Subclinical Hypothyroidism and Its Effect on Serum Lipids in Pediatric Systemic Lupus Erythematosus

Thesis

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By

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List of Abbreviations

AACE	**:** American Association of Clinical Endocrinologists
ACR	**:** American College of Rheumatology
ANA	**:** Antinuclear antibody
APCs	**:** Antigen presenting cells
ATA	: American Thyroid Association
ATG	: Anti-thyroglobulin antibodies
C	**:** Complement
CBC	**:** Complete blood count
CD	**:** Cluster of differentiation
CRH	**:** Corticotrophin releasing hormone
CTL	: Chronic lymphocytic thyroiditis
CTL A	**:** Cytotoxic T lymphocyte-associated protein
DCs	**:** Dendritic cells
DEHA	**:** Dehydroepiandrosterone
DR	**:** D-Region
ds-DNA	**:** Double-stranded deoxyribonucleic acid
ESR	**:** Erythrocyte sedimentation rate
FcγRA	**:** Fragment constant gamma receptor allele
FT4	**:** Free thyroxine hormone
HDL	**:** High density lipoprotein
HLA	**:** Human leucocyte antigen
HnRNP	**:** Heteronuclear ribonucleoprotein
HPA	**:** Hypothalamo-pituitary-adrenal
HRP	**:** Horseradish peroxidase
ICs	**:** Immune complexes
IFN	**:** Interferon
IgG	**:** Immunoglobulin G
IL	**:** Interleukin
IL-R	**:** Interleukin –receptor
ISCs	**:** Immunoglobulins secreting cells
LDL	**:** Low density lipoprotein

List of Abbreviations (Cont.)

mDCs	**:** Myeloid dendritic cells
MHC	**:** Major histocompatibility complex
NKT	: Natural killer T- cells
PBMCs	: Peripheral blood mononuclear cells
PCPs	**:** Plasma cell precursors
pDCs	**:** Plasmacytoid dendrtic cells
SCH	**:** Subclinical hypothyroidism
SLE	**:** Systemic lupus erythematosus
SLEDAI	**:** Systemic lupus erythematosus disease activity index
Sm	**:** Smith
T3	: Tri-iodothyronine
TBG	: Thyroxin- binding globulin
TC	**:** Total cholesterol
TCR	**:** T- cell receptor
TD	**:** T-cell dependent
TG	: Triglycerides
TR	**:** Thyroxine replacement
Th	**:** T-helper
TNFR	**:** Tumor necrosis factor receptor
TPO Abs	**:** Thyroid peroxidase antibodies
TRH	**:** Thyrotropin-releasing hormone
TRS Ab	**:** Thyrotropin receptor-stimulating antibodies
TSH	**:** Thyroid stimulating hormone
U-RNP	**:** Uridylate- rich ribonucleoproteins
U-snRNP	**:** Uridylate- rich small nuclear ribonucleoproteins
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).***

Thyroid autoimmune diseases have been associated with a variety of rheumatological diseases, including SLE. The thyroid disorders, including subclinical hypothyroidism and clinical hypothyroidism, were more prevalent in patients with SLE than in general population ***(Viggiano et al., 2008).***

Subclinical hypothyroidism (SCH) is characterized by normal thyroid hormone levels (total thyroxine and tri-iodothyronine) with elevated thyroid stimulating hormone (TSH) ***(McDermott and Ridgway, 2001).***

SCH is associated with a pro-atherogenic dyslipidaemias and increased risk of cardiovascular disease ***(Chu and Crapo, 2002)***. These effects are being greater at higher thyroid stimulating hormone (TSH) levels ***(Kahaly, 2000).***

Thyroid function and Thyroid peroxidase antibody (TPO Ab) tests should be performed as a part of the biochemical and immunological profile respectively in SLE patients ***(Chan et al., 2001).***

Thyroxine replacement therapy in SCH induces favorable changes in lipid profiles (reduction in low density lipoprotein, total cholesterol, and to a lesser extent, apolipoprotein A), especially in patients with higher base line TSH levels (>10-12Mu/L) ***(Meier et al., 2001).***

AIM OF THE WORK

The aim of the present study is to evaluate the frequency of subclinical hypothyroidism among the studied Egyptian children with systemic lupus erythematosus outlining its effects on serum lipids and its correlation with disease activity.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an episodic, multisystem, prototypic autoimmune disease characterized by wide spread inflammation of blood vessels and connective tissues and by the presence of antinuclear antibodies (ANAs), especially antibodies to native double-stranded deoxy-ribonucleic acid (dsDNA) ***(Petty & Laxer, 2005).***

Children represent ~15–20% of all SLE patients ***(Stichweh et al., 2004)***. Although the presentation, clinical symptoms and immunological findings of pediatric SLE are similar to those of adult SLE, children usually have a more severe disease at onset. They also have higher rates of organ involvement, and a more aggressive clinical course than adults ***(Brunner et al., 2002)***.

