SOLUBLE INTERCELLULAR ADHESION MOLECULE-1 (sICAM-1) IN PATIENTS WITH RHEUMATOID ARTHRITIS

Thesis

Submitted for partial fulfillment of Master Degree in Clinical and Chemical Pathology

By

Afaf Abd- El-Aleem Mostafa

Under the supervision of

Prof. Dr. Haggar Ismail Abou Gabal

Professor of Clinical Pathology

Faculty of Medicine

Ain Shams University

Dr. Aisha Yassin Abd- El- Ghaffar

Lecturer of Clinical Pathology

Faculty of Medicine

Ain Shams University

Dr. Nahla M. Zakaria Yousef

Lecturer of Clinical Pathology

Faculty of Medicine

Ain Shams University

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

1995

بسم الله الرحمن الرحيم

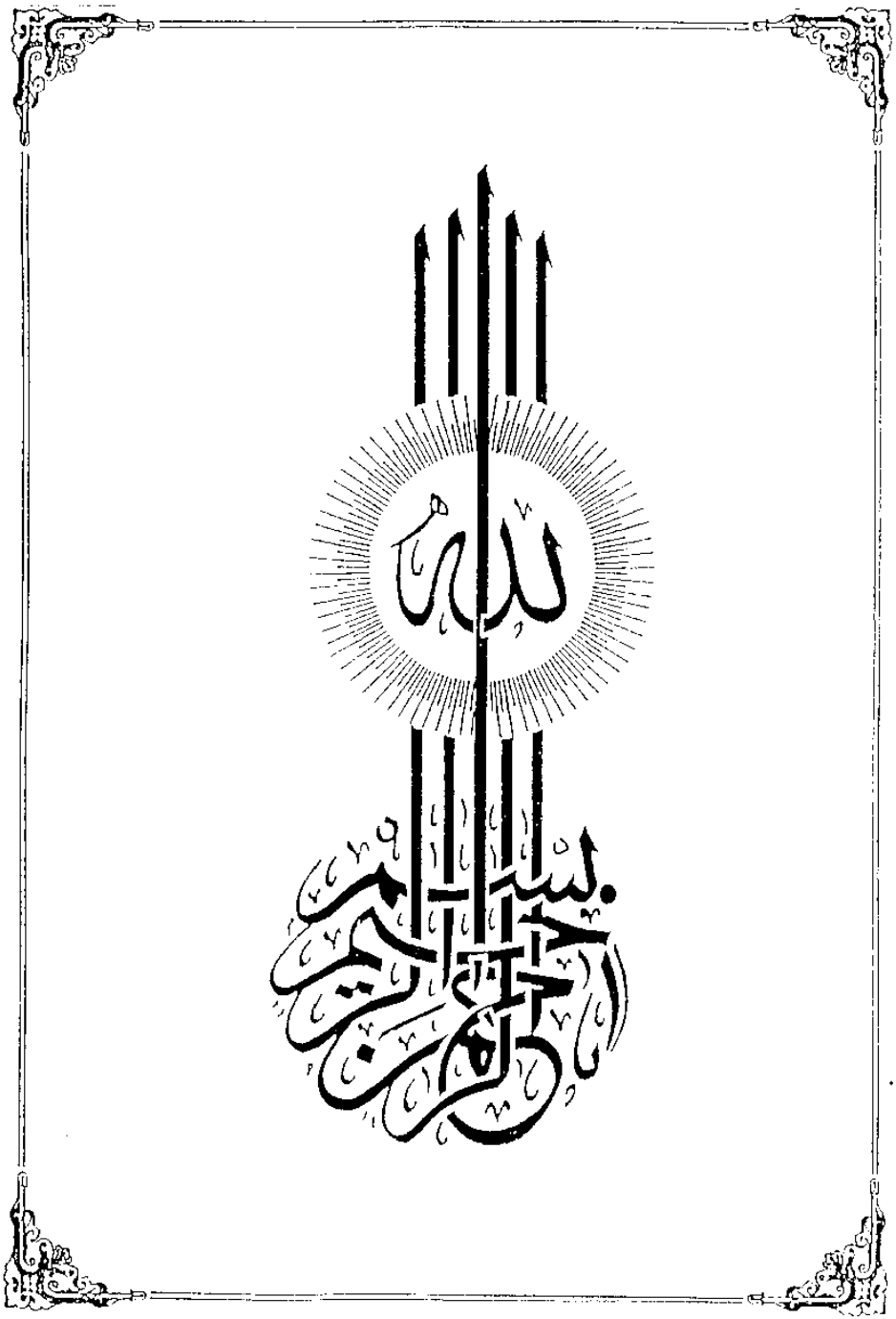
اقرأ باسم ربك الذي خلق

خلق الإنسان من علق

اقرأ وربك الأكرم الذي علم بالقلم

علم الإنسان ما لم يعلم

العلق ١-٥



ACKNOWLEDGEMENT

First of all, thanks to **GOD**.

