INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ, autoimmune, inflammatory disease ***(Miah et al., 2008).*** It is predominantly affects adults, usually women of child bearing age (20 to 40 years), at a female to male ratio of 9:1 to 15:1. Approximately 8% to 15% of SLE cases occur in children ***(Amissah-Arthur and Gordon, 2009).*** Genetic and racial factors are also associated with an increased risk of developing SLE ***(Bongu et al., 2003).***

The development of SLE is a complex immune process that is brought about by dysregulation of B and T-lymphocytes, the production of autoantibodies, and the formation of immune complexes ***(Suh and Kim, 2008)***. There is also some evidence that hormone abnormalities are associated with SLE. Estrogen and androgen metabolism have been found to differ in men and women with SLE compared with healthy controls ***(McAlindon, 2000).***

The diverse presentations of lupus range from rash and arthritis through anemia and thrombocytopenia to serositis, nephritis, seizures, and psychosis lupus should be port of the differential diagnosis in virtually any patient presenting with one of these clinical problems, especially in female patients ***(Anisur and David, 2013).***

Lupus nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE). The general consensus is that 60% of lupus patients will develop clinically relevant nephritis at some time in the course of their illness. Prompt recognition and treatment of renal disease is important, as early response to therapy is correlated with better outcome. The vast majority of patients who develop nephritis are younger than 55 years, and children are more likely to develop severe nephritis than are elderly patients ***(Bertsias et al., 2008).***

Diagnosis of lupus nephritis depend on clinical features which include: proteinuria, microscopic hematuria, hypertension, reduced glomerular filtration rate and acute kidney injury ***(Ramesh et al., 2011).***

Vitamin D is a steroid hormone that plays a crucial role in calcium metabolism and bone homeostasis. It is increasingly recognized that vitamin D also has important roles in multiple other systems, including effects on muscles, vasculature, reproduction, cellular growth and differentiation, malignancy and the immune system ***(Kamen and Arnow, 2008).***

Vitamin D deficiency is highly prevalent in patients with systemic lupus erythmatosus (SLE) as a result of avoidance of sunshine, photo protection, renal insufficiency and the long-term use of medications that alter vitamin D metabolism. Some

studies reveal a low vitamin D level in patients with new-onset SLE, suggesting vitamin D as an environmental trigger of the disease in genetically susceptible individuals ***(Chi, 2013).***

Few controversial studies dealing with the relation between low level of vitamin D and lupus nephritis ***(Kittiwan et al., 2013).***

AIM OF THE WORK

To assess the relation between the serum level of vitamin D, lupus nephritis and SLE disease activity.

Chapter (1)

SYSTEMIC LUPUS ERYTHEMATOSUS

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting almost all organs and tissues, including the skin, joints, kidneys, lungs, nervous system and serous membrane ***(Alunno et al., 2012)***.

SLE is protean in its manifestations and follows a relapsing and remitting course ***(Bartels et al., 2006)***. While the etiology of SLE is thought to be multifactorial, the disease is characterized by the production of autoantibodies which leads to immune complex (IC) deposition, inflammation and eventually, permanent organ damage ***(Lam and Petri, 2005)***.

In genetically predisposed subjects, environmental factors, such as viral infections and smoking, induce the breakdown of self-tolerance eventually triggering autoimmune response ***(Alunno et al., 2012)***.

SLE manifestations are caused by autoantibodies and ICs that activate the complement system in various tissues. This results in acute and chronic inflammation and tissue damage ***(Munoz et al., 2010)***.

It is characterized by a loss of tolerance to nuclear antigens and various immunological abnormalities, including deregulated activation of both T and B lymphocytes and subsequent polyclonal activation of circulating B lymphocytes which produces a large quantity of auto reactive antibodies and the formation of ICs causing tissue and organ damage ***(Shui-Lian et al., 2012)***.

The clinical course of SLE is variable and may be characterized by periods of remissions and chronic or acute relapses. Women, especially in their 20s and 30s, are affected more frequently than men ***(Cervera et al., 2003)***.

