The Relationship between Hypogonadism and Osteoporosis among Adolescent Patients with Systemic Lupus Erythematosus

Thesis

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By

Ahmed Elhussieny Abdellatif
M.B, B.Ch (2004)
Faculty of Medicine- Ain Shams University

Under Supervision of

Prof. Dr. Khaled Salah Awwaad
Professor of Pediatrics
Faculty of Medicine - Ain Shams University

Prof. Dr. Eman Saleh El-Hadidy
Professor of Clinical Pathology
Faculty of Medicine - Ain Shams University

Dr. Dalia Helmy El-Ghoneimy
Lecturer of Pediatrics
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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Ahmed Elhussieny Abdellatif

List of Abbreviations

aCL	anticardiolipin antibodies
ACR	American Colleague of Rheumatology
ANA	Antinuclear antibody
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
AVN	Avascular necrosis
BMC	Bone mineral content
BMD	Bone mass density
BMI	Bone mass index
C-	Complement
CBC	Complete blood count
CD	Cluster of Differentiation
CH	Hemolytic complement
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computerized Tomography
CVA	Cerebrovascular accident
DEXA	Dual emission x-ray absorbiometry
DHEAS	Dehydroepiandrosterone sulfate
ds-DNA	Double-stranded deoxyribonucleic acid
E2	Estradiol
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FSH	Follicular stimulating hormone
GC	Glucocorticoid
ICAM	Intercellular adhesion molecule
IVC	Intravenous infusion of cyclophosphamide
LA	lupus anticoagulant
LH	Leutinizing hormone
LN	Lupus nephritis
M-CSF	Macrophage colony stimulating factor

List of Abbreviations (Cont.)

MHC	Major histocompatibility complex
MRI	Magnetic Resonance Imaging
NPSLE	Neuropsychatric systemic lupus erythematosus
NSAIDs	Non steroidal anti-inflammatory drugs
OP	Osteoporosis
OPG	Osteoprotegerin
pSLE	Pediatric systemic lupus erythematosus
QCT	Quantitative computed tomography
RANK	Receptor activator of nuclear factor κB
RANKL	Receptor activator of nuclear factor κB and its ligand
RDI	Recommended daily intake
SD	Standard deviation
SERMs	Selective estrogen receptor modulators
SHBG	Sex hormone binding globulin
SLEDAI	Systemic lupus erythematosus disease activity index
T-	Testosterone
TGF	Transforming growth factor
TNF	Tumor Necrosis Factor
WBPA	Weight bearing physical activity

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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).***

Factors influencing bone mass density (BMD) as measured by dual energy x-ray absorptiometry (DEXA) include age, body mass index, genetic factors, ethnicity and weight-bearing physical activity. In addition, impaired absorption or low dietary intake of vitamin D and calcium are risk factors for low BMD ***(Krieg et al., 2008).***

One of the mechanisms by which glucocorticoid (GC) therapy influences bone metabolism is by its influence on gonadal function, both in men and in women. Hypogonadism is indeed a complication of glucocorticoid therapy. The mechanisms involved include inhibition of pituitary gonadotrophin secretion and a direct effect on the ovaries and testes. This may result in increased bone turnover and bone loss. In premenopausal women, GC can induce hypo/ amenorrhoea, especially when other immunosuppressive drugs

are added. This has been shown in systemic lupus erythematosus, where 10% of premenopausal women had amenorrhoea ***(Redlich et al., 2000).***

The majority of men with osteoporosis have at least one (sometimes more than one) secondary cause. In cases of secondary osteoporosis, the loss of bone mass is caused by certain lifestyle behaviors, diseases, or medications. The most common causes of secondary osteoporosis in men include exposure to glucocorticoid medications, hypogonadism (low levels of testosterone) and immobilization ***(Bethesda, 2006).***

