79. Minami, Y., et al., *Intakes of vitamin B6 and dietary fiber and clinical course of systemic lupus erythematosus: a prospective study of Japanese female patients.* Journal of epidemiology, 2011. **21**(4): p. 246-254.
80. Wright, T.B., et al., *Hypovitaminosis D is associated with greater body mass index and disease activity in pediatric systemic lupus erythematosus.* The Journal of pediatrics, 2009. **155**(2): p. 260-265.
81. Lane, N.E., *Vitamin D and systemic lupus erythematosus: bones, muscles, and joints.* Current rheumatology reports, 2010. **12**(4): p. 259-263.
82. Abe, J., et al., *Prevention of immunological disorders in MRL/l mice by a new synthetic analogue of vitamin D3: 22-oxa-1α, 25-dihydroxyvitamin D3.* Journal of nutritional science and vitaminology, 1990. **36**(1): p. 21-31.
83. Arnson, Y., H. Amital, and Y. Shoenfeld, *Vitamin D and autoimmunity: new aetiological and therapeutic considerations.* Annals of the rheumatic diseases, 2007. **66**(9): p. 1137-1142.
84. Aghdassi, E., et al., *The use of micronutrient supplements is not associated with better quality of life and disease activity in Canadian patients with systemic lupus erythematosus.* The Journal of rheumatology, 2010. **37**(1): p. 87-90.
85. Chou, C., *Alternative therapies: what role do they have in the management of lupus?* Lupus, 2010. **19**(12): p. 1425-1429.
86. Cutolo, M. and K. Otsa, *Vitamin D, immunity and lupus.* lupus, 2008. **17**(1): p. 6-10.
87. Costenbader, K.H., et al., *Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women.* Annals of the rheumatic diseases, 2008. **67**(4): p. 530-535.