In genetically predisposed subjects, environmental factors, such as viral infections and smoking, induce the breakdown of self-tolerance eventually triggering autoimmune response ***(Alunno et al., 2012)***.

Epidemiology

The reported prevalence of SLE in the population is 20 to 150 cases per 100, 000 ***(Lawrence et al., 1998)***. In women, prevalence rates vary from 164 (white) to 406 (African American) per 100, 000. Due to improved detection of mild disease, the incidence nearly tripled in the last 40 years of the 20th century ***(Chakravarty et al., 2007)***.

Geographic and racial distribution:

The disease appears to be more common in urban than rural areas ***(Pons-Estel et al., 2010)***.

The prevalence of SLE is higher among Asians, Afro-Americans, Afro-Caribbean, and Hispanic Americans compared with Americans of European decent in the United States, and among Asian Indians compared with Caucasians in Great Britain. In comparison, SLE occurs infrequently in Blacks in Africa ***(Rus et al., 2007)***.

Gender:

SLE principally affects women during childbearing years. The female-to-male ratio is around 9:1. Although virtually all patients have skin and joint disease, between 30 and 50% will also develop renal, lung, heart and central nervous system (CNS) involvement ***(Li & Isenberg et al., 2005)***.

The increased frequency of SLE among women has been attributed in part to an estrogen hormonal effect ***(Chung et al., 2009)***. In children, in whom sex hormonal effects are presumably minimal, the female-to-male ratio is 3:1. In adults, the ratio ranges from 7:1 to 15:1 ***(Chakravarty et al., 2007)***. In support of the potential role of estrogens in predisposing to SLE, the Nurse's Health study showed that women with early

menarche, or treated with estrogen-containing regimens, such as oral contraceptives or postmenopausal hormone replacement therapies, have a significantly increased risk for SLE ***(Cooper et al., 2008)***.

Factors related to the X chromosome may also be important in predisposing women to SLE. At least three predisposing genes are located on X chromosomes ***(Lahita, 2009)***. There is also evidence for a gene dose effect, since the prevalence of XXY (Klinefelter's syndrome) is increased 14-fold in men with SLE when compared with the general population of men, whereas XO (Turner's syndrome) is underrepresented in women ***(Buyon et al., 2005)***.

Age of onset:

Sixty-five percent of patients with SLE have disease onset between the ages of 16 and 55 ***(Ballestar et al., 2006)***. Of the remaining cases, 20 percent present before age 16, and 15 percent after age 55 ***(Lockshin, 2006)***.

Pathophysiology/ Etiology

The development of SLE is a complex immune process that is brought about by dysregulation of B and T lymphocytes, the production of auto-antibodies, and the formation of immune complexes ***(Suh chet et al., 2008).***

Cytokines are thought to play a key role in SLE; however, the extent to which they affect progression of lupus is not clear. Their involvement may help explain the variations seen in the clinical manifestations of patients ***(Bongu et al., 2003).***

While it is known that the immune system plays a role in the development of the disease, what causes the immune system to function abnormally is unknown ***(Reidenberg et al., 1998).*** It is speculated that environmental factors play a role, but the data have not consistently supported this theory ***(Petri et al., 1992).***

There is, however, evidence to suggest that genetic components play a role ***(Bongu et al., 2003).*** Several immunologic gene abnormalities (e.g., interferon regulatory factor 5, protein tyrosine phosphatase nonreceptor type 22, and integrin alpha M) have been identified ***(Jim Nez et al., 2003).***

Additionally, research in homozygous twins has shown a higher incidence of SLE in families where the prevalence of the disease in other family members was low ***(Hess et al., 1997).***

Furthermore, those with infantile-onset SLE occurring within the first year of life have a high incidence of having family members with a history of autoimmune diseases ***(Zulian et al., 2008).***

There is also some evidence that hormone abnormalities are associated with SLE. Estrogen and androgen metabolism

have been found to differ in men and women with SLE compared with healthy controls ***(McAlindon et al., 2008).***

