Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disease characterized by chronic erosive arthritis that mainly involves peripheral joints the with average prevalence of 0.5–1% in developed population ***(Gabriel et al., 2009)*** and of 0.3–0.5% in developing countries ***(Osiri et al., 2010).***

RA affects activities of daily living, significantly decreasing the quality of life of affected patients. Comorbidity is a major issue in this disorder ***(Scott et al., 2010).***

Cardiovascular (CV) disease has been described as the main cause of premature mortality and sudden death in patients with RA ***(Wolfef et al., 2003 and Libby 2008).*** It is the result of a process of accelerated atherosclerosis ***(Gonzalez-Gay et al., 2005 and Shoenfeldy et al., 2005)*** patients with RA are at a 50% increased risk of CV mortality compared with the general population ***(Avina-Zubieta et al., 2008).***

Traditional CV risk factors such as smoking, diabetes mellitus, hypertension, dyslipidemia and obesity are independently associated with the development of CV disease ***(Dessein et al., 2005 and Gonzalez et al., 2008).***

Chronic inflammation also appears to play an important role in the development of subclinical atherosclerosis and CV events in patients with RA ***(Dessein et al., 2007, Gerli et al., 2007 and Gonzales-Gay et al., 2007)*** even patients with early RA show evidence of increased subclinical atherosclerosis ***(Hannawi et al., 2007)***, as assessed by carotid plaque, carotid intima media thickness and coronary calcification ***(Roman et al., 2007).***

Another contributing factor was altered endothelial reactivity as shown in the study of ***(Vaudo et al., 2004)*** that young to middle-aged RA patients with low disease activity and free from traditional CV risk factors and overt CVD have altered endothelial reactivity**.**

Adequate CV risk stratification has special relevance in RA to identify patients at risk of CV disease. However, current CV risk screening and management strategies underestimate the actual CV risk in RA ***(Crowson et al., 2011).*** Consequently, the search of markers that may help to identify RA patients at high CV risk has become a priority in the last years ***(Gonzalez-Gay et al., 2012).*** Non-invasive, reproducible and cheap clinical surrogates, such as carotid ultrasonography, have been found to

be excellent predictors of future CV events ***(Gonzalez-Juanatey et al., 2009 and Evans et al., 2011).***

Women with RA were found to have more than 2-fold higher risk of developing myocardial infarction compared with women without this pathology, even after adjusting for other potential CV risk factors ***(Solomon et al., 2003).***

RA extra-articular manifestations, usually related to uncontrolled inflammation, are also associated with increased CV mortality, suggesting that processes intrinsic to RA pathogenesis play important roles in CV damage and its clinical consequences ***(Van Doornum et al., 2002).*** Patients with prolonged arthritis have more atherosclerosis than patients of the same age with more recent disease onset, suggesting that atherogenesis accelerates after the onset of RA ***(Del Rincon et al., 2007).***

Articular bone erosions are a characteristic feature of rheumatoid arthritis (RA) and destruction of articular bone is associated with significant morbidity and with a poor prognosis ***(Scott 2000).***

Clinical trials with all major anti-rheumatic agents approved for disease-modification of RA have been validated for their ability to retard, or even arrest, structural damage, which is

a composite of bone erosion and cartilage degradation. Furthermore, radiography is widely used to assess structural damage in clinical practice and to monitor the efficacy of therapy in retarding structural damage. Thus, at present, detection and quantification of bone erosion constitutes a major instrument for disease diagnosis, as well as for monitoring and measurement of efficacy of drug therapy in patients with RA.

Recently, Ultrasonography (US) has become a major tool for follow-up examinations and therapy monitoring of RA disease activity ***(Hammer et al., 2011).*** The detection of erosive lesions in articulating surfaces by imaging techniques has a great diagnostic relevance and plays an important role in the early diagnosis of rheumatoid arthritis. Erosions by US in patients with rheumatoid arthritis are defined as a discontinuity of the bone surface which is visible in two perpendicular planes ***(Wakefield et al., 2005).***

The detection of erosive bone lesions by US is superior to conventional X-ray in relation to the metacarpophalangeal (MCP), proximal interphalangeal (PIP) and metatarsophalangeal (MTP) joints ***(Scheel et al., 2006).***

The relation between erosive changes and cardiovascular risk needs to be clarified. A lot of queries are there regarding

whether patients with early erosive changes have also early cardiovascular changes, also whether the extent of the erosions and or the inflammatory articular changes correlate with cardiovascular changes. Also, are the erosive and or the inflammatory articular changes correlate with myocardial and or vascular changes? Another issue that needs to be studied is that whether the cardiovascular changes occur early in erosive patient or they are late complications of the disease?

