Tumor necrosis factor -alpha associated with atherosclerotic vascular disease in patients with systemic lupus erythematosus

Thesis submitted for partial fulfillment of master degree in internal medicine

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Abstract

Thirty consecutive SLE patients and fifteen healthy control individuals will be included into the study. All patients must fulfill the ACR criteria for diagnosis of SLE, all SLE patients will be recruited from Rheumatology and Immunology clinic, ELKaser –ELAni hospital .

The control subjects will be excluded if they had HTN or DM.

All SLE patients will be subjected to: Full history, Full clinical examination , SLEDAI , CBC , Creatinine and Urea , ESR , C3 and C4, Urine analysis, 24hrs Urinary proteins and Lipid profile.

Key word

TNF –α - Doppler Ultrasonography- lupus erythematosus- factor - alpha associated

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Yousef Ojra

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aCL	Anti cardiolipin
ACR	The American College of Rheumatology
ADAM	Alkenyldiarylmethane
ATF2	Activating transcription factor 2
ATGL	Adipocyte triglycerides lipase
AIHA	Autoimmune hemolytic anemia
AIP3	Alpha induced protein 3
ANAs	Antinuclear antibodies
Anti-Sm	Anti smith antibodies
APC	Apoptotic cells
APS	Anti phopholipid syndrome
A=RE	A U= rich element
ASCVD	Atherosclerotic cardiovascular disease
AT	Atherosclerosis
4-1 BBL	Alternative protein names: 4-1BB ligand / Cd137l / Cd157l / Ly63l / P41273 / P41274 / TNFSF9 / Tu mor necrosis factor ligand superfamily member 9
BP	Blood pressure
Blys	Beta lymphocyte stimulators
BMI	Body mass index
C3	Complement 3
C4	Complement 4
CACs	Circulating angiogenic cells
CAD	Coronary artery disease
c-ANCA	Cytoplasmic antineutrophil cytoplasmic antibody
CBC	Complete blood count
CD	Cluster of differentiation
CHD	Coronary heart disease
CIMT	Carotid intima media thickness
CNS	Central nervous system
COX-2	Cyclooxygenase-2

CR1	Complement receptore1
CRH	Corticotropin relasing hormone
CRP	C-reactive protein
CT	Computed tomography
CMV	Cytomegalovirus
CV	Cardiovascular
CVA	Cerebrovascular attack
CVD	Cardiovascular disease
DBP	Distolic blood pressure
DCs	Dentritic cells
DG	Diglyceride
DHEA	Dehydroepiandrosterone
DHFR	Dihydrofolate reductase
DL	Disciod lupus
DM	Diabetis mellitus
DNA	Deoxy neuclic acid
DR3	Death receptor 3
dsDNA	Native double-stranded DNA
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECs	Endothelial cells
EDV	End diastolic volume
ELISA	Enzyme-linked immunosorbant assay
ENA	Extractable nuclear antibodies
EPCs	Endothelial progenitor cells
ESR	Erythrocyte sedimentation rate
EULAR	The European League Against Rheumatism
F	Female
FADD	FAS-associating death domain-containing protein
FASL	Fas ligand

FC	Fragment crystallizable
Fc γ R	Fragment crystallizable gamma receptor.
GFR	Glomerular filtration rate
GIT	Gastrointestinal tract
GnRH	Gonadotrophin releasing hormone
GP	Glyco-protien
gm/dl	Gram per decileter
Hb	Hemoglobin
HDLc	High density lipoprotein
HGF	Hepatic growth factor
HLA	Human leukocyte antigens
HM	Hepatomegaly
HMG-CoA	Hydroxymethylglutaryl CoA reductase
HPA	Hypothalamo-pituitary-adrenal axis
hrs	Hours
HSL	Hormone sensitive lipase
HTN	Hypertension
IC	Intra cellular
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IMPDH	Inosine monophosphate dehydrogenase
IR	Insulin receptor
IRS-1	Insulin receptor substrate-1
IVIG	Intravenous immunoglobulin
J	Jaundice
JNK	Jun N-terminal kinase.
KDa	Kilo dalton
L	Left
Lc	Lymphocyte
LDLc	Low density lipoprotein