For example, women with SLE metabolize estrogen to a more potent form, 16a-hydroxyestrone, instead of 2-hydroxyestrone, and can have irregular menstruation cycles and increased risk of miscarriage. Prolactin levels can also be elevated in patients with SLE ***(McAlindon et al., 2008).*** Use of hormone replacement therapy has also been shown to increase the risk of developing SLE ***(Snchez-Guerrero et al., 1995).***

Infection with the Epstein-Barr virus has been associated with the production of autoantibodies that are present in up to 38% of patients with SLE ***(McAlindon et al., 2008).***

Lupus may also develop as a result of exposure to various medications ***(Marzano et al., 2009).***

Up to 10% of patients presenting or diagnosed with SLE may actually have drug induced lupus erythematosus (DILE), and approximately 80 drugs have been implicated in causing DILE ***(Sarzi-Puttini et al., 2005).*** Several mechanisms have been implicated in DILE, including genetics and auto-antibody production. Agents such as procainamide, hydralazine, and isoniazid generally cause DILE in patients with genetic abnormalities ***(Sarzi-Puttini et al., 2005).***

These medications all undergo acetylation as part of their metabolism, so patients who are slow acetylators tend to have more problems with DILE compared with those who have normal or fast acetylation **(Marzano et al., 2009**).

Clinical Manifestations

A) Constitutional Symptoms

1-Fatigue

Fatigue is the most common complaint, and occasionally the most debilitating. It occurs in 80 to 100 percent of patients and its presence in not clearly correlated with other measures of disease activity ***(McKinely et al., 2005)***.

However, fatigue may not be due to active SLE, but to one or more of the following: use of certain medications (including prednisone, beta-blockers), coexistent fibromyalgia ***(Wolfe et al., 2009)***.

2-Fever

Fever that is thought to be due to active disease is seen in over 50 percent of patients with SLE. Fever may also represent infection or a drug reaction ***(Cervera et al., 2003)***.

The history and the pattern of fever may be helpful diagnostically. Episodic fever is suggestive of active SLE or

infection; in comparison, sustained fever may reflect CNS or an adverse effect to a drug ***(Zhou and Yang, 2009)***.

Risk factors for infection include: active SLE disease, neutropenia, lymphopenia, hypocomplementemia, renal involvement, neuropsychiatric manifestations, and the use of glucocorticoids (GCs) and other immunosuppressive drugs ***(Cuchacovich and Gedalia; 2009)***.

B) Specific Organ Involvement — SLE affects multiple organ systems. The course is marked by remissions and relapses and may vary from mild to severe.

1-Musculoskeletal manifestations

Arthralgia and nonerosive arthritis are among the most common clinical features of SLE and are experienced by more than 85% of patients. The proximal interphalangeal and metacarpophalangeal joints of the hand are most commonly symptomatic, along with the knees and wrists. In some patients (about 5%), deformities resulting from damage to periarticular tissue can occur, a condition termed Jaccoud's arthropathy ***(Crow, 2011)***.

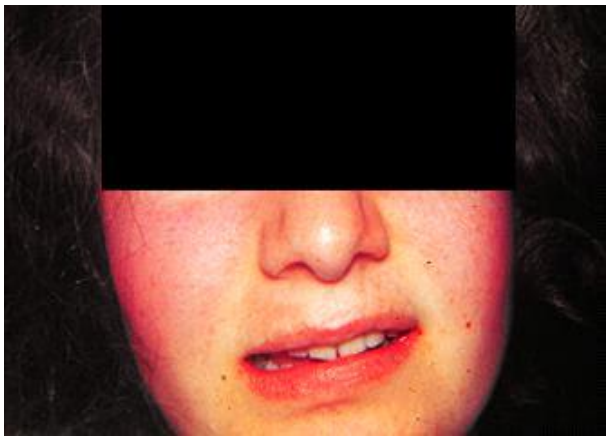
The arthritis tends to be migratory and asymmetrical. The arthritis is moderately painful, and rarely deforming ***(Greco et al., 2003)***.

