Subclinical Atherosclerosis in Patients with Systemic Sclerosis

Thesis

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in Internal Medicine

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List of Contents

List of Tables

List of Tables (Cont.)

List of Figures

List of Abbreviations

ABPI	Ankle brachial pressure index
ACA	Anticentromere antibodies
ACE	Angiotensic converting enzyme
ACH	Acetyl choline
aCLs	Anticardiolipin antibodies
ACR	American college of rheumatology
ADNA	Asymmetric dimethylarginine
AECA	anti-endothelial cell antibodies
AFA	anti-fibroblast antibodies
ANA	Anti-nuclear antibody
ANCA	anti-neucleocytoplasmic antibody
Anti-FBN-١	anti-fibrillin-١ antibodies
Anti-PM-Scl	anti-polymyositis-scleroderma antibodies
Anti-RNAP	anti-RNA polymerase antibodies
anti-RNP	anti- ribonucleoprotein antibody
Anti-Scl-٧٠	anti-slceroderma-٧٠
Anti-Th/To antibodies	Antibodies to Th/To ribonucleoprotein
Anti-Topo I	anti-topoisomerase I antibody
Anti-U٣-RNP	anti-U٣-ribonucleoprotein antibodies
aOXLDL	anti-oxidised low density lipoprotein antibody
aPLS	antiphospholipid antibodies
APS	Antiphispholipid syndrome
ATP	Adenosine triphosphate
BAL	Bronchioalveolar lavage
bFGF	basic fibroblast growth factor
$BH_٢$	Dihydrobioprotein

List of Abbreviations (Cont.)

BH_4 ····· Tetrahydrobioptein
CAC ····· Coronary artery calcification
CAD ····· Coronary artery disease
CCA ····· Common carotid artery
CCL٢ ····· Chemokine (C-C motif) ligand ٢
CEC ····· Circulating endothelial cells
CFR ····· Coronary flow reserve
cGK-I ····· Cyclic GMP-dependent kianse I
cGMP ····· Cyclic guanosine monophosphate
CI ····· Confidence internal
CMV ····· Cytomegalovirus
CREST ····· Calcinosis, Raynaud's phenomenon, sclerodactyle, telangiectasia
CRP ····· C-reactive protein
CTGF ····· Connective tissue growth factor
dcSSc ····· diffuse cutaneous systemic scelrosis
DM ····· Diabetes mellitus
DOCA ····· Desozycorticosterone acetate
EBCT ····· Electron beam computed tomography
ECG ····· Electrocardiography
EDCF ····· Endothelium derived constricting factor
EDRF ····· Endothelium derived relaxing factor
ELAM ····· Endothelial leukocyte adhesion molecule
EMPs ····· Endothelial microparticles
eNOS ····· endothelial nitric oxide synthase
EPC ····· Endothelial progenitor cells
EScSG ····· European scleroderma study group

List of Abbreviations (Cont.)

ET ····· Endothelin
EUSTAR ····· Eular scleroderma trials and research
EULAR ····· European league against rheumatism
FMD ····· Flow mediated vasodilatation
GFR ····· Glomerular filtration rate
HAV ····· Hepatitis A virus
HDL ····· High density lipoproteins
HLA ····· Human leukocytic antigen
HMG-Co-A ····· Hydroxy methyl glutaryl Co-A
HRCT ····· High-resolution computed tomography
HSP ····· Heat shock protein
HSV ····· Herpes simplex virus
ICAM ····· Intracellular adhesion molecules
IFN-α ····· Interferon gamma
IGF ····· Insulin-like growth factor
IIF ····· Indirect immuneflurescence
IL ····· Interleukin
IL^{3} ····· Inositol triphosphate
ILD ····· Interstitial lung disease
IMT ····· Intima media thickness
IRAG ····· Inositol triphosphate-receptor-associated G-kinase substrate
IVIgs ····· Intravenous immunoglobulins
JRA ····· Juvenile rheumatoid arthritis
kD ····· kiloDalton
lcSSc ····· Limited cutaneous systemic sclerosis
LDL ····· Low density lipoprotein

List of Abbreviations (Cont.)

LFA ····· Lymphocyte function associated antigen
L-NAME ····· Notro-L-arginine methyl ester
L-NMMA ····· Notroglycerine monomethyl-L-arginine
Lp(a) ····· Lipoprotein (a)
MCP ····· Monocyte chemotactic protein
MMP ····· anti-extracellular matrix metalloproteinase antibodies
MRCA ····· Magnetic resonance coronary angiography
MRP ····· Mitochondrial RNA processing
MRSS ····· Modified Rodnan skin score
NAD ····· Nicotinamide dinucleotide
NADPH ····· Nicotinamide adenosine dinucleotide phosphate
NK ····· Natural killer cells
NMD ····· Nitrate mediated vasodilatation
NO ····· Nitric oxide
NOS ····· Nitric oxide synthase
NSIP ····· Nonspecific interstitial pneumonitis
NTG ····· Nitroglycerine
NVC ····· Nailfold video capillaroscopy
OxLDL ····· Oxidised low density lipoprotein
PAI-١ ····· Plasminogen activator inhibitor-١
PAT ····· Peripheral artery tonometery
PCA ····· Pulse curve analysis
PDGF ····· Platelet derived growth factor
$PGO_{٢}$ ····· Prostacyclin

List of Abbreviations (Cont.)