I wish to express my thanks and gratitude to **Prof. Dr. HAGGAR ISMAIL ABOU GABAL,** *Professor of Clinical Pathology, Ain Shams University, for her constructive criticism, valuable comments and kind advice.*

My deepest thanks and special regards are due to **Dr. AISHA YASSIN ABD EL-GHAFFAR,** *Lecturer of Clinical Pathology, Ain Shams University, for her generous help and continuous encouragement. She provided me with invaluable comments and enthusiastically revised the thesis.*

I am profoundly grateful to **Dr. NAHLA M. ZAKARIA YOUSEF,** *Lecturer of Clinical Pathology, Ain Shams University, for her devotion, all the time and effort she sacrified and the valuable friendship she offered me in order to start and complete this work.*

Last, but not least, no words could even express my deepest gratitude to **my evergiving family** *and* **my husband.** *Their favour is unforgettable.*

LIST OF ABBREVIATIONS

APCs:	Antigen presenting cells.
bFGF:	Basic fibroblast growth factor.
CBC:	Complete blood count.
CD:	Cluster of differentiation.
cDNA:	Cloned deoxyribonucleic acid.
cICAM:	Circulating intercellular adhesion molecule.
cVCAM:	Circulating vascular cell adhesion molecule.
CRP:	C-reactive protein.
CYA:	Cyclosporin A.
DIC:	Disseminated intravascular coagulopathy.
DNA:	Deoxyribonucleic acid .
EGF:	Epithelial growth factor.
ELAM:	Endothelial leucocyte adhesion molecule.
ESR:	Erythrocyte sedimentation rate.
FACS:	Fluorescence activated cell sorter.
GM-CSF:	Granulocyte monocyte-colony stimulating factor.
GMP:	Granule membrane protein.
gp:	Glycoprotein.
GPI:	Glycophospho-inositol.
HEV:	High endothelial venule.
HLA:	Human leucocyte antigen
HRP:	Horseradish peroxidase.

ICAM:	Intercellular adhesion molecule.
IFN-gamma:	Interferon-gamma.
Ig:	Immunoglobulin.
IL-1:	Interleukin-1.
LAD:	Leucocyte adhesion deficiency.
LAM:	Leucocyte adhesion molecule.
LECAM:	Lectin adhesion molecule.
LFA:	Lymphocyte function associated antigen.
LPS:	Lipopolysaccharide.
mAb:	Monoclonal antibody.
MHC:	Major histocompatibility complex.
mRNA:	Messenger ribonucleic acid.
NCAM:	Neural cell adhesion molecule.
NK:	Natural killer.
NSAIDs:	Non steroidal anti-inflammatory drugs.
P150/95:	Protein 150/95.
PADGEM:	Platelet activation dependent granule to external membrane.
PMA:	Phorbol myrisate acetate.
RA:	Rheumatoid arthritis.
RF:	Rheumatoid factor.
RGD:	Arginine-glycine-aspartate.
RNA:	Ribonucleic acid.

sICAM:	Soluble intercellular adhesion molecule.
SLE:	Systemic lupus erythematosus
TCR:	T cell receptor.
TMB:	Tetramethyl benzidine.
TNF:	Tumour necrosis factor.
VCAM:	Vascular cell adhesion molecule.
VLA:	Very late activation molecule.

TABLE OF CONTENTS

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION AND AIM OF THE WORK

Introduction:

ICAM-1 (intercellular adhesion molecule-1), a member of immunoglobulin (Ig) supergene family with a five domain structure (an 80-110 KD glycoprotein) has recently been characterized as one of the natural ligands to LFA-1 (lymphocyte function associated antigen-1) molecule, which is an alpha/beta heterodimer expressed on all leucocytes (Dustin et al., 1988).

ICAM-1 shows a limited range of tissue expression, and most epithelial cells are ICAM-1 negative under normal conditions, but its expression is upregulated by inflammatory cytokines such as interleukin-1 (IL-1) and interferon-gamma (IFN-gamma) (Smith et al., 1990).

