INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Althoughthe specific cause of SLE is unkown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and enviromental factors ***(Rahman and Isenberg, 2008).***

The disease occours nine times more often in females than in males, espescially in women in child-bearing years ages 15 to 35 ***(American College of Rheumatology 2013).***

Assessment of disease activity and organ damage in Systemic Lupus Erythematosus (SLE) remain challenging because of the Lack of reliable biomarkers and disease heterogeneity.Ongoing inflammation can be difficult to distinguish from permanent organ damage caused by previous flare-ups or medication side effects, circulating soluble urokinase Plasminogen Activator Receotors (suPAR) has emerged as a potential marker of inflammation and disease severity, and an outcome predictor in several disparate conditions ***(Toldi et al., 2012)***.

AIM OF WORK

We aimed to measure plasma suPAR levels in SLE patients and its relation to disease activity and organ damage.

Chapter (1)

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease in which the body's immune system mistakenly attacks healthy tissue. It can affect the skin, joints, kidneys, brain, and other organs.The underlying cause of autoimmune diseases is not fully known ***(Gary et al., 2012).***

The course of the disease is unpredictable, with periods of illness (called *flares*) alternating with remissions. The disease occurs nine times more often in women than in men, especially between the ages of 15 and 50 ***(Rahman and David, 2008)***.

Epidemiology:

A review of SLE across Asia-Pacific countries revealed considerable variation in prevalence and survival rates**.** For example, overall prevalence rates ranged from 4.3 to 45.3 per 100,000, and the overall incidence ranged from 0.9 to 3.1 per 100,000 per year. Moreover, Asians with SLE had higher rates of renal involvement than whites did, and cardiovascular involvement was a leading cause of death in Asians ***(Jakes et al., 2012)***.

1- **Gender:**

More than 90% of cases of SLE occur in women, frequently starting at childbearing age ***(Symmons et al., 2012)***.

The use of exogenous hormones has been associated with lupus onset and flares, suggesting a role for hormonal factors in the pathogenesis of the disease ***(Costenbader et al., 2007)***.

The risk of SLE development in men is similar to that in pre-pubertal or post-menopausal women. Interestingly, in men, SLE is more common in those with Klinefelter' syndrome ie; (genotype XXY), further supporting a hormonal hypothesis. In fact, a study done found that men with Klinefelter' syndrome had a more severe course of SLE than women but a less severe course than other men ***(Dillon et al., 2011)***.

2-Race:

The incidence of SLE appears to vary by race. However, there are different prevalence rates for people of the same race in different areas of the world. The contrast between low reported rates of SLE in black women in Africa and high rates in black women in the United Kingdom suggests that there are environmental influences ***(Danchenko et al., 2007).***

The lowest documented prevalence (~20/100,000) is found in white northern European population, while the highest prevalence (~150-200/100,000) is found in African-Americans or

African-Caribbean populations living in the US or UK ***(Borchers et al., 2010).***

3-Age:

SLE can occur at any age, it is most common in child bearing period sixty-five percent of patient with SLE have disease onset between the ages of 16 and 55 ***(Lam and Petri, 2005).***

A review of the worldwide literature (predominantly North America, Europe, and Asia) found that the incidence of pediatric-onset SLE ranged from 0.36 to 2.5 per 100,000 per year and the prevalence ranged from 1.89 to 25.7 per 100,000 ***(Pineles et al., 2011)***.

Etiology:

Systemic lupus erythematosus is an autoimmune disorder. In a normal immune system, the body releases proteins (antibodies) to fight viruses, toxins and other potentially harmful foreign substances (antigens). With lupus and other autoimmune diseases, the immune system does not work properly. It produces auto-antibodies that mistakenly attack and destroy the body's own healthy cells and tissue. These auto-antibodies also trigger inflammation, which can lead to organ damage.

Auto-antibodies called antinuclear antibodies (ANA) are detectable in most, although not all, patients with SLE. Tests for

the presence of ANA are used as part of the diagnostic work-up for the condition ***(Gabreil et al., 2013).***

Although the specific cause of SLE is unknown, multiple genetic predispositions and gene-environment interactions have been identified (see the chart in the figure (1) below). This complex situation perhaps explains the variable clinical manifestations in persons with SLE.