Answering these queries would certainly help in the management of RA patients with high risk of cardiovascular disease.

Aim of the Work

The aim of this work is to find out the relationship between development of cardiovascular affection and erosive articular changes in RA patients in order to detect if the presence of erosive articular changes could predict the presence of cardiovascular risk factors and or complications in a trial to have strict disease control in those having early erosive disease to prevent both articular destruction as well as extra-articular cardiovascular complications.

Chapter (1)

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder affecting the joints and has extra articular manifestation. It is by definition polyarticular; that is, it affects many joints. Most commonly, small joints (including the hands, feet and cervical spine) are affected, but larger joints (shoulders, knees etc…) can also be involved; the pattern of joint involvement can differ from patient to patient ***(Majithia, 2007).***

It is characterized by fibroblastic proliferation, infiltration of the synovial lining with mononuclear cells especially T-lymphocytes and macrophages together with synovial lining hyperplasia and paucity of apoptosis ***(Firestein, 2001).***

Rheumatoid Arthritis may affect many tissues and organs (lungs, heart, blood vessels, skin and muscles) but principally attacks the joints, producing a non-suppurative proliferative and inflammatory synovitis that often progress to destruct the articular cartilage and lead to joint ankylosis ***(Rosenberg, 2005).***

It shortens survival and significantly affects quality of life in most patients. Essentially all patients exhibit some systemic features such as fatigue, low-grade fevers, anemia, and elevations of acute phase reactants (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]). Despite these features, the primary target of RA is the synovium, and this is responsible for most of the clinical features ***(O'Dell, 2007).***

Epidemiology:

The average prevalence is 0.5–1% in developed population ***(Gabriel et al., 2009)*** and of 0.3–0.5% in developing countries ***(Osiri et al., 2010).***

The annual incidence rate of RA varies between 20-50 cases/ 100,000 among people in North America and Northern Europe ***(Soderlin et al., 2002).***

The disease can occur at any age, its prevalence increases with age, with peak incidence between the fourth and sixth decades ***(Gabriel, 2001).*** It is clear that women are affected more than men at a ratio of 3:1 in both incidence and prevalence with lower differential between the sexes in older patients ***(Takagi et al., 2000).***

Pathology of Rheumatoid Arthritis

Joints in Rheumatoid Arthritis:

RA causes a broad spectrum of morphologic changes being severely manifested in the joints. Initially the synovium becomes grossly edematous, thickened, and hyperplastic, transforming its smooth contour to one covered by delicate and bulbous fronds ***(Rosenberg, 2005).***

The characteristic histological features include:

1. Infiltration of synovial stroma by dense perivascular inflammatory cells, consisting of B cells and CD4+ helper T cells (often forming lymphoid follicles), plasma cells, and macrophages.
2. Increased vascularity owing to vasodilatation and angiogenesis, with superficial hemosiderin deposits.
3. Aggregation of organizing fibrin covering portions of the synovium and floating in the joint space as rice bodies.
4. Accumulation of neutrophils in the synovial fluid and along the surface of synovium but usually not deep in the synovial stroma.

5. Osteoclastic activity in underlying bone, allowing the synovium to penetrate into the bone forming juxta-articular erosions, subchondral cysts, and osteoporosis.
6. Pannus formation (which is a mass of synovium and synovial stroma consisting of inflammatory cells, granulation tissue, and fibroblasts), growing over the articular cartilage causing its erosion.

By the time, after the cartilage has been destroyed, the pannus bridges the opposing bones, forming a fibrous ankylosis, which eventually ossifies leading to bony ankylosis ***(Rosenberg, 2005).***

They are the most common cutaneous lesions in RA. They occur in approximately 25% of patients, usually those with severe disease, arising in regions of the skin that are subjected to pressure, including the ulnar aspect of the forearm, elbows, occiput, and lumbosacral region. Less commonly, they form in the lungs, pericardium, myocardium, heart valves, and other viscera ***(Smith et al., 2006).***

Blood vessels:

Patients with severe erosive RA, rheumatoid nodules, and high rheumatoid factor titers are at risk of developing vasculitic syndromes ***(Voskuyl et al., 2003).***

