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Review Article

# Dietary Support for Lupus Cytokine and Viral Underlying Inflammation

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## Abstract

SLE is a multisystem multifactorial autoimmune disease with excessive immune cell cytokine production and concomitant increases in autoreactive autoantibodies. Aberrant cytokine production exists alongside immortal activated T and B cells which is an exacerbation of pre-existing heightened autoimmunity. Dietary support including well known immune-modulating essential vitamins can be harmful to the SLE patient in excess and must be given in low doses and paired with other supportive agents including antioxidiants, anti-virals, and methyl donors.

**Keywords:** SLE; Lupus; EBV; HERV; NFkB; Vitamins; Antioxidants; Dietary Interventions

## Introduction

Systemic Lupus Erythmatosus (SLE) is a multisystem multifactorial autoimmune disease with excessive immune cell cytokine production and concomitant increases in autoreactive autoantibodies [1,2]. Sunlight UV exposure [3] and systemic viral load, especially Epstein Barr Virus EBV [4-6] and Human Endogenous Retrovirus HERV [5-7], each progressively and negatively influence the aberrant cytokine populations exacerbating the heightened autoimmunity.

### Immune system aberrant production of cytokines

Activated immune T and B cells with immortality:

The underlying driver of disease and pathogenic progression in SLE is a pro-inflammatory cytokine storm of IL-2, IL-4, IL-6, IL-10, IL-12, IL-17, as well as IFN and TNF from activated immune cells including dendritic and monocyte antigen-presenting cells, activated T-helper cells of both Th1 and Th2 subsets along with autoimmune Th17 subset, and activated antibody-producing B-cells [2]. The presence of excess pro-inflammatory cytokines up-regulates expression of the pro-inflammatory transcription factor NFkB for further dumping of more pro-inflammatory cytokines continuing to activate T-cell and B-cell populations [2] as well as create an optimal environment for viral persistence [9]. Excess IFNy has been demonstrated in the development of SLE [10] and SLE progression is dependent on CD4+ T-helper cells [11]. There is an immortality of activated T-cells found in SLE patients correlated with a mutation in the apoptosis-inducing Fas gene allowing unwarranted survival [12] and an abnormal population of T-cells displaying apoptosis marker B220 who have escaped the Fas-mediated T-cell activation-induced cell death (AICD) [1,13,14]. In addition to the cytokine storm and non-dying activated T-cells, the SLE scenario is compounded by similar mechanisms of aberrant activity and aberrant cell death in the antibody-producing B-cell population. SLE hyperactive B-cells display polyclonal activation upon antigen-presentation where increases are seen from both non-autoreactive (conventional) and autoreactive B-cells generating hyperimmunoglobulinemia, "These results demonstrate for the first time that systemic autoimmunity arises from polyclonal B cell activation rather than the preferential stimulation of autoreactive lymphocytes" and "not from specific stimulation of autoreactive clones" [15]. They also display extended lifespans through up-regulation of the anti-apoptotic bcl2 gene from the TNF family [16].

T-Helper cells – Th1 and Th2 cytokines

There are 3 primary subsets of CD4+ T-helper cells: Th1, Th2, and Th17. The primary Th1 cytokines are IL-2, TNF, and IFN-gamma; these are mostly involved in intracellular infections and macrophage activation which leads to an up-regulation of pro-inflammatory transcription factor NFkB. The Th2 cytokines are IL-4, IL-6, and IL-10; these are primarily involved in B-cell activation and its release of antibodies. During excess inflammation and increased T-cell responses the Th1 and Th17 become prominent and correlate to autoimmunity.

Interestingly, the Th1 and Th2 subsets act in an autocrine manner to sustain their cytokine secretion while inhibiting the opposite's cytokine production. For example, an immune reaction with Th1 response would promote the Th1 cytokines IL-1, IFN, and TNF and while in the focal microenvironment would then simultaneously suppress the secretion of Th2 cytokines IL-4, IL-6, IL-10. The presence of Th17 subset is a pro-inflammatory release of IL-6 and IL-17, where especially the IL-17 induces a concomitant decrease and down regulation of the Treg importantly involved in peripheral self-tolerance and prevention of autoimmunity. SLE-susceptible mice with elevated Th17 demonstrated low Treg and increased ANA alongside accelerated ANA immune complex mediated glomerulonephritis.

