Evaluation Of Endothelial Function In Patients With Behcet's Disease By Brachial Artery Doppler Ultrasonography Of Flow Mediated Vasodilatation

Thesis
Submitted for partial fulfillment of the
Master Degree in Rheumatology and Rehabilitation

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2010

ACKNOWLEDGEMENT

This work would have never been accomplished without the blessing and the help of God, to whom I am extremely grateful.

I am greatly thankful to ***Professor Dr.Soha El Desouky****, Assistant Professor of Rheumatology and Rehabilitation ,Faculty of Medicine, Cairo University; to her I wish to express my profound gratitude and sincere thanks for her patience, great help, and meticulous supervision.*

I would also like to express my gratitude and appreciation to ***Dr.Doaa Abbas****, Lecturer of Rheumatology and Rehabilitation, Faculty of Medicine, Cairo University for her help and effort.*

I extend my deepest thanks to ***Dr.Mervat Ismail****, Lecturer of Rheumatology and Rehabilitation, Faculty of Medicine, Beni Suef University for all her effort, kind advice, encouragement and brotherly support throughout this work.*

Finally I would like to express my extreme gratitude to ***Dr.Lamia Adel*** *Assistant Professor of Radiodiagnosis, Faculty of Medicine, Cairo University and to my family especially my parents, who have all been very supportive and patient with me and last but not least, all my colleagues for their help and support.*

ABSTRACT

Objective: The present study was performed to study the role of Doppler ultrasonography in the assessment of endothelial function in patients with Behcet's disease. Correlation with disease activity, clinical manifestations and laboratory investigations was performed.

Patients & Methods: Thirty Behcet's disease (BD) patients diagnosed according to the criteria published by the International Study Group for Behcet's Disease in 1990 were included in this work. The patients were subjected to the following: Full history taking and clinical examination including ophthalmic, skin examination and Doppler ultrasonography (US) of the brachial artery. Routine laboratory tests including complete blood count (CBC), erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), liver and kidney function tests and lipid profile were also done.

Body mass index was calculated and skin pathergy test was performed.

Ten healthy adults of matched age and sex served as control.

Results: The patients age ranged from 26 to 45 years with a mean of 33.1±4.9 years and their disease duration ranged from 1 to 18 years with a mean of 5.8±4.1 years and the mean age at disease onset was 27.3±5.2 years. The mean base line diameter of the brachial artery was 3.6 ± 0.8 mm and no significant difference was found between it and that of the control group ($p = 0.723$) , the mean flow mediated dilatation (FMD) in BD patients was 8.1± 6.4% and it was significantly reduced in comparison to that of the control group ($p = 0.044$).

The mean of the base line diameter in BD patients with vascular involvement was found not significantly different from those without vascular involvement or to healthy controls (p = 0.858). The FMD was significantly lower in BD patients with vascular involvement than those without any vascular involvement or to healthy controls (p = 0.007). The correlation between albumin and FMD whether non-vascular or vascular was positive and significant (r= 0.74 and 0.89 respectively).

Conclusion: We conclude that there is evidence of subclinical atherosclerosis in patients with disease and endothelial dysfunction plays an important role in both early and later stage of coronary artery disease. Endothelial dysfunction documented by brachial artery FMD is a feature of BD, and it is more prominent in patients with vascular involvement. Measurement of brachial artery flow-mediated dilation may provide a simple, reproducible and noninvasive technique to identify patients at increased risk of vascular disease.

Keywords: Behcet disease, Endothelial dysfunction, Doppler US, BDCAF and Dyslipidemia.

LIST OF ABBREVIATIONS

Abs	Antibodies
aCL	Anticardiolipin antibodies
AECA	Antiendothelial cell antibodies
ADMA	Asymmetric dimethylarginine
ALT	Alanine transaminase
ANA	Antinuclear antibodies
ANCA	Antineutrophil cytoplasmic antibodies
Anti-dsDNA	Anti double stranded DNA
APCs	Antigen presenting cells
aPL	Antiphospholipid antibodies
APS	Antiphospholipid syndrome
ARE	Arylesterase
AST	Aspartate transaminase
BD	Behcet's disease
BDAI	Behcet's disease activity index
BDCAF	Behcet's disease current activity form
β2GPI	β2Glycoprotein-I
BMI	Body mass index
C	Complement
CAD	Coronary artery disease
CBC	Complete blood count
CCA	Common carotid artery
CDS	Color doppler sonography
cGMP	Cyclic guanosine monophosphate
CIMT	Carotid artery intima media thickness
CKD	Chronic kidney disease
CNS	Central nervous system
CP	Ceruloplasmin
CPK	Creatinine Phosphokinase
CRP	C-reactive protein
CS-A	Cyclosporin-A
CSF	Cerebrospinal Fluid
CT	Computerized tomography
CTS	Carpal tunnel syndrome
CVD	Cardiovascular disease
DIP	Distal interphalangeal

DVT	Deep venous thrombosis
ECA	External carotid artery
ECD	Endothelial cell dysfunction
ECG	Electrocardiogram
eNOS	Nitric oxide synthase
ESR	Erythrocyte sedimentation rate
FMF	Familial mediterranean fever
G-CSF	Granulocyte - Colony -Stimulating Factor
GFR	Glomerular filtration rate
GIT	Gastro intestinal tract
GM-CSF	Granulocyte - Macrophage Colony -Stimulating Factor
Hb	Haemoglobin
HDL	High density lipoprotein
HLA	Human leucocytic antigen
H_2O_2	Hydrogen peroxide
HSP	Heat shock protein
HSV	Herpes simplex virus
ICA	Internal carotid artery
ICAM-1	Inter-cellular adhesion molecule-1
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IMT	Intima media thickness
ISG criteria	International study group criteria
IV	Intravenous
IVC	Inferior vena cava
kHZ	Kilohertz
LACI	Lipoprotein associated coagulation inhibitor
LDL	Low density lipoprotein
LOOHs	Lipid hydroperoxides
Lp(a)	Lipoprotein (a)
LPO	Lipid peroxidation
MAGIC syndrome	Mouth and genital ulcers with inflamed cartilage
MCP	Metacarpophalangeal
MCP-1	Monocyte chemoattractant protein-1
MHC	Major histocompatibility complex
MHz	Megahertz
MI	Myocardial infarction