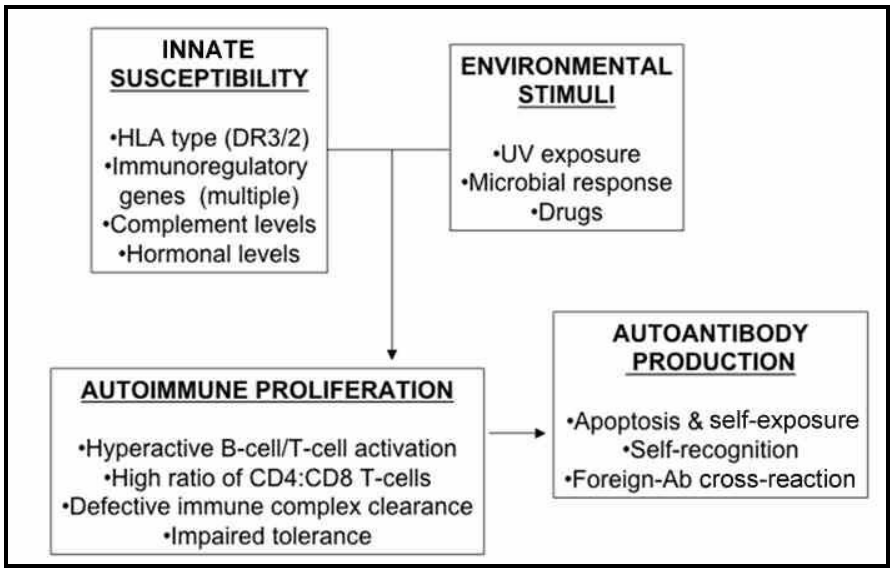

Figure (1): Etiology of SLE, ***(Yurasov et al., 2005)***.

In systemic lupus erythematosus (SLE), many genetic-susceptibility factors, environmental triggers, antigen-antibody (Ab) responses, B-cell and T-cell interactions, and immune clearance processes interact to generate and perpetuate autoimmunity ***(Sanchez et al., 2011).***

SLE has a modest recurrence rate in families: 8% of affected patients have at least one first-degree family member (parents, siblings, and children) with SLE; this is in contrast to 0.08% of the general population.In addition, SLE occurs in both twins in 24% of identical twins and 2% of non-identical twins, which may be due to a combination of genetic and environmental factors.Some studies have synthesized what is known about the mechanisms of SLE disease and genetic associations ***(Rahman and Isenberg, 2008).***

1-Genetic effects:

At least 35 genes are known to increase the risk of SLE ***(Sestak et al., 2011).***

A genetic predisposition is supported by 40% concordance in monozygotic twins; if a mother has SLE, her daughter's risk of developing the disease has been estimated to be 1:40, and her son's risk,1:250 ***(Sanchez et al., 2011)***.

A genome-wide study in a northern European population replicated the association of SLE with susceptibility genes related to B-cell receptor pathway signaling, as well as confirmed the association of SLE with genes at the interferon regulatory factor 5 (IRF5)-TNPO3 locus. The investigators also confirmed other loci associations with SLE (TNFAIP3, FAM167A-BLK, BANK1 and KIAA1542); however, it was determined that these loci had a

lower significance level and a lower contribution to individual risk for SLE ***(Järvinen et al., 2012)***.

Studies of human leukocyte antigens (HLAs) reveal that HLA-A1, HLA-B8, and HLA-DR3 are more common in persons with SLE than in the general population. The presence of the null complement alleles and congenital deficiencies of complement (especially C4, C2, and other early components) are also associated with an increased risk of SLE. Numerous studies have investigated the role of infectious etiologies that may also perpetuate autoimmunity ***(Blank et al., 2009).***

2-Epigenetic effects:

Epigenetic refers to inherited changes in gene expression not due to changes in the DNA sequence .It is an exciting field that is serving as a link between genetic susceptibility and the environment in predisposing to lupus. DNA methylation, histone modifications and micro- RNA are the major epigenetic alterations seen among lupus patients ***(Altorok and Sawalha, 2013).***

Hydralazine and procainamide inhibit DNA methylation and can induce manifestations of lupus in healthy persons ***(Ballestar et al., 2006)***.

The regulatory regions of some genes known to be involved in the pathogenesis of the disease (ITGAL, CD40LG, CD70, and PPP2CA) have been reported to be hypomethylated in

SLE. Recruitment of histone deacetylase 1 to the *IL2* promoter suppresses its expression ***(Tenbrock et al., 2006)***.

