INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown cause that primarily affects the peripheral joints in a symmetrical pattern. Constitutional symptoms including fatigue, malaise and morning stiffness are common. Extra articular involvement of organs such as the skin, heart lungs and eyes can be significant *(Howard et al., 2006)*.

RA causes joint destruction and thus often leads to considerable morbidity and mortality; furthermore, it was found that the increased mortality is predominantly due to accelerated coronary artery and cerebrovascular atherosclerosis *(Kaplan et al., 2006)*.

The increased risk of cardiovascular (CV) disease in particular with RA is due to a number of different triggers including traditional and disease related factors. Persistent inflammation and immune dysregulation of RA may contribute to favor other well known CV risk factors such as dyslipidemia. It is now clear that the disease itself represents an independent risk factor for CV disease by the action of RA chronic inflammatory process as well as humoral and cell mediated immune mechanisms. Additionally it was found that CV risk is associated with severity and

extension of the disease and it is of interest the fact that the presence of circulating anticyclic citrullinated peptide antibodies appears to be associated with stronger evidence of subclinical atherosclerosis in RA. *(Gerli et al., 2007)*.

The association between connective tissue disease and thyroid disease is well recognized *(Jara et al., 2007)*.

Thyroid dysfunction is seen at least three times more often in women with RA than in women with similar demographic features with non inflammatory rheumatic diseases such as osteoarthritis and fibromyalgia *(Shiroky et al., 1993)*.

Clinical hypothyroidism was observed three times more often in female RA patients than males in the general population. In female RA patients, clinical hypothyroidism was associated with a fourfold higher risk of CVD in comparison with female euthyroid RA patients independently of the traditional risk factors. *(Raterman et al., 2008)*.

AIM OF THE WORK

Our objective is to determine the prevalence of thyroid disorders in RA patients and to study the risk of CVD in RA patients with hypothyroid abnormalities.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (**RA**) is a chronic systemic inflammatory disease that may affect many tissues and organs, but principally attacks the joints in a symmetric pattern producing an inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. It is a chronic disabling disease with considerable impact on patient's lives, on their families and on society as whole *(Majithia, 2007).*

In most cases, rheumatoid arthritis is a chronic progressive disease that, if left untreated, can cause joint damage and disability. Physical findings are most notable for joint swelling, deformities and painful or reduced joint motion. Extra-articular disease occurs in seropositive patients and includes rheumatoid nodules, Sjögren's syndrome, interstitial lung disease, and vasculitis *(Christopher et al., 2008).*

Epidemiology:

The annual incidence of RA has been reported to be around 20 and 50 cases per 100.000 inhabitants in North American and North European countries. The disease prevalence is about 1 percent in Caucasians,

but varies between 0.1 percent (in rural Africans) and 5 percent (in Pima and Indian) *(Soderlin et al., 2002).*

The prevalence of RA in rural Egypt is 0.29%, similar to other oriental rural populations, but lower than Western populations *(Abdel-Tawab et al., 2004).*

RA can occur at any age, but the incidence increases with age; the peak onset is between the fifth and six decades and women are affected two to three times as often as men. High standardized mortality rates have been observed in the RA population compared with the general population *(Doran et al., 2002).*

Etiology:

1- Gender specific factors:

RA is predominates in women more than in men at a ratio of 3:1, perhaps due in part to the stimulatory effects of estrogen on the immune system. Estrogen inhibits T-suppressor cell function and enhances T helper cell function. In addition, estrogen receptors are present on synovial cells and memory T cells, and a receptor polymorphism has been associated with the disease *(Takagi et al., 2000).*

Pregnancy is usually associated with remission of the disease in the last trimester, and improvement

starts in the first or second trimester. The mechanism of protection is not defined but might be due to the expression of suppressive cytokines such as IL-10 during pregnancy or alterations in cell-mediated immunity. The risk of RA may be reduced by breast feeding for one year or more *(Karlson et al., 2004)*.

Male sex also appears to affect disease phenotype. Compared with female RA patients, male patients have significantly later disease onset, are more likely to be RF-positive, and have higher titers of anti-CCP antibodies *(Jawaheer et al., 2006)*.

2- Genetic factors:

It has been estimated that genetic factors contribute from 53 to 65 percent of the risk of developing RA. Twin and sibling studies illustrated that the concordance rate is markedly higher for monozygotic twins compared with dizygotic twins (12% to 15% versus 3.5 %, respectively). In addition, the risk of developing RA in first-degree relative of a rheumatoid patient is more than 1.5 higher than general population *(Macgregor et al., 2000)*.

