INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease, characterized by immune-mediated inflammation in multiple organs. The course of the disease is characterized by exacerbations and remissions, and the severity of the clinical picture is greatly affected by the number and nature of the various organ manifestations ***(Deák et al., 2014)*.**

The aetiology of SLE is unknown with a variety of presenting features and manifestations. It affects women more frequently compared to men, more than 90% of new patients presenting with SLE are women in the childbearing years. Symptoms vary in different people depending on the part of the body involved and can be mild, moderate or severe ***(Cojocaru et al., 2011).*** The most common pattern is a mixture of constitutional complaints with skin, musculoskeletal, mild haematologic, and serologic involvement, but some patients predominately have haematologic, renal, or central nervous system manifestations ***(Gladman, 2018)*.**

Angiogenesis plays a significant role in the pathogenesis of SLE by formation of new blood vessels with sprouting of existing ones through endothelial cell proliferation, extracellular matrix remodelling, endothelial

cell migration and capillary tube formation. Angiogenesis is stimulated by a large number of cytokines. The most important mediators of angiogenesis are the basic fibroblast growth factor (bFGF) and the vascular endothelial growth factor (VEGF), the latter being the major factor that stimulates angiogenesis. SLE is characterized by several functional abnormalities of the immune system and an imbalanced cytokine production with abnormal regulation in the synthesis and expression of various cytokine genes, resulting in the immune dysregulation ***(Fischer et al., 2015)***.

VEGF has important physiological actions on embryonic development, healing, and menstrual cycle. It also has a great role in pathological conditions that are associated to autoimmune diseases. There is considerable evidence in various autoimmune diseases such as in SLE, rheumatoid arthritis, and multiple sclerosis of an interrelationship between the VEGF system and these disorders. Serum levels of VEGF correlate with disease activity in a large number of autoimmune diseases and fall with the use of standard therapy ***(Granger and Senchenkova, 2010).***

Nailfold Capillaroscopy (NFC) is a non-invasive imaging technique for morphological analysis of nutritional capillaries in the nail fold area, which is of considerable

importance for the evaluation of microcirculation in vivo, in order to reveal the peripheral angiopathy, with both diagnostic and prognostic purpose, in patients with connective tissue diseases. In SLE patients, NFC alterations have been known to have a lower specificity and the most frequently lesions are apparently represented by capillaries with an increased tortuosity, an increased length of capillaries, an increased diameter and a prominent subpapillary plexus ***(Ragab et al., 2011).*** However, several studies show a direct relation between certain capillaroscopic findings, disease activity and high immunological activity, as well as a more frequent presence of NFC changes in patients with multisystem involvement ***(Lambova and Müller-Ladner, 2013).***

There is a crucial role of endothelial activation and vascular changes in SLE pathogenesis by correlation of VEGF and NFC changes with SLE activity. Interdependence between VEGF serum levels and vascular capillaroscopic abnormalities reflects intensity of changes in microcirculation in the course of SLE. Therefore, the use of both methods may be a useful complementary diagnostic and prognostic tool for better evaluation of patients with this disease ***(Ciołkiewicz et al., 2010).***

Aim of the Study

The aim of this study is to quantify serum vascular endothelial growth factor level and its inter-relation with microvascular damage, assessed by nailfold capillaroscopy, and to establish the possible relationship with SLE activity.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune connective tissue disorder affecting multiple organs and systems often with a relapsing and remitting clinical course. It can affect the skin, joints, kidneys, eye, brain and other organs. The underlying cause of autoimmune diseases is not fully known ***(Liu et al., 2016).***

Epidemiology of SLE:

Incidence and prevalence

The reported prevalence of SLE in United States is 20 to 150 cases per 100,000. Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century. Estimated incidence rates are 1 to 25 per 100,000 in North America, Europe and Asia ***(Gergianaki et al., 2017).***

Race

The African American are affected more compared to Caucasians with a prevalence of 2.3-fold higher in black persons than in white persons. An increased prevalence among Asians, Hispanics and Native Americans was noted ***(McDonald et al., 2015).***