MICA	Major histocompatibility complex class I chain-related gene A
MNC	Mononuclear cell
MRI	Magnetic resonance imaging
MSUS	Musculoskeletal ultrasonography
MTP	Metatarsophalangeal
MTX	Methotrexate
MUS	Medical ultrasonography
NK cells	Natural killer cells
NO	Nitric oxide
NSAID	Non steroidal anti-inflammatory drugs
$O2^{\bullet-}$	Superoxide radical
OA	Osteoarthritis
$OH^{\bullet}$	Hydroxyl radical
oxLDL	Oxidized low-density lipoprotein
PAI-1	Plasminogen activator inhibitor-1
PC	Prothrombin concentration
PCR	Polymerase chain reaction
PDS	Power doppler sonography
PDUS	Power doppler ultrasonography
PGI2	Prostacyclin
PIP	Proximal interphalangeal
PON	Paraoxonase
PsA	Psoriatic arthritis
PSVs	Primary systemic vasculitides
PT	Prothrombin time
PW Doppler	Pulsed wave doppler
RA	Rheumatoid arthritis
RBCs	Red blood cells/ corpuscles
RHD	Rheumatic heart disease
RF	Rheumatoid factor
RNP	Ribonuclear protein
ROS	Reactive oxygen species
ROU	Recurrent oral ulcers
SH	Free sulphydryl
sIL-2R	Soluble IL-2 receptors
Sip1 C-ter	Carboxy-terminal subunit of Sip1
SLE	Systemic lupus erythematosis
SMI	Silent myocardial infarction
SMRs	Standardized mortality ratios

SPECT	Single proton emission computed tomography
SPT	Skin pathergy test
SSc	Systemic sclerosis
SVC	Superior vena cava
TACE	TNF-α-converting enzyme
TAP genes	Type IV Aeromonas pilus genes
Tc-99	Technicium-99
TFPI	Tissue factor pathway inhibitor
Th/ T_H cells.	T helper cells
TNF	Tumor necrosis factor
TNF-R	Tumor necrosis factor-receptor
t-PA	Tissue plasminogen activator
US	Ultrasonography
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
VLDL	Very low density lipoprotein
WBC	White blood cells
WG	Wegener granulomatosis
wk	Week

Contents

List of Tables

List of Appendixes

تقييم وظيفة بطانة الاوعيه الدمويه فى مرضى متلازمة بهجت بقياس التمدد الناتج عن تدفق الدم بالشريان العضدى بواسطة جهـــاز الدوبـــلر

رســـــــالـــه

توطئة للحصول على درجة الماجستير فى الروماتيزم والتاهيل

مقدمه من الطـــبيب

حسام معروف فتحى

بكالوريوس الباطنة والجراحة

تحـــــت اشـــــراف

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INTRODUCTION

Behcet's disease (BD) is a multisystem disease characterized by variable clinical manifestations. Almost all patients have recurrent oral aphthae, followed in frequency by genital ulcers, variable skin lesions, arthritis, uveitis, thrombophlebitis, gastrointestinal and central nervous system involvement **(Yurdakul et al., 2008).**

It is usually recognized as an unclassified vasculitis, involving both veins and arteries of all sizes with a tendency towards thrombotic events **(Kosar et al., 2005).** BD, together with systemic lupus and Buerger's disease, is one of the few vasculitides that can involve the venous side of the circulatory system along with the arterial side. Furthermore, in contrast to the other two, it can involve the vena cavae **(Yazici et al., 2004).**

Venous thrombosis is often an early and characteristic feature of BD. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, dural sinus thrombosis, and other venous obstructive lesions can occur in addition to the more common superficial and deep vein thrombosis. Recurrent thrombosis of the lower extremities may lead to a post-thrombophlebitic syndrome **(Seyahi et al., 2007).**

Endothelial activation in affected blood vessels has been proposed as a mediator of vascular inflammation as well as thrombosis in Behcet's disease **(Lee et al ., 2006).**

Immune-mediated vascular injury with increased expression of proinflammatory and T-helper type 1 (Th 1) cytokines, adhesion molecules and free oxygen radicals has been suggested as the main pathology underlying the endothelial dysfunction. However, none of the endothelial findings were shown to be different between BD patients with and without overt vascular involvement **(Espinosa et al ., 2002).**

Patients with Behcet's disease have increased intima-media thickness and decreased arterial distensibility compared to other normal people **(Alan et al ., 2004).**

Under basal conditions, the endothelium functions to maintain the vessel in a relatively dilated state. However, the endothelium has the capacity to respond to various physical stimuli, such as shear stress. Blood vessels dilate in response to shear stress, a process called flow-mediated vasodilation "FMD" **(Davignon et al ., 2004).**

Measurement of FMD is a clinical method for evaluating endothelial function. Brachial artery doppler ultrasonography during reactive hyperemia is a tool for quantifying endothelium-dependent vasomotion and establishing the presence of endothelial dysfunction impaired vasomotion **(Roman et al ., 2006)**.

There is some evidence that endothelial dysfunction on brachial artery doppler ultrasonography may correlate with endothelial dysfunction noted on coronary angiography after acetylcholine injection **(Halcox et al ., 2007).**