Thyroid dysfunction and thyroid autoantibodies in Egyptian patients with SLE and its impact on the musculoskeletal manifestations of the disease

Thesis
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Abstract

SLE is a chronic, autoimmune, multifaceted inflammatory disease that can affect any organ system of the body. One of the commonest organs to be affected by organ-specific autoimmune injury is the thyroid gland.

Many studies discussed its prevalence. Hypothyroidism found to be the most common abnormality. These studies also found that thyroid auto-antibodies found more frequently in SLE patients than general population.

Studies have also proved that there is differences in the incidence of SLE manifestations (such as skin symptoms, arthritis and kidney disease) in SLE patients with thyroid dysfunction than euthyroid patients.

Musculoskeletal manifestations of SLE found to be more frequent among SLE patients with thyroid dysfunction than patients without it.

Key words: SLE, thyroid gland, autoantibodies, dysfunction, musculoskeletal, euthyroid.
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**List of abbreviations**

ACL: Anticardiolipin.

ACR: American College of Rheumatology.

ACTH: Adrenocorticotropic hormone.

AECA: Anti-endothelial-cell antibodies.

ANA: Antinuclear antibody.

ANCA: Anti-neutrophil cytoplasmic antibody.

APS: Antiphospholipid syndrome.

ATMA: Anti-thyroid microsomal antigen.

BMR: Basal metabolic rate.

CAC: Coronary artery calcification.

CAT: Chronic autoimmune thyroiditis.

CCLE: Chronic Cutaneous Lupus Erythematosus.

CLS: Carolina Lupus Study.

CRP: C-reactive protein.

CT: Computed tomography.

CVS: Cerebrovascular stroke.

DILE: Drug Induced lupus Erythematosus.

DVT: Deep venous thrombosis.

E.C.G: Electrocardiographic.

EBV: Epstein-Barr virus.

ELISA: Enzyme-linked immunosorbent assay.

EMG: Electromyography.

ENA: Extractable nuclear antigens.
List of abbreviations (con.)

FMS: Fibromyalgia syndrome.
FT₃: Free Tri-iodothyronine.
FT₄: Free Tetra-iodothyronine.
GCA: Giant cell arteritis.
GH: Growth hormone.
HLA: Human leukocyte antigen.
HRT: Hormone replacement therapy.
HT: Hashimoto's thyroiditis.
IGFI: Insulin like growth factor I.
IHD: Ischemic heart disease.
LA: Lupus anticoagulant.
LHRH: Luteinizing hormone releasing hormone.
LN: Lupus nephritis.
MCTD: Mixed connective tissue disease.
MHC: Major histocompatibility complex.
MR: Magnetic resonance.
NA: Nuclear antigens.
OA: Osteoarthritis.
PMR: Polymyalgia rheumatica.
RA: Rheumatoid arthritis.
RNP: Ribonucleoprotein.
SCH: Subclinical hypothyroidism.
SCHT: Subclinical hypothyroidism.
List of abbreviations (con.)

SCLE: Subacute Cutaneous Lupus Erythematosus.

SLE: Systemic lupus erythematosus.

Sm: Smith.

TG: Thyroglobulin.

TPO: Thyroid microsomal (peroxidase).

TRH: Thyrotropin-releasing hormone.

TSH: Thyroid stimulating hormone (Thyrotropine).

UV: Ultraviolet.
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Introduction
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibodies directed against self-antigens and resulting in inflammatory damage to target organs including the kidneys, blood cells and central nervous system (*Klein and Miller, 2004*). SLE is the prototype of a systemic autoimmune disorder in which immune complexes or cytotoxic antibodies give rise to tissue damage, often resulting in end organ damage, failure, or death (*Manger et al., 2002*).

The incidence of SLE varies significantly in different ethnic groups and populations, with annual incidence rates in adults ranging from 1.9 to 5.6 per 100,000. Sex-specific incidence rates differ between men and women, with rates between 0.4 and 0.6 for white males, 3.5 and 4.6 for white females, 0.7 for African American males, and 9.2 for African American females (*McCarty et al., 1995*).