HLA and non-HLA susceptibility genes:

The most potent genetic risk for RA is conveyed by HLA (Human Leukocytic Antigen) alleles. Increased prevalence of RA was reported to be associated with a subset of DR4 alleles in most western European populations or a subset of DR1 alleles in other population *(Jean-Marc and Firestein, 2008)*.

The firmest link between a genetic susceptibility factor and RA is the association of the disease with an epitope in the third hypervariable region of the HLA-DR ß-chains, known as the "shared epitope". Individuals with the sequence leu-glu- lys-arg-ala (OKRAA) in residues 67, 70, 71, 72, and 74 have a much higher incidence and prevalence of RA than those who do not have this epitope *(de Vries et al., 2002)*.

Other genetic polymorphisms:

Microsatellites and single nucleotide polymorphisms are being studied extensively in RA. An increased risk of RA with single nucleotide polymorphism of the protein tyrosine phosphatase N22 (PTPN22) gene that encodes a phosphatase involved in intracellular T cell signaling has been confirmed in several different populations. The same PTPN22 polymorphism may also increase the rate of progression of RA *(Lie et al., 2007)*.

3- Infectious Agents:

Many viruses and bacteria have been implicated as causative agents. These include the Epestien-Barr virus, parvo virus, lenti viruses and bacterial organisms such as Mycoplasm, Mycobacteria and Yersinia *(Buch and Emery, 2002)*.

A significant effort has been devoted to evaluate a possible association between Epstein Barr Virus (EBV) and RA. EBV is a polyclonal activator of B lymphocytes and increase production of RF. Patients with RA may have an increased EBV viral load with an increased humoral and cellular immune response to EBV antigens that contain the QKRAA sequence, which is the same sequence found in the shared epitope (*Jean-Marc and Firestein, 2008)*.

Considerable attention has been directed at apotential role for mycoplasma and chlamydia in arthritis. Mycoplasma derived superantigens can directly induce T cell independent cytokine production by macrophages and can exacerbate or trigger arthritis in mice immunized with type II collagen *(Cole and Griffiths, 1993)*.

4- Superantigen and heat shock proteins:

Superantigens can activate multiple clones of T cells (1 in 10 cells) through a largely MHC independent process. Examples of superantigens are the staphylococcal endotoxins and heat shock proteins (HSPs). HSPs are intracellular proteins induced by environmental insults, including heat, infectious agents, and oxidative injury, and are remarkably conserved across species *(Eduard et al., 2008)*.

The most logical hypothesis implicating HSPs as causative in RA is that these proteins share antigenic determinant with other host proteins, thereby resulting in the development of crossreacting antibodies that could induce an autoimmune response (ie, molecular mimicry). As an example, two proteins that possess the shared epitope (QKRAA) on DRß1*0401 are EBV gp110 and Escherichia coli DnaJ. The latter molecule is a heat shock protein and strongly antigenic. Specific antibodies against DnaJ crossreact with DRß1*0401 (Dw4) cells, but not those expressing other alleles *(Albani et al., 1995)*.

5- Smoking:

Cigarette smoking is a strong risk factor for the development of RA, particularly in individuals with the

shared epitope. Women who smoked at least 25 cigarettes a day for more than 20 years had a relative risk of 1.4 for developing RA compared to those who had never smoked *(Karlson et al., 1999)*.

In addition to increasing disease susceptibility, cigarette smoking may also be a risk factor for greater disease severity. Compared with those who had never smoked, patients with a 25 or more pack-year smoking history are more likely to be seropositive, have nodules, or have radiographically apparent erosions *(Wolfe et al., 2000)*.

Pathogenesis of rheumatoid arthritis:

The pathogenesis of RA remains poorly understood. It is widely accepted that the development of the disease requires an orchesterated series of both autoimmune and inflammatory processes, as well as acomplex interplay between different cell types *(Aidinis et al., 2003)*.

Activated CD4+T cells stimulate B cells to produce immunoglobulins, including rheumatoid factor (RF). Activated CD4+T cells express osteoprotegerin ligands that stimulate osteoclastogenesis. The activated macrophage, lymphocytes, and fibroblast, as well as their products, stimulate angiogenesis, which may explain the increased vascularity found in the synovium of RA patients *(Choy and Panayi, 2001)*.