Th1 cytokines IL-1, IFN, TNF

Th2 cytokines IL-4, IL-6, IL-10

Th17 cytokines IL-6, IL-17

SLE is commonly recognized with a Th2 dominance leading to B-cell activation and antibody immune complexes which cause tissue damage and risk of end organ failure [2]. The primary Th2 dominance presents with hyperactivity of the B-cells producing not only autoreactive autoantibodies but excess conventional antibodies with an overall increased total B-cell generated antibody response; this is an exaggerated antibody and autoantibody as well as largely anticipated generation of subsequent immune complexes, all to a regular antigen stimulus [15]. The necrotic cell damage spillover then further exacerbates the immunoglobulin (Ig) anti-DNA nuclear antibodies (ANA) [2] with the feed forward cycle of more autoreactivity. SLE sun-exposed skin causes apoptotic bodies with nuclear spillover and promotion of IgG/ANA [17] as well as dermal/glomerular immune complex tissue damage and nuclear spillover (18). High levels of IFNy are associated with Ig shifts from less pathogenic IgG1 to severely pathogenic IgG2a with attack on chromatin as well as both single and double stranded DNA; lowering of IFN was successful in reversing the IgG shift however the hypergammaimmunoglobulinemia remained with significant improvements in fatality and glomerulonephritis [10].

## Cytokines and viral load

Concomitantly, there is also an overexpression of Th1 cytokines; a source of controversy and dilemma for whether SLE is truly a Th2 dominance or mixed Th1/Th2. The autoimmune presentation is then an interlude of Th1 release of IFN, which relates to viral titres such as EBV and co-stimulated HERV transactivation and its superantigen. Both EBV and HERV are correlated with hypomethylation and up-regulated NFkB. High viral titres stimulate NK cells and Th1 response for release of antiviral IFN-y [19]. Vazquez explains systemic hypomethylation from deficient nutritional methyl donors such as Betaine,

B9 recommended as Folinic acid, B12, and SAMe decrease the healthy cell's ability to gene silence, the role of methylation. In addition, overexpression of NFkB from inflammation serves as another advantage to viral replication mechanisms [9]. During EBV chronic infection the IFN gamma acts to stimulate the indoleamine-2,3-dioxygenase which degrades tryptophan into kyneurenine; worsened symptom presentation correlates with more severe tryptophan IFN-induced catabolism [20]. In addition, the EBV latent membrane proteins displayed on host B-cells causes transactivation of the (HERV) and concomitantly releases superantigen which activates T-cells. The same group also found the superantigen is also generated even earlier than EBV established latency and occurs when EBV binds to resting B-cells by inducing the HERV gene [8].

Therefore, SLE is a complex immune cell imbalance with Th2 cytokines activating antibody producing B-cells both excess conventional and autoreactive, simultaneously a myriad of Th1-cytokine overexpression most likely from chronic viral and other superantigens; each in a feed forward cycle.

## Dietary support to address aberrant cytokines

Limited Vitamin D, Zinc, and Selenium

Dietary intervention needs to address vitamins/minerals for proper enzyme physiological functions especially for immune cell and antioxidant in addition to their cofactor roles, but without excess or over stimulation of the immune system. Several vitamins play important roles in immuno-modulation but can be harmful for the SLE overactive humoral and adaptive immune responses in excess including Vitamin D, Zinc, and Selenium.

Vitamin D is a positive immunomodulator able to increase the IL-10 and quiet down Th2 dominance [21]; however excess and pro-inflammatory levels of IL-10 have been observed in SLE; autoantibody attack and end organ disease were halted with anti-IL-10 [2]. Additionally, animal models that supplemented with Vitamin D presented with kidney damage markers [22] and 1,25(OH) Vitamin D autoantibodies have been detected confirming the widespread inconsistent display of mixed autoantibodies [23]. Vitamin D deficiency is common in SLE due to mandatory sun avoidance and use of sunscreen [21], however Vitamin D has successfully been used up to 4000 iu daily for 12 weeks with positive effect on lowering IFN [24].