Worldwide, the prevalence of SLE appears to vary by race. However, different prevalence rates occur among people of the same race in different geographical locations. The contrast between low reported rates of SLE in Africa and high rates among black women in the United Kingdom suggests the importance of environmental influences (*Symmons, 1995*). In general, black women have a higher rate of SLE than any other race, followed by Asians, then white women (*Danchenko et al., 2006*).

Children and adolescents who have SLE frequently present with systemic constitutional symptoms, such as fever, diffuse hair loss, fatigue, weight loss, and evidence of diffuse inflammation as demonstrated by lymphadenopathy and hepatosplenomegaly, and these manifestations are seen throughout the course of the disease. Skin, musculoskeletal, and renal systems are the most common organ systems involved in SLE. Gastrointestinal disease, including significant liver involvement, myositis, and myocarditis, are rare in children (*Huong et al., 1999*).

Autoimmune diseases can be divided into organ-specific and systemic illness. The systemic inflammatory autoimmune diseases include rheumatoid arthritis (RA), SLE, dermatomyositis, polymyositis and systemic sclerosis. One of the commonest organs to be affected by organ-
specific autoimmune injury is the thyroid gland. The occurrence of two or more organ specific autoimmune diseases in a single adult person is known as type 2 autoimmune polyglandular failure (Blich et al., 2004).

Both hypothyroidism and hyperthyroidism are seen, but hypothyroidism is the most common abnormality. Up to 35% of SLE patients have antithyroid antibodies, with 10% to 15% of patients developing overt hypothyroidism (Eberhard et al., 1991).

The association between SLE and thyroid abnormalities was first described in 1961 by White & Williams and Hijmans et al., who showed that the presence of thyroid disturbance appeared to be more frequent in SLE patients than in the general population. However, divergences still exist in relation to prevalence (Byron, 1987). Furthermore, antiperoxidase and antithyroglobulin antibodies have been frequently found in SLE patients (Weetman and Walport, 2004).

Many SLE patients are initially treated for thyroid dysfunction before the diagnosis of lupus is made or vice versa. Symptoms of thyroid disease can be confused with those of lupus. To identify the thyroid function in lupus patients many studies have been conducted. Although the relationship between autoimmune thyroid disease and SLE has been revealed, the prevalence of thyroid disease in lupus patients is controversial. Reported prevalence of autoimmune thyroid disease (3.9–24%) and anti thyroid antibodies (11-51%) in SLE patients varied considerably (Pyne and Ienberg, 2002).

A study by Weetman and Walport, 2004 has shown that 51% of SLE patients had thyroid antibodies compared to 27% of controls, and elevated TSH were detected in 25% of SLE patients and 12.5% in the control group. In China, prevalence of thyroid antibodies and thyroid dysfunction in SLE patients was 46.7% and 22.2% respectively (Chang et al., 1993).

The prevalence of antithyroid microsomal (TPO) and antithyroglobulin (TG) antibodies was 32.2% in SLE patients in Singapore (Boey et al., 1993). In Korean patients with SLE, prevalence of Hashimotos' thyroiditis, euthyroid sick syndrome, and graves' disease were 9.5%, 14.3% and 4.8% respectively, while antithyroid antibodies were 27% (Park et al., 1995).
The study by *Chan et al, 2001* has shown that 13% of SLE patients had subclinical hypothyroidism (SCH) and 4.3% had hypothyroidism and positive anti TPO were detected in 23.2% of SLE patients.

In Egypt, *El Sharif et al, (2004)* revealed that thyroid disorders in SLE patients were 50% and TPO antibody was found in 15% of SLE patients.