Sex and age:

SLE is found to be prevalent among younger individuals. Primarily those aged in their (20s to 40s) and it was found that rates are consistently higher in women compared to men. The prevalence rate in women was nearly 9 times higher than that in men ***(McDonald et al., 2015).***

Childhood incidence and prevalence rates of SLE are considerably lower than adult rates. The annual incidence rate of SLE in children (<16 years) was less than 1 per 100,000 persons in studies from Europe and North America ***(Pons-Estel et al., 2010).***

Etiopathogenesis:

SLE occurs when a genetically susceptible individual meets an environmental trigger, most likely an infective agent, which could be responsible for inducing antinuclear antibodies (ANA). After a variable lag of time from ANA appearance, deposits of immune material can be found in tissue without concomitant inflammatory lesion. These deposits can potentially initiate an inflammatory process which can subsequently lead to overt clinical manifestations ***(Gatto et al., 2013).***

Five major pathogenetic issues can be pointed out in SLE include**;** contribution of genetics and epigenetics**,** B

and T cell signaling abnormalities, dysregulated apoptosis and defective clearance of cellular debris, antibody formation and perpetuation, autoantibodies and organ damage ***(Gatto et al., 2013)***.

All pathways in SLE lead to endogenous nucleic acids mediated production of interferon α (IFNα) which helps to enhance autoimmunity by breaking self-tolerance by activation of antigen-presenting cells. Once initiated, immune reactants such as immune complexes exaggerate and sustain the inflammatory response ***(Bertsias et al., 2012).***

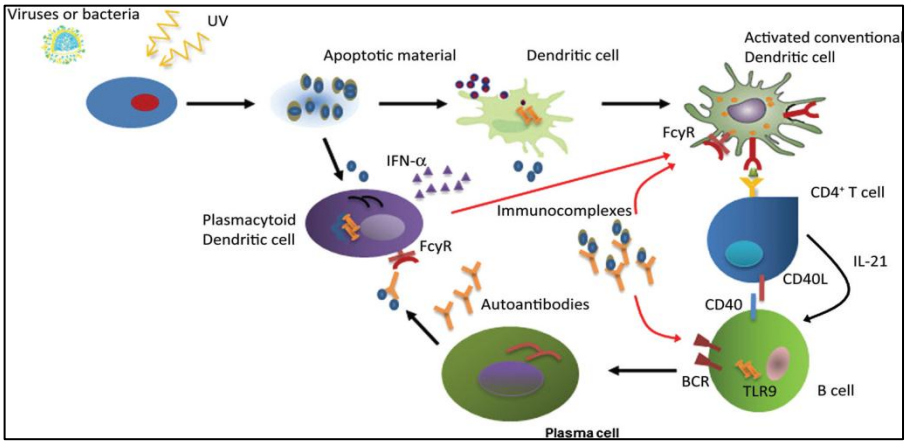

Figure (1): Pathogenesis of SLE ***(Bertsias et al., 2012).***

The B cells has long been considered central to the pathogenesis of SLE and has been regarded as an important target for biologic drugs, B cells produce pathogenic autoantibodies in addition to their roles in the autoimmune process they act as antigen presenting cells (APC), which

provide costimulatory signals for T cell activation and differentiation, secrete and respond to cytokines, link innate and acquired immunity by Toll-like receptors ***(Paran and Naparstek, 2015).***

1. Genetic factors:

SLE is a clinically heterogeneous disease with a strong genetic component, as demonstrated by the tenfold increase in concordance rates between monozygotic and dizygotic twins and familial aggregation ***(Bentham et al., 2015).*** There are more than 60 risk loci with Coding region single nucleotide polymorphisms (SNPs) is detected for SLE susceptibility across populations, borders and ethnicities ***(Teruel and Alarcón, 2016).***