3-Enviromental factors:

a-Infection:

Many viruses have been implicated in the etiology of SLE, which include the Epstein-Barr virus (EBV), transfusion-transmitted virus, retrovirus, paramyxovirus, cytomegalovirus (CMV), and corona virus ***(Francis and Perl, 2010).***

b- Ultraviolet (UV) light:

Two-thirds of people with lupus have increased sensitivity to ultraviolet rays, either from sunlight or from artificial inside light, such as fluorescent light. Normally, skin and other cells that are sufficiently damaged die through a process known as programmed cell death, or "apoptosis." The body then gets rid of the dead cells. But in lupus, apoptosis in the skin seems to occur more often than it should, which may in turn lead to more inflammation and other complications. In addition to worsening of skin lupus lesions, many patients also experience more generalized skin or systemic reactions to light that are not their typical skin lupus ***(Kristen et al., 2013).***

c- Smoking:

Smoking has been found to be a risk factor for the development of autoimmune diseases. Cigarette smoke contains

innumerable toxic agents that could cause genetic mutation and influence both humoral and cell mediated immune response harmfully. Current smokers and past exposure had a higher prevalence of SLE than non smokers ***(Ekblom-Kullberg et al., 2013).***

d- Drug induced lupus:

Drug induced lupus is an autoimmune disorder. This means your body attacks healthy tissue by mistake. It is caused by an overreaction to a medicine. The most common medicines known to cause drug-induced lupus are: Isoniazid, Hydralazine, and Procainamide; other less common drugs may also cause the condition. These may include: Capoten, Infliximab, Anti-seizure medications, Chloropromazine, Etanercept, Methyldopa, Minocycline, D-Penicillamine, Quinidine, and Sulfasalazine. Symptoms tend to occur after taking the drug for at least 3 to 6 months ***(Wright et al., 2010)***.

e-Others:

Crystalline silica exposure from both agricultural exposure in the fields and industrial occupations in urban areas has been associated with an increased risk of SLE ***(Finckh et al., 2006)***.

There is also some new data that supports the link between insecticide exposure and SLE ***(Parks et al., 2011).***

Pathogenesis and pathophysiology:

Immune responses against endogenous nuclear antigens are characteristic of SLE. Auto-antigens released by apoptotic cells are presented by dendritic cells to T- cells leading to their activation. Activated T-cells in turn help B-cells to produce antibodies to these self constituents by secreting cytokines such as interleukin 10 (IL10) and IL23 and by cell surface molecules such as CD40L and CTLA-4. In addition to this antigen-driven T-cell dependent production of auto-antibodies, recent data support T-cell-independent mechanisms of B-cell stimulation via combined B-cell antigen receptor (BCR) and TLR signaling. The pathogenesis of SLE involves a multitude of cells and molecules that participate in apoptosis, innate and adaptive immune responses ***(Bertesias et al., 2012).***

Apoptosis:

A source of auto-antigens and molecules with adjuvant/cytokine (interferon α (IFNα) inducer activity. Apoptotic cell blebs are rich in lupus auto-antigens. Increased spontaneous apoptosis, increased rates of ultraviolet-induced apoptosis in skin cells, or impaired clearance of apoptotic peripheral blood cells have been found in some lupus patients ***(Bertsias et al., 2009).***

Innate immunity:

Toll-like receptors (TLRs):

The innate pattern recognition receptors, such as Toll-like receptors (TLRs), play important roles in the development of autoimmunity. TLR proteins are localized on the cell surface or in endosomes, and play critical roles in innate immune responses against different pathogens ***(Barbalat et al., 2011).*** Internalized nucleic acid immune complexes act as endogenous ligands that activate intracellular TLRs, and these initiate several signaling pathways that lead to increased production of type I interferons (IFNs) in plasmacytoid dendritic cells (pDCs) ***(Ewald and Barton, 2011)***. Increased production of type I IFNs increases apoptosis, neutrophil cell death via neutrophil extracellular trap (NETosis), innate immune signaling, and viral infection-induced autoimmunity ***(Elkon and Wiedman, 2012)***. Aberrant stimulation of the innate immune system through intracellular TLRs may lead to hyperactive immune responses and contribute to the pathogenesis of SLE ***(Kontaki and Boumpas, 2010).***

TLR3, TLR7, and TLR8 are primarily associated with endosomal membranes and they recognize microbial nucleic acids. TLR3 binds to viral double-stranded RNA (dsRNA), and induces antiviral immune responses by promoting the production of type I IFN and pro-inflammatory cytokines. TLR7 binds to single-stranded RNA (ssRNA) from RNA viruses, and triggers

pDCs to produce type I IFN. TLR8 is phylogenetically related to TLR7 and also mediates recognition of viral ssRNA. Thus, these 3 TLRs are responsible for pathogen clearance, antigen recognition, and induction of cytokine production ***(Gelliet et al., 2008).***

Interferon α:

Excess serum IFN and IFN-response gene expression are characteristics of lupus and are most likely the result of excessive PDC activation. Such high levels of interferon could contribute to lupus by promoting immune activation rather than tolerance. Dendritic cells are the primary activators of T cells, and affect both T-cell tolerance and activation, depending on the state of the dendritic cell. When treated with interferon alpha, dendritic cells mature and become more prone to activate T cells ***(Tonel et al., 2008).***