ICAM-1 plays an important role in many inflammatory diseases (Greve et al., 1989) and has been identified as the cellular receptor for a subgroup of rhinoviruses. It also participates in T-cell infiltration and accumulation within the thyroid gland in autoimmune thyroid disease (Marlin et al., 1990).

In rheumatoid arthritis (RA), it has been reported that ICAM-1 is expressed on macrophage-like synovial cells,synovial fibroblasts, as well as tissue macrophages and vessel endothelium within the inflammatory synovial microenvironment (Aoki et al., 1993). Recently, Iigo et al., (1991) have clearly shown that ICAM-1 is involved in the pathogenesis of adjuvant arthritis in rats, since the in-vivo administration of anti-ICAM-1 antibody exerted a very strong suppressive effect on the development of arthritis.

With the availability of relatively simple and sensitive detection methods, it has been possible to measure ICAM-1 in its soluble form (sICAM-1) in cell-free fluids such as culture supernatants or body fluids. Recent reports have suggested a possible diagnostic use of soluble circulating ICAM-1 in the assessment of disease activity in systemic lupus erythematosus (SLE) and allograft rejection. Thus, it has been suggested that the determination of circulating ICAM-1 (cICAM-1) may be of clinical significance in the assessment of disease activity and of the clinical course of inflammatory processes (Machold et al., 1993).

Aim of the Work:

This work aims at measuring sICAM-1 levels among Egyptian RA patients and to determine its possible role in the assessment of the clinical status and inflammatory activity of the disease.

REVIEW OF LITERATURE

INTERCELLULAR ADHESION MOLECULES

Introduction:

At present, there are 78 "cluster of differentiation" (CD) molecules on the surface of cells of the hemopoietic system, defined by monoclonal antibodies (mAbs) and clarified in four International Leucocyte Workshops (Knapp et al., 1989). Some of those mediate adhesion. Thus, the term adhesion molecules refers to those cell surface structures that directly play a decisive mechanical role in the bringing of a cell to its environment, allowing direct cell-cell interaction (Fig. 1). Moreover, cellular adhesion also plays a central role in many biologic processes such as morphogenesis and cell migration. It now appears likely that interaction between endotheliur and circulating leucocytes involves a number of different pairs of these molecules. Structurally, these molecules often traverse the cell membrane and are linked to the cytoskeleton, so that the cell can use them to gain traction on other cells or on the extracellular matrix as it moves (Roitt et al., 1993).

Cellular adhesion in man is mediated via multiple molecular pathways which involve specific intermolecular events. These pathways are made of multimolecular complexes, and each pathway may strongly influence the affinity of

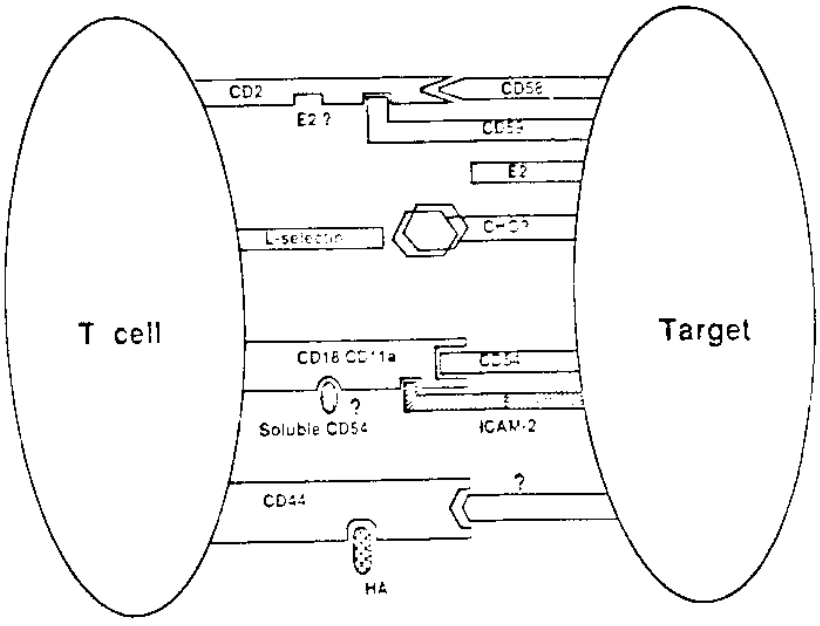


Fig. (1): Schematic, simplified model of the multiple adhesion/signalling molecules involved in T cell/target interactions.

HA: hyaluronic acid; CHO: carbohydrate; ?: uncertain site or molecule of interaction. These interactions are bidirectional.

(Quoted from Makgoba and Bernard, 1993)