SLE is predominantly a female disease. The factor that predisposes more women to develop SLE is still unknown. There are two hypotheses. The first is based on the role of sex determination and female hormones on the immune response. The second focuses on an undefined gene on the X chromosome that exerts its effect by being present in a double dose ***(Reeves et al., 2005).***

Epidemiology:

In childhood, girls are affected 4.5 times more frequently than boys, although the overall ratio varies with age at onset ***(Petty & Laxer, 2005).***

The median age at pediatric SLE diagnosis was 12.2 years. However, the diagnosis was made as early as the age of one year. The time from onset of symptoms to diagnosis varied from 1 month to 3.3 years ***(Bogkanovic et al., 2004).***

There is increasing evidence that susceptibly genes vary considerably among different ethnic groups providing evidence for the genetic heterogenecity of SLE that contributes to the clinical and pathological heterogenecity ***(Olsen et al., 2002).***

The Pathogenesis of Systemic Lupus Erythematosus:

The exact patho-aetiology of SLE remains elusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved. Multiple genes contribute to disease susceptibility. The interaction of sex, hormonal milieu, and the hypothalamo–pituitary–adrenal axis modifies this susceptibility and the clinical expression of the disease ***(Mok and lau, 2003).***

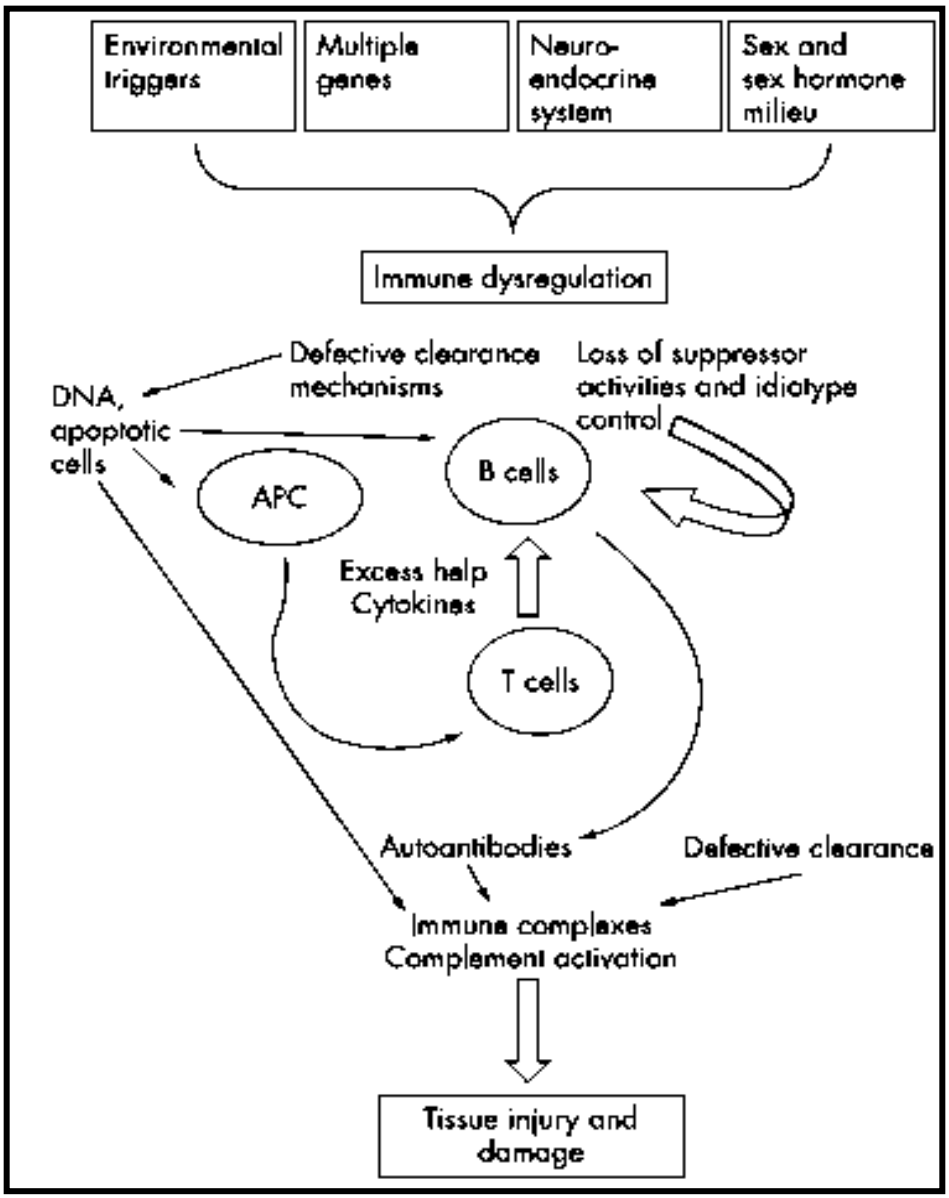

Figure 1: The pathogenesis of systemic lupus erythematosus; APC: Antigen presenting cell. ***Quoted from (Mok and lau, 2003).***

➢ ***Genetics Susceptibility of SLE:***

Family Studies have found a higher than expected prevalence of SLE in relatives of patients with the disease. In case- control study, 10% of patients with SLE had a first degree relative with SLE, compared with 1% in control families ***(Petty & Laxer, 2005).***

The concordance of the disease in identical twins is approximately 25–50% and that in dizygotic twins is around 5%. This suggests that genetic factors play an important role in the predisposition of the disease. However, most cases of SLE are sporadic without identifiable genetic predisposing factors, suggesting that multiple environmental or yet unknown factors may also be responsible ***(Sullivan, 2000).***

An association of HLA DR2 and DR3 with SLE is a common finding in patients of different ethnicities, with a relative risk for the development of disease of approximately two to five. The region containing the major Histocompatibility (MHC) locus on chromosome 6 is not the most prominent susceptility locus, suggesting that there are at least six other loci on chromosome 1, 2, 4, and 16 that contribute to the genetic predisposition to SLE ***(Tsao, 2003).***

Homozygous deficiency of any of the early components of