Aim of the Work

The aim of this study was to evaluate the frequency of osteoporosis and hypogonadism in adolescents with SLE. The interplay between both conditions, in addition to the effect of SLE status and the treatment given will be demonstrated.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an episodic multisystem disorder characterized by persistent antinuclear antibody (ANA) seropositivity, widespread inflammation, and immune-complex deposition in key target organs. It is a prototype of autoimmune diseases in humans that results from altered immunologic reactivity and a genetic predisposition ***(Petty et al., 2005).***

Incidence:

The incidence of SLE varies significantly in different ethnic groups and populations ***(Alamanos et al., 2003).*** Pediatric data suggest the incidence of SLE with onset before age 19 years is probably between 6 and 18.9 cases per 100,000 in white females and higher in black (20–30 per 100,000). The median age at pediatric systemic lupus erythematosus (pSLE) diagnosis was 12.2 years. The time from onset of symptoms to diagnosis varied from 1 month to 3.3 years (median, 4 months) ***(Bogdanovic et al., 2004).***

Sex-specific incidence rates differ between men and women, with rates between 0.4 and 0.6 cases per 100,000 for

white males, 3.5 and 4.6 cases per 100,000 for white females ***(Nossent, 2001).***

Etio-pathogenesis:

The etiology of SLE is still not completely understood, but multiple factors such as genetic predisposition, environmental exposure such as (infection with Epstein-Barr virus, high fat/low antioxidant diet, ultraviolet rays) and hormones are considered to be important ***(Molina and Shoenfeld, 2005).*** A number of triggers occurring together or sequentially over a limited period of time are required for disease to develop, which happens when a threshold of genetic and environmental susceptibility effects is reached ***(Rhodes and Vyse, 2008).***

There is a marked female predominance in SLE, with a 9:1 female to male ratio, suggesting a role for hormones in SLE susceptibility. In regard to this, estrogen has been widely studied as a risk factor in SLE, but with conflicting results. Thus it is likely that a more complex interaction of multiple sex hormones is involved, possibly with a protective effect of male hormones. A potential gene dose effect of genes located on the X chromosome may also be contributing to the female predominance ***(Jacob et al., 2009).***

It is well recognized that in some patients exposure to ultraviolet radiation may exacerbate either skin or systemic disease. In vitro studies have shown that exposure of cells, and particularly keratinocytes, to ultraviolet radiation leads to apoptosis, allowing blebs containing autoantigens to appear on the cell surface, which can then be processed and lead to an autoimmune response ***(Poole et al., 2009).***

For many years it has been proposed that exposure to viruses, in particular herpes families of viruses, can lead to polyclonal immune activation of the immune system, molecular mimicry, and then to the development of SLE ***(Kono and Theofilopoulos, 2006).***

SLE is characterized by immune dysregulation involving both the innate and adaptive immune systems and all effector mechanisms have been shown to be defective. Current hypotheses regarding loss of tolerance in SLE suggests that one or more of the following factors play a role: the generation of self-antigens on cell surfaces following apoptosis; abnormalities of innate immunity including Toll-like receptors; abnormalities of all arms of the adaptive immune system including antigen-presenting cells, T cells, and B cells;

epigenetics; and, most recently, abnormal regulation of interferon-α ***(Malleson et al., 1996).***

During normal apoptosis, nuclear and cytoplasmic antigens appear on the surface of the dying cells within blebs surrounded by the cell membrane. Abnormal clearance and/or regulation of clearance or abnormal presentation of blebs (containing autoantigens) to autoreactive cells may drive the autoimmune process. Abnormal clearance may be secondary to defects in complement components and/or abnormal complement receptors. In human SLE, there is evidence of abnormal apoptosis of lymphocytes, macrophages and neutrophils, and sera from SLE patients is pro-apoptotic ***(Miettunen et al., 2004).***

Cytokines may act as key players in the immunopathogenesis of SLE. These cytokines assume a critical role in the differentiation, maturation and activation of cells and also participate in the local inflammatory processes that mediate tissue insults in SLE. Certain cytokines such as the IL-6, IL-10, IL-17, type I interferon (IFN) and tumor necrosis factor-α (TNF-α) are closely linked to pathogenesis of SLE ***(Yap and Lai, 2010).***