LH	Luteinizing hormone
LLE	Lower limb edema
LN	Lupus nephritis
LT-Beta	Lymphotoxin-beta
M DC	Myeliod –derived dendritic cells.
MAPK	Mitogen-activated protein kinases
MCACs	Myelomonocytic-circulating angiogenic cells
MCs	Mesangial cells
MHC	Major histocomptability complex
MI	Myocardial infarction
MIF	Macrophage migration inhibitor factor
mm	Millimeter
mmHg	Millimeter mercury.
MMP3	Matrix metalloproteinases 3
MR	Malar rash
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messanger ribo-neuclic acid
MTRR	Methionine synthase reductase
N	Normal
NF KB	Nuclear factor kappa beta
NK s	Natural killer cells
NO	Number of patients
NS	Non significant
NSAIDS	Non steroidal anti-inflammatory drugs
p-ANCA	Perinuclear antineutrophil cytoplasmic antibody
PBMCs	Peripheral blood mononuclear cells
PCAN	Proliferating cell nuclear antigen
PCDC	Plasma cytoid dendritic cells
PD-1	Programmed cell death-1
PDL	Poorly differentiated lymphocyte
PCR	Polymerase chain reaction

PEL	Puffnes of eyelids
PGE2	Prostagalndin E2
Pg/ml	Picogram per milliliter
PHA	Phytohaemagglutinin
PLT	Platlets
PSV	Peak systolic velocity
R	Right
RBCs	Red blood count
RI	Resistivity index
RNP	Ribonucleoprotein
SBP	Systolic blood pressure
SD	Standard of deviation
Sig	Significant
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
Ss –A	Single-stranded annealing
Ss-B	Single-stranded binding
SODD	Suppressor of Death Domain
TACE	TNF- alpha converting enzymes
Temp	Temprture
TG	Triglycerides
TH	T helper cells
TIA	Transient ischemic attack
TLC	Total leukocytic count
TNFAIP3	Tumor necrosis factor alpha-induced protein 3
TNF-α	Tumor necrosis factor alpha
TRADD	TNF Receptore1-Associated Death Domain
TRAIL	TNF-related apoptosis inducing ligand
TTP	Thrombotic thrombocytopenic purpura
UTR	Untranslated regions
UV	Ultraviolet
UVB	Ultraviolet radiation B

VEGF	Vascular endothelial growth factor
VSMCs	Vascular smooth muscles
vs	Versus
WHO	World health organization
Yrs	Years

Introduction and Aim of the Work

SLE is an autoimmune disorder characterized by multisystem microvascular inflammation with the generation of autoantibodies. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease, including genetic, racial, hormonal, and environmental factors. **(Cooper et al., 1998) and (Rahman et al., 2008).**

The natural history of SLE varies from relatively benign disease to rapidly progressive and even fatal disease. SLE often waxes and wanes in affected individuals throughout life, and features of the disease vary greatly between individuals. The disease course is milder and survival rate higher among persons with isolated skin and musculoskeletal involvement than in those with renal and CNS disease, Infectious complications related to active SLE and immunosuppressive treatment are now the most common cause of death in early active SLE, and accelerated arteriosclerosis is a key cause of late mortality. **(Trager et al., 2001)**

Autopsy studies have demonstrated that the coronary and cerebral vessels of SLE patients have the usual atherosclerotic plaque, and that most cardiovascular events are not attributable to active vasculitis. However, atherosclerotic plaque development is now better understood, not all cardiovascular events are due to large obstructive plaques, Smaller plaques susceptible to plaque rupture can cause occlusive events.

In general, acute coronary syndromes are caused by acute disruption of unstable atheroma. It is believed that patients with

inflammatory disease, including SLE, are more likely to have vulnerable plaque rupture. These unstable atheromatous plaques have three histologic components: a large lipid core, many inflammatory cells, and a thin fibrous cap. It is postulated that systemic inflammation causes the fibrous cap to be thinned, with decreased smooth muscle synthesis and increased collagen breakdown. **(Haider et al., 1981)**

Tumor necrosis factor-α is a multifunctional cytokine with effects on lipid metabolism, coagulation, insulin resistance, and the function of endothelial cells lining blood vessels.

TNF was thought to be produced primarily by macrophages, but it is produced also by a broad variety of cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue,fibroblasts, and neuronal tissue. **(Bouwmeester et al., 2004)**

Large amounts of TNF-α are released in response to lipopolysaccharide, other bacterial products, and Interleukin-1 (IL-1). It has a number of actions on various organ systems, generally together with IL-1 and Interleukin-6 (IL-6). **(Bouwmeester et al., 2004)**

Aim of the work:

The aim of this study is to discuss the relation between serum TNF-α and atherosclerotic vascular disease in SLE patients. In our study we do carotid duplex for all patients to assess the carotid intima media thickness, and to detect the correlation of serum TNF-α level with SLEDAI, and other atherosclerotic risk factors in SLE patients as DM, HTN, hyperlipidemia and CRP.