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STUDY OF THROMBOMODULIN LEVEL IN RHEUMATOID ARTHRITIS PATIENTS.

Thesis

Submitted to the Faculty of Medicine,

University of Alexandria,

In partial fulfillment of the requirements of the degree of

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By

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Contents

Abbreviations

APC : Activated protein C.

ARDS : Adult respiratory distress syndrome.

ARA : American Rheumatism Association.

CRP : C – reactive protein.

DM : Diabetes mellitus.

DIC : Disseminated intravascular coagulation.

EC : Endothelial cell.

ELISA : Enzyme Linked Immunosorbent Assay.

EGF : Epidermal growth factor.

ESR : Erythrocyte sedimentation rate.

EDTA : Ethylene diamine tetra-acetic acid.

HRP : Horseradish peroxidase.

IFN γ : Gamma interferon.

LDL : Low density lipoprotein.

MHC : Major histocompatibility complex.

PMA : Phorbol myristate acetate.

RA : Rheumatoid Arthritis.

RD : Rheumatoid disease.

RF : Rheumatoid factor.

RW : Rose – Waaler.

SDS : Sodium dodecyl sulfate.

SLE : Systemic lupus erythematosus.

TM : Thrombomodulin.

TNF : Tumour necrosis factor.

INTRODUCTION

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RHEUMATOID DISEASE

Definition:

Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease primarily manifested by inflammatory arthritis of peripheral joints usually in a symmetrical distribution and characterized by non-suppurative joint changes with systemic manifestations which include haematological, pulmonary, neurological and cardiovascular abnormalities [1,2].

Etiology:

Rheumatoid disease (RD) is a disease of unknown, possibly complex etiology. The disease can be attributed to one of the following causes:

1. Infection:

The inflammatory features and constitutional manifestations of the disease, synovitis, granulomatous lesions, fever, tachycardia, leucocytosis, lymphadenopathy and elevated sedimentation rate; are all facts which made infection is reasonable cause for the pathogenesis of rheumatoid disease [3]. Some viruses e.g rubella can produce an inflammatory polyarthritis following either clinical

infection or immunization. Epstein-Barr virus, parvovirus and mycoplasma species have all been considered as candidates.

It should be pointed out that failure to culture an organism from a joint does not exclude its involvement in rheumatoid disease. It has become increasingly clear that dead whole bacteria, cell wall, toxins, and other components of micro-organisms have the capacity to include chronic inflammatory joint disease. For example, cell wall peptidoglycans from many bacteria induce severe, chronic and destructive arthritis resembling RD in genetically prone experimental animals [4].

2. Autoimmunity

The identification and characterization of rheumatoid factor (RF) as an autoantibody was the first direct evidence antoimmunity might play a role in RA. More recent paradigms of RA posit that cellular immune process predominate while RFs amplify rheumatoid synovitis through activation of complement and formation of immune complexes that are ingested by neutrophils in synovial fluid. This acute inflammatory response can ultimately recruit additional cells to the joint. Some patients who are seronegative but otherwise have a clinical diagnosis consistent with RA have "hidden" rheumatoid factors in their 19S or 7S serum fractions and these can be identified by antibody specific for the major rheumatoid factor cross-reactive idiotype [5].

It is often assumed that the initiation phase of the disease is marked by localization of an arthrotropic agent in the joint followed by antigen presentation and specific T cell activation. Stimulated T cells would subsequently generate a panoply of cytokines, including IFN γ (Gamma Interferon) that activate macrophages, other T cells, B cells (which produce rheumatoid factor), and endothelial cells. Activation of the vascular endothelium by cytokines includes adhesion molecules and recruits new cells that express the appropriate counterreceptors into the joint. The accumulation of T cells would ultimately result from nonspecific infiltration of the synovium with cells from the blood as well as local proliferation of lymphocytes in the synovium that recognize their specific antigen in the context of MHC/molecules (major histocompatibility).

3. Heredity:

Rheumatoid factor titres were found to be higher in relatives of rheumatoid patients than relatives of controls, but heredity has not yet been settled in the pathogenesis of rheumatoid disease [6,7].

4. Environmental Factors:

Environmental factors that lead to altered emotional, nutritional or physical state may also contribute to the inception of rheumatoid disease [8].

Pathogenesis of Rheumatoid Disease

Approximately 70% of patients with rheumatoid arthritis carry the HLA-DR_4 haplotype. This haplotype has several different variants that determine both susceptibility to and severity of the disease [9] .

On the primary stimulus; synovial lymphocytes produce IgG, monomeric IgM, and pentameric IgM anti-immunoglobulins (rheumatoid factors). The presence of IgG aggregates or IgG – rheumatoid factor complexes activate the complement system and lead to a number of inflammatory phenomena, including histamine release, the production of chemotactic factors for polymorphonuclear neutrophils (PMN) and mononuclear cells, and membrane damage with cell lysis. Prostaglandins and leukotrienes produced by inflammatory cells, and lysosomal enzymes released into the synovial space by leukocytes further amplify the inflammatory and proliferative response of the synovium. The mononuclear cellular infiltrate characteristically seen within the synovium includes perivascular collections of CD_4 cells and interstitial collections of CD_8 cells, B lymphocytes, lymphoblasts, plasma cells, and macrophages. The immunologic interaction of these cells leads to the liberation of cytokines responsible for the accumulation of macrophages within the inflammatory synovium. The various inflammatory cells in the joint produce proteinases and collagenases that damage cartilage and articular supporting structures.