2-Mucocutaneous

Most patients have skin lesions at some time during the course of the illness. The most common lesion is the butterfly rash, which appears after sun exposure (figure 1) ***(Durosaro et al., 2009)***. Some patients will develop discoid lesions, which are more inflammatory and have a tendency to scar. Typical discoid lesions in a malar distribution are illustrated in a patient who had no systemic feature of lupus (figure 2). Hair loss (alopecia) is common ***(Walling and Sontheimer, 2009)***.

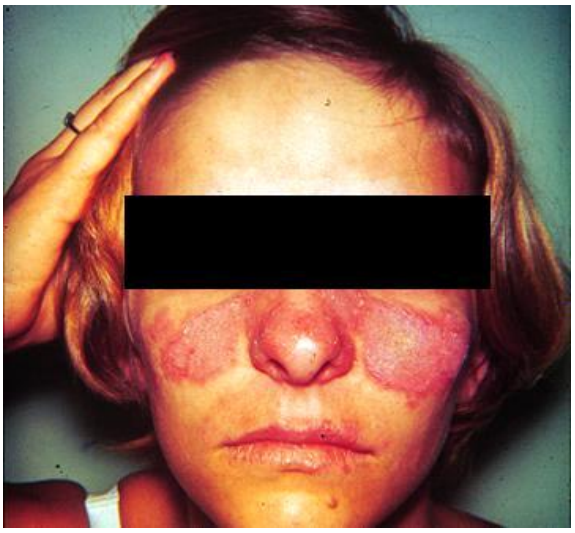
Many patients develop oral and/or nasal ulcers, which are usually painless, in contrast to herpetic chancre blisters ***(Lin et al., 2007)***. Such ulceration has been noted in 12 to 45 percent of patients. Perforation of the nasal septum occurs infrequently ***(Callen, 2006)***.

Figure (1): Malar erythema in SLE-Malar erythema (butterfly rash).



Adapted from **(Durosaro et al., 2009)**

Figure (2): Butterfly discoid lupus-Discoid LE with "butterfly" distribution.

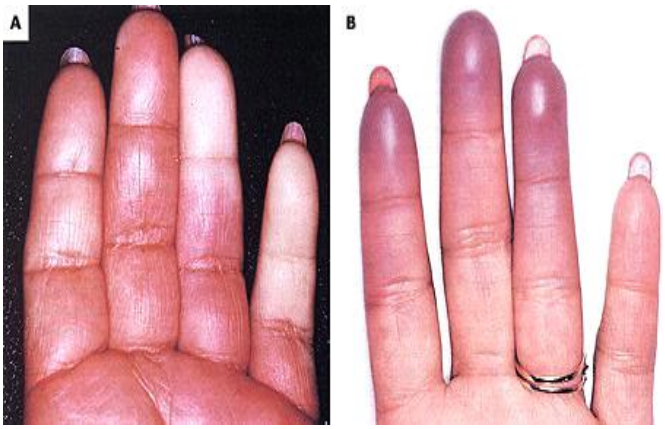


Adapted from **(Walling and Sonteimer, 2009)**

3-Raynaud phenomenon

Cold or emotion-induced color changes of the digits of the hands and/or feet, the Raynaud phenomenon, is a frequent problem and may antedate other features of the disease (figure 3). Self-reported skin color changes consistent with Raynaud phenomenon occurred in 16 to 40 percent of patients in two large series ***(Greco et al., 2003)***.

Figure (3): Raynaud phenomenon-Panel A shows sharply demarcated pallor resulting from the closure of digital arteries. Panel B shows digital cyanosis of the fingertips in a patient with primary Raynaud phenomenon



Adapted from **(Wigley, 2002)**

4- Renal

Renal involvement becomes clinically apparent in approximately 50 percent of patients; however, most of the remaining patients have subclinical disease that can be demonstrated if renal biopsy were performed ***(Kasitanon et al., 2006)***. IC deposits in the kidneys result in a variety of pathologic and clinical manifestations ***(To and Petri, 2005)***.

The histological abnormalities help determine prognosis and guide treatment. Several forms of glomerulonephritis(GN) can occur and renal biopsy is useful to define the type and extent of renal involvement ***(Morel, 2007)***.