RA ····· Rheumatoid arthritis
rDNA ····· recombinant DNA
RF ····· Rheumatoid factor
RI ····· Reflection index
RP ····· Raynaud's phenomenon
RPS ····· Reactive oxygen species.
RVSP ····· Right ventricular systolic pressure
sGC ····· Soluble guanylate cyclase
SLE····· Systemic lupus erythematosus
SSc····· Systemic sclerosis
TGF-beta ····· Transforming growth factor-beta
TNF ····· Tumor necrosis factor
To NO ····· Toxic nitric oxide
UIP ····· Usual interstitial pneumonitis
VCAM····· Vascular cell adhesion molecules
VLDL····· Very low density lipoproteins

Introduction

Systemic sclerosis (SSc) is a generalized autoimmune inflammatory disorder of connective tissue characterized by microvascular and immunological abnormalities, as well as increased fibroblastic activity, leading to fibrosis in the skin and various internal organs ***(Andersen et al., ٢٠٠٠)*** .

In SSc, vascular involvement, particularly endothelial injury, is an early and fundamental pathogenetic step. Endothelial dysfunction, consisting in impairment of blood vessel constriction and dilation (vasomotor regulation), is followed by structural changes of arterial wall as intimal proliferation, thrombosis, and blood vessel occlusion. Vascular disease affects capillaries and arterioles, although there is an increased evidence for large-vessel involvement ***(Le Roy, ١٩٩٦).***

Early in the disease, peripheral microangiopathy maybe well recognized and studied by nailfold capillaroscopy, a non-invasive and safe technique that is reported to have both diagnostic and prognostic value also in the presence of isolated Raynaud's phenomenon (RP) ***(Von Bierbrauer et al., ١٩٩٦).***

Recently, the attention has been focused on macro-vascular disease in SSc. Morphological and functional characteristics of arteries of lower and upper limbs, carotid and coronary extramural arteries have been investigated to establish the importance and the nature of macrovascular involvement in SSc ***(Szucs et al., ٢٠٠١).***

Two theories of macrovascular disease have been hypothesized in SSc; the first is the extension of the vascular injury to

the macrovascular circulation, with an accelerated atherosclerosis in a pathogenesis similar to that of the microvascular damage ***(Fiori et al., ٢٠٠٣).***

The second theory suggests that the development and acceleration of atherosclerosis in SSc can be favored by inflammation, cytokines, lipid oxidation, and autoantibodies. SSc and atherosclerosis share similar pathologic modifications of the vessel wall ***(Matucci-Cerinic et al., ٢٠٠٣).***

Brachial artery (BA) flow-mediated vasodilation (FMD) and Carotid artery intima-media thickness (IMT) are currently used as noninvasive tests for vascular function and structure respectively, in addition to other alternative measures of subclinical atherosclerosis ***(Marwick et al., ٢٠٠١).***

Carotid IMT identifies early structural abnormalities of the vascular wall. Its increase correlates with cardiovascular risk factors, and is an independent predictor or cardiovascular and cerebrovascular events ***(Riley et al., ٢٠٠١).***

Brachial FMD measures vascular endothelial function. It also correlates with cardiovascular risk factors and it seems to have prognostic significance for vascular events ***(Mancini, ٢٠٠٤).***

Aim of the Study

The aim of this study is to assess subclinical macrovascular involvement in SSc(using non-invasive tests) and its possible pathogenesis by correlating findings with the traditional cardiovascular risk factors and with the pattern of microvascular disease (assessed by nailfold capillaroscopy).

Systemic Sclerosis

Introduction

Scleroderma is systemic disorder of the connective tissue; manifested by hardening and thickening of the skin, by abnormalities involving the microvasculature and larger vessels, and by fibrotic degenerative changes in various body organs including the heart, lungs, kidneys, and gastrointestinal ***(Charles, ٢٠٠٦).***

It is characterized by formation of hyalinized and thickened collagenous fibrous tissue, with thickening of the skin and adhesion to underlying tissues (especially of the hands and face), dysphagia due to loss of peristalsis and submucosal fibrosis of the esophagus, dyspnea due to pulmonary fibrosis, myocardial fibrosis, and renal vascular changes resembling those of malignant hypertension. Raynaud phenomenon, atrophy of the soft tissues, and osteoporosis of the distal phalanges (acrosclerosis), sometimes with gangrene at the ends of the digits, are common findings ***(Sakkas, ٢٠٠٥)***.

Historical aspect

Hippocrates first described this condition as thickened skin. **Carlo Curzio (١٧٥٢)** offered the first detailed description of this condition when a patient presented with hard skin, which he described as woodlike or containing a dry hide.

In ١٨٣٦, **Giovambattista Fantonetti** applied the term scleroderma to a patient's condition. He applied the term to describe a