INTRODUCTION

Systemic lupus erythematosus (SLE) is one of the most prominent chronic autoimmune disorders which involves a number of organs, including skin, joints, hematopoietic system, vascular system and kidney ***(Rothfield et al., 2006; Fortuna and Brennan, 2013).*** Renal involvement is the major concern. Half or more (45%-85%) of SLE patients will develop lupus nephritis over the course of their life time ***(Borchers et al., 2012; Zubair and Frieri, 2013).***

Although advances in immunosuppressive treatment have been made, the 5-year survival rate of SLE patients with severe renal damage is still very low ***(Koutsokeras and Healy, 2014).***

Early prediction and diagnosis of lupus nephritis (LN) are of great importance. So far, renal biopsy remains the gold standard for diagnosis and plays a critical role in management and prognosis of renal damage in SLE patients. However, renal biopsy carries high risks of hemorrhage and infection, and some patients have contraindications to this surgery, which indicates the need for a noninvasive method of evaluating the severity of renal damage ***(Chan, 2015).***

Serum uric acid (SUA) is usually considered as a marker of renal dysfunction, but previous study has reported that it may be a risk factor for progression of renal disease ***(Kang et al., 2002).***

SUA is a circulating end- product of purine metabolism that is excreted by the kidney and the intestinal tract ***(Tingting et al., 2016).***

Hyperuricemia occurs in conditions of sUA overproduction, such as increased intake of purine rich diets, malignancies, rhabdomyolysis, cellular proliferation, or in conditions of reduced sUA excretion, such as chronic kidney disease, diabetic ketoacidosis and starvation ***(Nickavar, 2013).***

Other conditions associated with hyperuricemia include diabetic nephropathy ***(Liu et al., 2015)***, IgA nephropathy ***(Cheng et al., 2013),*** metabolic syndrome ***(Li et al., 2013)*** and cardiovascular disease ***(Sertoglu, 2015).***

Moreover, elevated sUA has been reported to be independently associated with the development of LN in SLE patients ***(Yang et al., 2012; Yang et al., 2015).***

However, no studies have assessed the correlation between sUA and the severity of renal damage in LN patients.

Aim of the Work

The aim of this work was to evaluate whether hyperuricemia is independently associated with the severity of renal damage in systematic lupus erythematosus(SLE) patients or correlate with disease activity among Egyptian patients.

Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic systemic autoimmune disease with a wide spectrum of potentially serious symptoms that may require extensive consumption of health care resources ***(Nasonov et al., 2013).*** It is characterized by autoantibody production and immune complex deposition showing unpredictable flares of activity and irreversible multiple organ damage ***(Yuan et al., 2011).*** It occurs predominantly among women of childbearing ages ***(Dhar and Sokol, 2006).***

In the past, the major cause of death in SLE was uncontrolled disease activity. Currently, atherosclerotic complications, malignancy, infections and to a lesser degree active disease are the chief causes of mortality in SLE ***(Bernatsky et al., 2005)***. It is well recognized that cumulative organ damage, in particular renal damage, is an important predictor of mortality in SLE ***(Bruce et al., 2015).*** Recurrent flares of disease activity such as lupus nephritis are associated with poor long-term outcomes ***(Danila et al., 2009)***.

Epidemiology:

SLE is worldwide disease, with incidence and prevalence rates differing geographically. Studies have shown that incidence rate of SLE around the world is about

1 to 10 per 100,000 person-years, while the prevalence rates range from 20-70 per 100,000 person-years ***(Pons-Estel et al., 2008).***

SLE predominantly affects women, with a reported peak female-to-male ratio of 12:1 during the childbearing years. The disease can also be seen in children and the elderly with a narrower gender distribution. Studies have shown racial/ethnic variations, with SLE being more common in non-Caucasian persons, occurring three to four times more often in African-Americans ***(Danchenko et al., 2006).***

In addition to African-Americans, Hispanics and Asians develop SLE more frequently than Caucasians ***(Danchenko et al., 2006).*** In these populations, SLE tends to be more active and severe, with a higher risk of relapses and organ system involvement or damage. Even with advances in diagnosis and treatment of the disease, the mortality risk in patients with SLE is higher than that of the general population. For newly diagnosed patients, the 5-year survival rate is over 90% and the 15 to 20 year survival rate is about 80% ***(Pons-Estel et al., 2008).***

Worse outcomes and higher mortality risk correlated with this ethnic disparity, which may be influenced by a lower socioeconomic status as well ***(Gonzalez et al., 2014).***

Etiology and Pathogenesis:

The precise reason for the abnormal autoimmunity that causes lupus is not known. Inherited genes, hormonal, immunologic, viruses, ultraviolet light, and certain medications may all play some role. Lupus is not caused by an infectious microorganism and is not contagious from one person to another ***(William and Shiel, 2016).***

1- Genetic factors:

Although in rare cases SLE may be associated with the deficiency of a single gene (e.g., the complement components C1q and C4), the disease more commonly results from the combined effect of variants in a large number of genes. Each allele contributes only minimally, and the cumulative effect of several genes is necessary to substantially increase the risk of SLE. Certain single-nucleotide polymorphisms (SNPs) linked to SLE have been identified for genes whose products may contribute to abnormal T-cell function in SLE ***(Tsokos, 2011).***

2- Endocrinal factors:

Sex hormones are probably partly responsible for the higher occurrence of autoimmune disorders given the female predominance in autoimmune diseases. However, studies have found that sex hormone levels in patients with autoimmune disorders are not significantly different from

patients without autoimmune disorders, indicating that other gender-associated differences including hormone regulation and effects on cytokine production, along with chromosomal factors, contribute to the high female predominance in these diseases compared with men ***(Nussinovitch and Shoenfeld, 2012).*** Thus, the relationship of sex hormones increasing serum levels of certain cytokines and the estrogen receptor may be important in disease development ***(Shoenfeld, 2012).***

Estrogen's primary effects are mediated via estrogen receptors alpha and beta (ER α/β) that are expressed on most immune cells. ERs have prominent effects on immune function in both the innate and adaptive immune responses. Genetic deficiency of ERα in murine models of lupus results in significantly decreased disease and prolonged survival, while ERβ deficiency has minimal to no effect in autoimmune models. These two isoforms of ER are able to modulate the cytokine production of various key target cells of the immune system ***(Cunningham and Gilkeson, 2011).***

Estradiol can modulate lymphocyte cytokine production, cytokine receptor expression, and activation of effector cells. Estrogens favor the Th2 immune response, and enhanced interferon-γ (INFγ), TNFα, TGFβ, interleukin (IL)-1, IL-5, IL-4, and IL-10 production. It causes a

proliferation of M2 macrophages, and myeloid-derived suppressor cells, further amplifying the Th2 immune response ***(Nussinovitch and Shoenfeld, 2012).*** Estrogen and prolactin are both capable of stimulating autoreactive B cells, promoting the failure of immune tolerance and secretion of autoantibodies ***(Shoenfeld, 2012).***

It also is known that some women with SLE can experience worsening of their symptoms prior to their menstrual periods. This phenomenon, together with the female predominance of SLE, suggests that female hormones play an important role in the expression of SLE ***(William and Shiel, 2016).***

3- Immune system dysregulation:

Imbalances between pro- and anti-inflammatory cytokines are hallmarks of the pathogenesis of SLE ***(Yu et al., 2012).*** It has been demonstrated that pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and cytokine IL-10 levels are significantly elevated in the serum of SLE patients and correlate with disease activity ***(Bezalel et al., 2012).*** In particular, the expressions of TNF-α, IL-6 and IL-10 are markedly elevated in SLE patients with lupus nephritis ***(Apostolidis et al., 2011).***

There are numerous immune defects in patients with SLE. However, the etiology of these abnormalities remains

unclear. In certain cases these immune defects are episodic, and some correlate with disease activity. SLE is primarily a disease with abnormalities in immune regulation, these abnormalities are thought to be secondary to a loss of self-tolerance; thus, affected patients are no longer totally tolerant to all of their self-antigens, and consequently develop an autoimmune response. The mediators of SLE are autoantibodies and immune complexes they form with antigens; the autoantibodies may be present for years before the first symptom of disease appears ***(Schur and Hahn, 2010).***

B-cells/plasma cells that make autoantibodies are more persistently activated and driven to maturation by B cell activating factor (BAFF, also known as B lymphocyte stimulator - BLyS) and by persistently activated T helper cells making B-supporting cytokines such as IL-6 and IL-10. BAFF, serum levels of which are elevated in some patients with SLE, promotes formation and survival of memory B cells and plasmablasts. This increased autoantibody persistence is not downregulated appropriately by anti-idiotypic antibodies, or by CD4+ regulatory T cells, or by CD8+ suppressor T cells ***(Schur and Hahn, 2010).***

4- Environmental factors:

A- Infection:

Infections have long been suspected as playing a role in SLE. No single infection has been found**.** Multiple infections have been invoked as potential triggers of SLE, including Epstein-Barr virus (EBV), hepatitis C virus, Cytomegalovirus (CMV), parvovirus ***(William and Shiel, 2016).***