The study by *Al Saleh et al, (2008)* in a cross-sectional and retrospective case-control study to report the prevalence of thyroid diseases in 110 Arabs with lupus who attended Rheumatology Clinic between January 2002 and January 2007, and to delineate the clinical and immunological features of Arabs lupus patients with thyroid diseases. They found hypothyroidism in 15 (13.7%) patients. Overall, 25.6% had elevated anti-TPO antibodies, 14.6% had elevated anti-TG antibodies, and 13.7% were positive for both antibodies. Lupus patients with hypothyroidism had a significantly higher frequency of polyarthritis, cutaneous manifestations, positive anti-TG antibodies, and TPO antibodies than lupus patients with normal thyroid function. Furthermore, neuropsychiatric and hematological manifestations were significantly lower in patients with hypothyroidism than in euthyroid patients. Surprisingly, the prevalence of antcardiolipin (aCL) antibody immunoglobulin G (aCL IgG), lupus anticoagulant (LA), and aCL syndrome were significantly lower in lupus patients with hypothyroidism than in lupus patients with normal thyroid function. The author concluded that the prevalence of hypothyroidism in Arabs with lupus is comparable to that reported in the literature. Arab lupus patients with hypothyroidism have distinctive clinical and immunological features that differentiate them from euthyroid patients.
Aim of the work
Our aim is to:

- Assess thyroid dysfunction, level of thyroid hormones and thyroid autoantibodies in a cohort of SLE Egyptian patients.
- Study its impact on the musculoskeletal manifestations of the disease in lupus patients with thyroid dysfunction.
Review of Literature
Systemic Lupus Erythematosus
**SLE** is a chronic, autoimmune, multifaceted inflammatory disease that can affect any organ system of the body.

The disease is protean in its manifestations and follows a relapsing and remitting course. SLE is characterized by the presence of a wide spectrum of circulating autoantibodies and a systemic inflammation, both due to a malfunctioning immune regulation (*Bartels et al., 2006*).

**Epidemiology:**

The prevalence of SLE in USA is approximately 50 cases per 100,000 populations. Worldwide, the prevalence is variable, from 12 cases per 100,000 populations in Britain to 39 cases per 100,000 populations in Sweden (*Bartels et al., 2006*).

SLE is rarely seen in rural tropical areas of Africa and Asia, yet people of African and Asian extraction living in industrial countries have amongst highest prevalence rates of lupus in the world (*Tikly and Navarra, 2008*).

Childhood incidence and prevalence rates 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*).

SLE is up to 10 times more common in women than men, and typically has a predilection for women in their child-bearing years (*Manson and Rahman, 2006*). Among children, it occurs three times more commonly in females than males (*Lahita, 1997*).

Of patients with SLE, 65% have disease onset between ages 16 and 55, 20% present before age and 15% present after the age of 55 (*Pons-Estel et al., 2010*).
Pathogenesis:

Although the specific cause is unknown, immune-system dysregulation and immune-complex tissue damage at sites such as the skin and kidneys, as well as direct antibody-mediated cytotoxicity that causes thrombocytopenia and hemolytic anemia are suspected causes. Multiple immune disturbances may predispose to SLE (Bartels et al., 2006).

SLE is classically characterized by elevated titers of antinuclear antibodies (ANA) and anti-dsDNA antibodies. The autoantibody profile may include a response to other extractable nuclear antigens (ENA) including Ro/SSA, La/SSB, ribonucleoprotein (RNP), and smith (Sm) (Frisoni et al., 2005).

The production of these autoantibodies could be antigen-driven, the result of polyclonal B cell activation, impaired apoptotic pathways, or the outcome of idiotypic network dysregulation (Sherer et al., 2004).

SLE is an autoimmune disorder characterized by multisystem micro-vascular inflammation with the generation of autoantibodies. Multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors (Rahman and Isenberg, 2008).

1- Genetic predisposition:

The concordance rate for lupus is 25% among monozygotic twins and approximately 2% among dizygotic twins; these rates indicate that a genetic contribution is important, but it is not sufficient to cause the disease (Sullivan, 2000).

Susceptibility to SLE depends on multiple genes. Susceptibility genes are defined as genes that increase the relative risk for a disease, even though most individuals with that gene are healthy. The number of genes is unknown. It is likely to be several, with full gene effect depending partly on other modifying or protective genes in the same individual gender, and the strength of environmental stimuli that can trigger disease (Harley et al., 1998).