T lymphocytes:

The activation of T cells by as yet unknown antigens in the immunogenetically susceptible host is most probably the event that initiates the rheumatoid process. Activation of T lymphocytes requires two signals from antigen presenting cells. The first signal, the binding of the T cell receptor to its antigen major histocompatiblity complex ligand, provides specificity of antigen. The second signal is mediated by costimulatory molecules, of which family of proteins called B7 appears to be the most potent. The B7 costimulatory pathway involves at least two molecules, B7-1 (CD80) and B7-2 (CD86), on antigen presenting cells, both of which can interact with their counter-receptors, CD28 and Cytotoxic T lymphocyte associated antigen 4 (CTLA-4), on T cells *(Reveille, 1998)*.

The interaction of the CD28 receptor on the lymphocyte with receptors of the B7 family on the antigen presenting cell is one of the most important of this costimulatory pathways. This signal induces T cell activation and clonal expansion and inhibits T cell apoptpsis. Activation of the T cell receptor without costimulation of the CD28 receptor does not induce activation but instead induces anergy or cell death *(Linsley and Ledbetter, 1993).*

Cytotxic T lymphocyte associated antigen 4 (CTLA4) is expressed on the surface of T cell hours or days after they become activated. CTAL4Ig binds both CD80 and CD86 on antigen presenting cells, thereby preventing these molecules from engaging CD28 on T cells. By blocking the engagement of CD28, CTLA4Ig prevents the delivery of the second costimulatory signal that is required for optimal activation of T cells. Blocking the second signal is a novel therapeutic concept *(Kremer et al., 2003).*

B lymphocytes and autoantibodies:

B lymphocytes play several critical roles in the pathogenesis of rheumatoid arthritis. They are the source of the rheumatoid factors and anticitrullinated protein antibodies, which contribute to immune complex formation and complement activation in the joints. B cells are also very efficient antigen presenting cells, and can contribute to T cell activation through expression of costimulatory molecules. B cells both respond to and produce the chemokines and cytokines that promote leukocyte infiltration into the joints, formation of ectopic lymphoid structures, angiogenesis, and synovial hyperplasia *(Gregg and Dennis, 2003).*

Rheumatoid factors (RF) are autoantibody directed against Fc portion of IgG, IgG and IgM RFs

are found in up to 90% of RA patients. Testing for IgM RF is about 70% sensitive and 80%specific for RA. However, this autoantibody can also be produced during chronic infection, Malignancy, and in a variety of inflamatory and autoimmune syndromes *(Jean-Marc and Firestein, 2008).*

Compared to those with "seronegative" RA, seropositive patients with polyarticular symmetrical arthritis are likely to have more erosion of bones and joints, more extra-articular manifestations, and worse function *(Van Zeben et al., 1992).*

Anti-citrullinated protein antibodies (ACPAs) are highly specific for RA. Citrulline is formed by the action of peptidylarginine deiminases (PADIs) on peptidylarginine. PADIs are expressed at high levels in inflamed rheumatoid synovium; one major substrate appears to be fibrin. The immunoreactivity of citrullinated fibrin with IgA and IgM in the RA synovium and the co-localization of PADI and citrullinated peptides supports the nation that citrullinated fibrin is a potential autoantigen of RA *(Chang et al., 2005).*

The most common tests for anti-citrullinated protein antibodies (ACPAs) are the anti-CCP (cyclic citrullinated peptide) test and the Anti-MCV assay

(antibodies against mutated citrullinated Vimentin). Recently a serological point-of-care test (POCT) for the early detection of RA has been developed. This assay combines the detection of rheumatoid factor and anti-MCV for diagnosis of rheumatoid arthritis and shows a sensitivity of 72% and specificity of 99.7% *(Luime et al., 2010).*

Anti-CCP antibody is present in the earliest stages of disease in almost 70 % of rheumatoid patients. RA patients positive for anti-CCP develop significantly more radiological damage than anti-CCP negative patients and are associated with severe extra-articular manifestation *(Visser et al., 2002).*

Anti-MCV is used as efficient biomarker for estimating progress of rheumatoid arthritis. Main advantage of testing for anti-MCV is the early appearance of the anti-MCV antibodies, what allows for detection of early RA and submits adequate therapy just after the disease's onset. Moreover, anti-MCV titres show strong correlation to disease activity, disease severity and the success of therapy *(Roland et al., 2008).*

Other cell types:

Lee et al. (2002) demonstrated a key role of mast cells in mediating the erosive and inflamatory events leading to joint destruction in RA. The activation of mast cells by complement, autoantibodies, and cytokines leads to the release of granule contents such as histamine, heparin, and proteinases, as well as cytoplasmic products such as cytokines and leukotriens which Activate chondrocytes, synovial fibroblasts, and macrophages to produce metalloproteinases, cytokines and prostaglandins that all contribute to joint destruction.