B- Ultraviolet (UV) radiations:

Exposure to ultraviolet (UV) rays causes flares of SLE in approximately 70% of patients, possibly by increasing apoptosis in skin cells or by altering DNA and intracellular proteins to make them antigenic ***(Hahn, 2010).***

C- Drugs: Drug-induced lupus erythermatosus (DILE):

Medications have been reported to trigger SLE. However, more than 90% of cases of "drug-induced lupus" occurs as a side effect of one of the following six drugs: hydralazine, quinidine and procainamide, phenytoin, isoniazid and d-penicillamine ***(William and Shiel, 2016).***

Diagnosis and Classification criteria:

The American College of Rheumatology (ACR) published criteria in 1982, which were revised in 1997 **(Table 1).** The Systemic Lupus international Collaborating Clinics (SLICC) group undertook the evaluation and further revision of ACR criteria resulting in a new classification system (SLICC 2012 criteria) that is based on clinical and immunologic manifestations **(Table 1)**. In an actual clinical practice setting, both criteria were analyzed; it was determined that the SLICC 2012 criteria were more sensitive and may allow patients to be classified with SLE earlier in the disease course ***(Ines et al., 2015)***

At least 4 criteria of ACR are needed for diagnosis of SLE ***(Hochberg, 1997).***

In SLICC, Classify a patient as having SLE ***(Petri et al., 2012)*** *if:*

- The patient satisfies 4 of the criteria listed in the table including at least 1 clinical criterion and 1 immunological criterion, OR
- The patient has biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies

Table (1): Classification criteria for SLE diagnosis ***(Adopted from Ines et al., 2015).***

	ACR 1997[b]	SLICC 2012 [c]
Cutaneous	1. Malar Rash 2. Discoid Rash 3. Photosensitivity 4. Oral or Nasopharyngeal ulceration	1. Acute cutaneous lupus (including malar rash, photosensitive lupus rash) OR Subacute cutaneous lupus 2. Chronic cutaneous lupus (including discoid rash) 3. Oral or nasal ulcers 4. Nonscarring alopecia
Joints	5. Nonerosive arthritis - involving ≥ 2 peripheral joints characterized by pain, swelling or effusion	5. Synovitis - involving ≥ 2 peripheral joints characterized by swelling or effusion or tenderness and ≥ 30 minutes of morning stiffness
Serositis	6A. Pleuritis (pleuritic pain/rub or pleural effusion) OR 6B. Pericarditis (by EKG, rub, or pericardial effusion)	6. Serositis (any of the following) - pleurisy - pleural effusions - pleural rub - pericardial pain - pericardial rub - pericardial effusion - pericarditis by EKG
Renal	7A. Persistent proteinuria (> 0.5g/day or > 3+ dipstick) OR 7B. Cellular casts	7. Renal (any of the following) - urine protein/creatinine (or 24 hour urine protein) > 0.5g/24hr - red blood cell casts
Neurologic	8A. Seizures OR 8B. Psychosis	8. Neurologic (any of the following) - seizures - psychosis - mononeuritis multiplex - myelitis - peripheral or cranial neuropathy - acute confusional state
Hematologic	9A. Hemolytic anemia OR 9B. Leukopenia (<4,000/mm3 on ≥ 2 occasions) OR 9C. Lymphopenia (<1,500/mm3 on 2 occasions) OR 9D. Thrombocytopenia (<100,000/mm3)	9. Hemolytic anemia 10. Leukopenia (<4,000/mm3 at least once) OR Lymphopenia (<1,000/mm3 at least once) 11. Thrombocytopenia (<100,000/mm3 at least once)
Immunologic	10A. Anti-dsDNA OR 10B. Anti-Sm OR 10C. Antiphospholipid Antibody (any of the following) - anticardiolipin antibodies (IgG or IgM) - lupus anticoagulant - false positive syphilis test or > 6 months (confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test) 11. Positive antinuclear antibody	1. Antinuclear antibody 2. Anti-dsDNA 3. Anti-Sm 4. Antiphospholipid antibody (any of the following) - lupus anticoagulant - false-positive RPR - medium or high titer anticardiolipin (IgA, IgG, or IgM) - anti-β2 glycoprotein I (IgA, IgG, or IgM) 5. Low complement - low C3, C4, CH50 6. Direct Coombs test
Classification of SLE	- Satisfy four out of the 11 criteria	- Satisfy four of the criteria, including one clinical criterion and one immunologic criterion OR - biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies
Sensitivity[12]	83%	97%
Specificity[12]	96%	84%

Clinical manifestations:

Constitutional symptoms and signs:

Fatigue, fever, and weight loss are common symptoms that occur during the course of the disease. Fatigue is the most common of these, occurring in 80% to 100% of patients, but it does not correlate with disease activity. Fatigue from other causes, such as anemia, hypothyroidism, medications (e.g., beta-blockers), depression, fibromyalgia, and social stresses, should be considered ***(Mckinley et al., 1995).***

Fever is reported in >50% of patients with SLE and is thought to represent active disease. This fever often resolves with non-steroidal anti-inflammatory drug (NSAID) or acetaminophen therapy. Fever persisting despite treatment with these agents should raise suspicions of an infectious or drug-related etiology ***(Sandman-Goddard and Schoenfeld, 2003)***.