2. Epigenetic factors

Epigenetic mechanisms include DNA methylation and histone modifications. Generally, these epigenetic mechanisms inhibit gene transcription, with subsequent silencing of the expression of unnecessary and harmful genes. In patients with SLE, the DNA of their CD4+ T-cells is hypomethylated, and their T-cells tend to be autoreactive in response to self-class MHC II molecules without strengthening of signals from autoantigens ***(Bentham et al., 2015).***

SLE patients commonly present with low serum levels of C4 and C3. Serum C4 levels are biomarkers for

lupus disease activity, low levels correlate with a flare, while normal levels correspond with remission. This deficiency of complements result in inability to clear apoptotic cells which will cause them to be a source of autoantigens and autoantibody production ***(Lintner et al., 2016).***

The Major Histocompatibility Complex (MHC) located on chromosome 6 contains the human leukocyte antigen (HLA) that contributes to the development of SLE. It includes HLA-DPB1, HLA-G and MSH5, which are independent of each other and HLA-DRB1 alleles ***(Fernando et al., 2012).*** In addition; there is a strong evidence for association between HLA-DRB1 and presence of anti-Ro and anti-LA antibodies in SLE patients ***(Morris et al., 2014).***

The hallmark of SLE is the production of IgG and IgM autoantibodies directed against one or more nuclear components, the most frequent of which are double stranded (ds) DNA and/or single stranded (ss) DNA. Both anti-ssDNA and anti-dsDNA are involved in disease development ***(Pavlovic et al., 2010).***

Although, the prevalence of ANA among SLE is very high; they may be detected in patients with other autoimmune, malignant or infectious diseases as well as healthy controls ***(Agmon-Levin et al., 2014).***

3. Hormonal

SLE is common in females in child-bearing age, where the reported female: male ratio is 8-15:1. Pre-pubertal and post-menopausal ratios are much lower at 2-6:1 and 3-8:1, respectively. This striking predominance in females probably relates to the effect of endogenous sex hormones, which have complex effects on the immune system ***(Murphy et al., 2013).***

The severity of SLE varies with pregnancy and menstrual cycle. Factors such as early menarche, oral contraceptive use, early menopause, surgical menopause, and postmenopausal use of hormones were associated with increased risk of SLE. Use of combined hormone replacement therapy in menopausal women was associated with a small risk of increasing mild-to-moderate flare-ups ***(Murphy et al., 2013).***

Male lupus is rare, comprising 4%–22% of patients with SLE in different series. Male patients had more renal involvement in some, but not all series with increased risk of renal failure. Male patients had more neurological involvement, thrombotic events, cardiovascular damage, serositis, arthritis, hepatomegaly, low C3, thrombocytopenia, later disease onset, fever, infection, weight loss, and hypertension in some, but not all series. In terms of serology, anticardiolipin antibodies, anti-dsDNA, and lupus anticoagulant (LAC) were more prevalent in men in a few studies ***(Tan et al., 2012).***

4) *Environmental factors:*

The onsets of SLE and lupus flares are triggered by various environmental factors in genetically susceptible individuals. Different environmental agents and toxicants such as cigarette smoke, alcohol, occupationally and non-occupationally related chemicals, ultraviolet light, infections, sex hormones, certain medications and vaccines have been entangled to induce SLE onset or flares ***(Mak and Tay, 2014).***

a. Ultraviolet (UV) light:

Ultraviolet light is the most well described environmental trigger of SLE. Both ultraviolet A2 and ultraviolet B (UVB) exposure, including through cosmetic sun tanning, can exacerbate skin disease in patients with the disorder ***(Murphy et al., 2013).***

b. Infections:

Infections have been contributed to be highly associated with the onset and/or exacerbations of SLE. They include particularly Epstein–Barr virus (EBV), parvovirus B19, retrovirus, and cytomegalovirus (CMV) infections and play a pivotal pathogenetic role. The interactions between infections and autoimmunity assist in causative or protective associations ***(Esposito et al., 2014).*** Also, there is increased prevalence of hepatitis C virus and human papilloma virus in SLE which considered as an autoimmune mosaic disease ***(Mahroum et al., 2017).***

c. Drugs:

Some drugs can induce lupus-like disease such as procainamide, hydralazine and anti-TNF biologic therapy which has been used in the treatment of inflammatory arthritis. The main distinguishing features between drug-induced and idiopathic lupus is the absence of end-organ inflammation ***(Mak and Tay, 2014).***

d. Smoking and alcohol:

It was found that previous and current smoking were associated with the risk of SLE and discoid lupus and current smoking appeared to be a stronger risk factor for SLE than past smoking. No clear association has yet been convincingly reported with respect to the potential risk of the development of SLE and alcohol consumption. But a significant protective effect of moderate alcohol consumption against SLE was found in those lupus patients who were treated for SLE for less than 10 years ***(Mak and Tay, 2014).***

e. Vitamin D deficiency:

The combination of vitamin D deficiency and carriage of specific SNPs was associated with significantly increased risk of SLE ***(Young et al., 2017).***

f. Silica exposure:

There is a higher risk of SLE in those with higher silica exposure, as the overall estimated risk ratios for SLE ranged from 1.6 to 4.9 within the general population and the risk ratio was >10 among highly exposed populations. Exposure to silica, mainly occur from crystalline silica or quartz that commonly comes from mining and dusty trades or that results from agricultural work in areas with high soil silica content ***(Miller et al., 2012).***

Clinical manifestations:

SLE is an autoimmune disease that has many manifestations. Fatigue and arthralgia are present in almost all patients with SLE, whereas renal involvement manifests in about 50% of patients. Also it affects the skin, musculoskeletal, renal, neuropsychiatric, hematologic, cardiovascular, pulmonary, and reproductive systems. Its course is typically recurrent, with periods of relative remission followed by flares. SLE can be fatal ***(Lam et al., 2016).***

1. Constitutional manifestations:

Fatigue is the most common symptom affecting up to 90% of patients, it can be due to active SLE, medications, lifestyle habits, or concomitant fibromyalgia or affective disorders. Fever is a nonspecific symptom of SLE, may also result from many causes, the most common of which

include active SLE, infection, and drug fever. Weight gain may also be due to corticosteroid treatment or active disease such as nephrotic syndrome anasarca. Also, malaise, arthralgias, myalgias, headache, and loss of appetite and weight are associated ***(Cojocaru et al., 2011).***

2. Mucocutaneous manifestations:

About 70% to 80% of patients with SLE develop skin lesions during the course of disease ***(Lam et al., 2016).*** Mucocutaneous manifestations are divided into 2 categories; lupus erythematosus specific skin lesions (LE specific), and nonspecific skin lesions (LE nonspecific) ***(Chiewchengchol et al., 2015).***

- ***SLE nonspecific skin lesions:***

Oral or nasopharyngeal ulcers*:* There are two types of these ulcers: those with classical lupus erythematosus (LE) histological changes representing oral discoid lesions and nonspecific ulcers in keeping with aphthous ulceration. The lupus specific lesions are painless and located on the hard palate. In contrast, the nonspecific aphthous ulcers are usually painful, with multiple lesions on the buccal mucosa, lips and nasal septum, whilst also having a tendency to bleed ***(Chiewchengchol et al., 2015).***

Diffuse non-scarring alopecia often presents with generalized hair loss without signs of inflammation ***(Chiewchengchol et al., 2015).***

Raynaud's phenomenon is characterized by the classic triphasic color changes limited to the digits; pallor (white or blanching) followed by the cyanosis (blue) then erythema (red or reactive hyperemia) ***(Filho et al., 2014).***

Figure (2): Raynaud phenomenon ***(Lam et al., 2016).***

Livedo reticularis characterized by erythematous or cyanotic discoloration of the skin with reticulated (net-like) pattern, usually on the lower extremities ***(Filho et al., 2014).***

Cutaneous vasculitis usually affects small blood vessels (leukocytoclastic vasculitis). The lesions are characterized as petechiae or palpable purpura and may occasionally blister. They are commonly found on the face, palms and soles of the feet ***(Chiewchengchol et al., 2015).***