Zinc in excess was found to be an aggravating substance in SLE population [25]. The ZIP8 Zinc transporter is highly expressed on

human T cells and upon Zinc supplementation enhanced T-cell activation and excess expression increases INFy where mild increased cytoplasmic Zinc allowed binding to the IFNy promoter and synthesis [26]. This is important for fighting infections requiring IFNy but also a concern for over-producers.

Selenium is an essential trace element and involved in Glutathione and thyroid function [27], and deficiency has been correlated to autoimmune diseases with several reported successful Selenium interventions [28]. Selenium has also been used successfully in the HIV population with CD4 T-cell recovery and viral suppression [29,30]; however the HIV population demonstrated low CD4 activity and needs the stimulation whereas the opposite occurs for SLE and over stimulation could aggravate the already overactive T-cell subsets.

Anti-viral and Hypomethylation support

As importantly is the integration of natural anti-virals such as non-blood pressure low dose Glycyrrhiza glabra Licorice [9,28,31] and anti-replication methyl donors to dampen the Th1 dominant cytokine excesses especially modulating IFN. Anti-viral anti-replication methyl donors such as Betaine, B9 recommended as Folinic acid, B12, and SAMe should be incorporated to ensure anti-replication of EBV and non-allowance of HERV transactivation. This requires modulation at the Methionine cycle for regeneration of SAMe from Homocysteine recycling and concomitant regeneration of methyl-folate and cofactor methyl-cobalamin, as well as N-Acetyl-Cysteine (NAC) and B6 intake further supporting Homocysteine metabolism via Transfulfuration cycle and synthesis of potent intrinsic antioxidant Glutathione [9,27]. Certain herbs can be chosen for their inhibitory effect on NFkB such as Boswellia, Curcumin, Green Tea Catechins, Resveratrol, and Alpha Lipoic Acid [9]. Additionally, the latter ALA has been shown to have a positive impact on autoimmunity by decreasing the autoimmune Th17 population [32,33].

As described with the contradictory supplementation of Vitamin D, Zinc, and Selenium for their important roles in immunomodulation but potentially harmful; the need for healthy levels of IFN, even though it's in excess, needs to not be dropped to levels where its protective infection-fighting role is lost. Homeostatic levels of IFN are needed for efficient viral and intracellular infections but chronic excess overproduction of IFN must also be addressed to dampen the pro-inflammatory cycle known to occur in SLE. The other Th1 cytokine IL-2 is necessary since IL-2 acts early in the immune cell initiation phase and plays an important role in T-cell apoptosis, another vitally lost function in SLE T-cell subsets [9]. Th1 IL-2 cytokine is deficient in SLE [1] and may be related to the abnormal subset of T-cells that have escaped the Fas-induced apoptosis, known as CD4-8-(DN) B220+ alpha beta+ T cells with low cytokine production [11] and poor clearance [14]. The complimentary use of empty stomach ingestion of proteolytic enzymes for addressing the cytokine protein excess and immune complexes would be highly recommended for assisting clearance of these unwelcomed excesses [34].

## Conclusion

SLE is a complex immune cell imbalance with Th2 cytokines activating antibody producing B-cells both excess conventional and autoreactive, simultaneously a myriad of Th1-cytokine overexpression most likely from chronic viral and other superantigens; each in a feed forward cycle. Dietary interventions should include multi-vitamins not excluding Vitamin D, Zinc, and Selenium but should be followed without excessive intake and be a combination of whole food sources and supplementation. The regime needs to additionally include Anhydrous Betaine (TMG), licorice, ALA, NAC, Resveratrol, antioxidants Boswellia/Curcumin, and Wobenzym proteolytic enzymes. Whole food sources can include all produce including smoothies, lots of leafy greens, low carb-ketogenic/Mediterranean [35], as well as lifestyle changes including exercise [36], sleep [37], and meditation [38] for their synergistic roles in down-regulating NFkB and up-regulating anti-inflammatory gene expression.

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