Weight loss in SLE may be related to disease activity or its treatment. Patients with SLE may have esophageal hypomobility leading to dysphagia. Vomiting and diarrhea may also be a feature contributing to weight loss; drugs should be excluded as a cause. There is also a higher prevalence of cancer in patients with SLE and this should be considered ***(Bernatsky et al., 2005).***

Mucocutaneous manifestations:

The classic facial rash of SLE is the malar or butterfly rash (figure 1). This is seen in 50% of SLE patients. It may be the first sign of the disease or accompany a patient's lupus flairs. The rash is described as a maculopapular rash over the cheeks extending over the bridge of the nose and worsened by sun exposure ***(Lehrmann et al., 2009).***

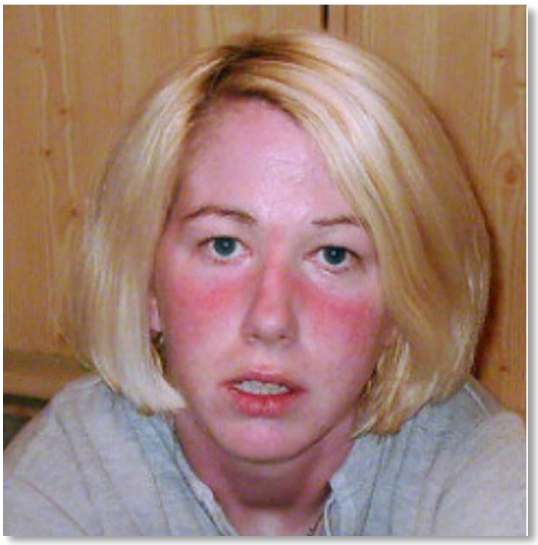

Figure (1): Malar rash in SLE (***Lehrmann et al., 2009)***.

Discoid lupus erythematosus (DLE) is described as raised plaques with scales on the face, head, or neck. DLE can occur in the absence of systemic disease. This is also called cutaneous lupus erythematosus ***(Brooke, 2016).***

Mucous membrane ulcerations are seen in between 8-45% of the SLE patients (figure 2) ***(Chi and Brad, 2010).*** This is one of the clinical criteria eligible to help make the diagnosis. The appearance may be similar to canker sores and can be present over the hard palate, the lips, and gingiva. Vasculitic lesions are also seen. Small vessel vasculitis is most commonly seen in SLE, but presentations range from ulcerations to purpura to digital infarcts and gangrene ***(Richard, 2016)***.

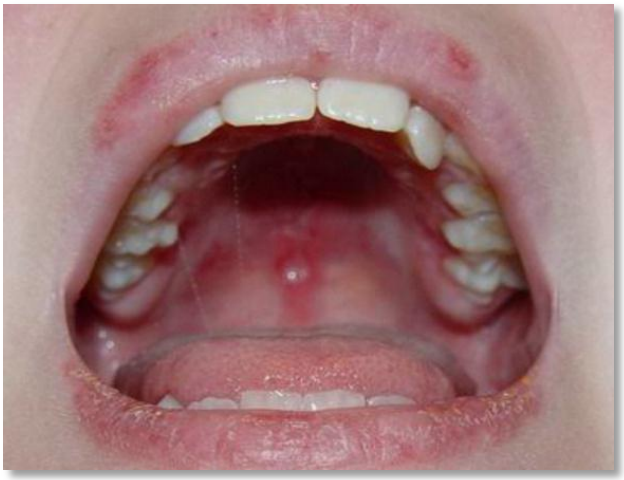

Figure (2): Oral ulcer in SLE ***(Chi et al., 2010).***

Musculoskeletal manifestations:

The musculoskeletal system is involved in around 90% of patients with SLE. In addition to myalgia and arthralgia, arthritis of small and large joints may occur. Tendinitis and synovitis can be detected by sonography and/or magnetic resonance imaging. Chronic recurring arthritis particularly of the finger joints may lead to joint