Complement:

The complement system involves both the innate and the adaptive immune systems and has important roles in the pathogenesis of SLE. Complement deficiencies within the classical pathway (C1q, C4 and C2) of activation predispose for development of the autoimmune disease SLE. The association between complement deficiencies and SLE could be explained by several mechanisms, including impaired clearance of immune complexes and impaired handling of apoptotic cells, aberrant

tolerance induction or changes in cytokine regulation. Also during SLE disease flares, the complement system is activated giving rise to partial deficiency or dysfunction due to consumption. On the other hand, complement also takes part in the inflammatory reaction in the disease that gives rise to the tissue and organ damage ***(Lennart et al., 2007).***

Adaptive immunity:

T cells have long been thought to play a central role in SLE pathogenesis, and T cells from patients with lupus show defects in both signaling and effector function. These T cells secrete less interleukin (IL)-2, and one defect in signaling seems to be linked to an increase in calcium influx, possibly due to changes in the CD3 signaling subunits. The following seem to be adversely affected in T cells from patients with SLE: effector activity such as CD8 cytotoxicity; T-regulatory, B-cell help; migration; and adhesion. However, the method by which each of these deficits contributes to the exact clinical syndrome seen in an individual patient is still unknown. These T-cell abnormalities are currently being explored as targets for therapy, as seen with the recent approval of belimumab, which targets the B-lymphocyte stimulator (BLys) signaling pathway ***(Cancro et al., 2009)***.

Clinical features:

Common initial and chronic complaints include fever, malaise, joint pains, myalgias, fatigue, and temporary loss of

cognitive abilities. Because they are so often seen with other diseases, these signs and symptoms are not part of the diagnostic criteria for SLE. When occurring in conjunction with other signs and symptoms (mentioned below), however, they are considered suggestive (figure 2) ***(Rahman and David, 2008).***

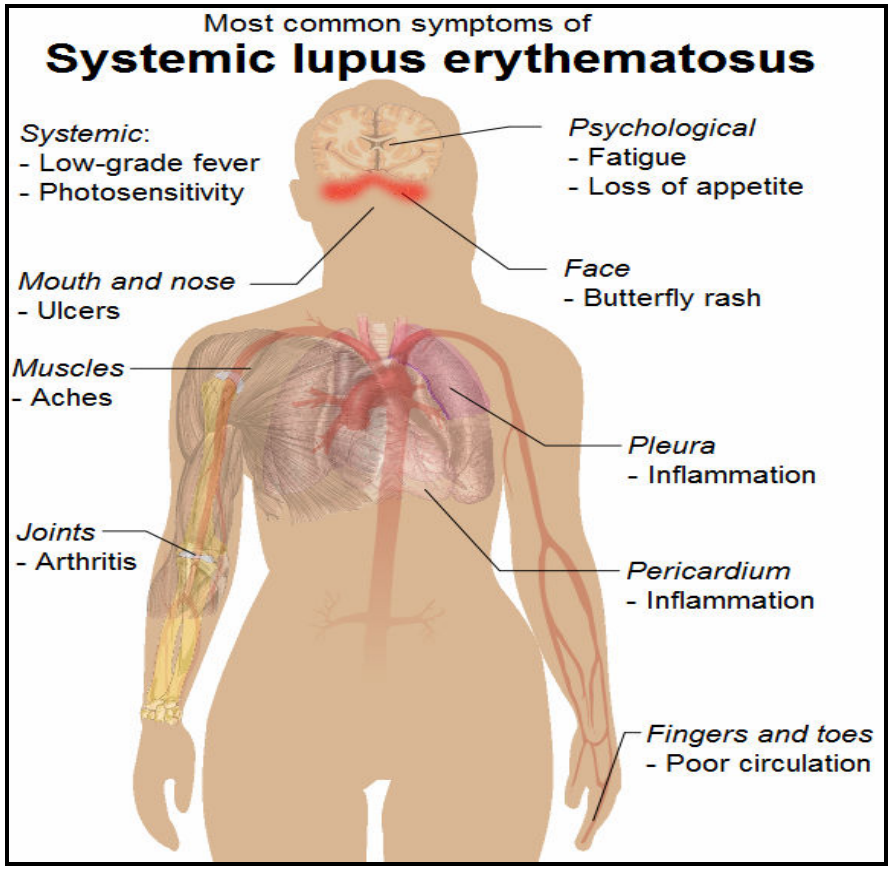

Figure (2): Common symptoms of SLE ***(Rahman and David, 2008)***.

1. **Dermatological Manifestations:**

Thirty to 50% of patients suffer from the classic malar rash (or *butterfly rash*) associated with the disease. Some may exhibit