Rheumatoid Vasculitis (RV) is a potentially catastrophic complication of RA, particularly when it affects vital organs. The involvement of medium to small sized arteries is similar to that occurring in polyarteritis nodosa except that in RA the kidneys are not involved ***(Rosenberg, 2005).***

Prognosis of RA:

Outcome is compromised when the diagnosis and treatment are delayed. The clinical course of RA is generally one of exacerbations and remissions. Approximately 40% of patients with this disease become disabled after 10 years, but outcomes are highly variable. Some patients experience a relatively self-limited disease, and others have a chronic progressive illness ***(Lipsky, 1994).***

RA that remains persistently active for longer than 1 year is likely to lead to joint deformities and disability. Periods of activity lasting only weeks or a few months followed by spontaneous remission predict a better prognosis ***(Sokka et al., 1999)***.

Pathophysiology:

In a normal joint, synovia consists of synovial membrane (1 or 2 cell layers) and a lower layer of loose connective tissue. The cells lining the synovia are known as "A synoviocytes" (macrophage-like synoviocytes) and "B synoviocytes" (fibroblast-like synoviocytes). In the early stage of RA, hyperplasia of the synovial membrane (a layer of 10 or more cells in thickness) occurs ***(Arend, 2001),*** RA synovial fibroblasts (RASFs) together with synovial macrophages, are the two leading cell types in the terminal layer of the hyperplastic synovial tissue that invades and degrades adjacent cartilage and bone. In this destructive process, RASFs actively drive inflammation and degradation of the joint by producing inflammatory cytokines and matrix-degrading molecules, matrix metalloproteinases (MMPs), include collagenases, stromelysin, gelatinases, and membrane-type (MT). Of these MMPs, collagenase-1 (MMP-1) cleaves collagens I, II, VII and X ***(Ulf Müller-Ladner et al., 2007),*** thus participating in joint destruction in concert with activated chondrocytes and osteoclasts. Villous projections protrude into the joint cavity, invading the underlying cartilage and bone where the proliferating tissue is called pannus.

The synovial hyperplasia, which consists mainly of an increase in cell numbers, especially in the synovial lining layer. To facilitate this growth, angiogenesis (blood vessel proliferation) is mandatory not only for synovial activation but also for subsequent joint destruction (***Distler et al., 2004).*** One of the triggering factors appears to be involved is the articular hypoxia, which stimulates both synthesis of proangiogenic factors but also the expression of chemotactic factors, MMPs such as MMP-1, MMP-3 and osteoclastogenic factors (***Kurowska et al., 2004)*** In the synovial sublining region, edema, angiogenesis, and increased cellularity lead to a marked increase in tissue volume *(figure 1)*. T and B lymphocytes, plasma cells, interdigitating dendritic cells (IDC) and follicular dendritic cells (FDC), and natural killer cells (NK cells) accumulate in rheumatoid synovium and can be distributed diffusely throughout the sublining or organized into lymphoid aggregates. The dominant cells, $CD4^+$ T cells, are mostly of the memory CD45RO and display the chemokine receptors CXCR3 and CCR5 characteristic of Th1 cells. $CD4^+$ T cells are especially enriched in aggregates, whereas $CD8^+$ T cells are present in the periphery of the aggregates or scattered throughout the sublining (***Jean-Marc, 2008).***

Also 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 co-stimulatory 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).***

Diagnosis of Rheumatoid Arthritis Patients:

Early diagnosis of RA is a prerequisite for early treatment and is not always easy to achieve. Diagnosis relies heavily on history taking, clinical examination and less on investigations ***(Petrie et al., 2000).***

A. Clinical diagnosis:

Patients often present with constitutional complaints including malaise, fever, fatigue, weight loss, and myalgia. They may report difficulty in performing activities of daily living (e.g. dressing, standing, walking, personal hygiene, using their hands) ***(Smith et al., 2006).***

A majority of rheumatologists regard *'early RA'* patients as having signs and symptoms of RA according to the criteria of the American College of Rheumatology (ACR) for less than 3 months; importantly, however, a majority of the patients are seen by rheumatologists well beyond that time frame, although referral within the first 6 weeks from symptom onset has doubled to more than 17% in recent years. Women appear to be referred significantly later than men ***(Palm and Purinszky, 2005).***

European and American rheumatologists have established new criteria for the classification of RA that the declared goal and purpose of the new criteria are to make it possible to carry out scientific studies about the treatment of RA in early undifferentiated stages of the disease. This has previously not been possible because hard and fast criteria for the definition of early RA were completely absent. Among patients newly presenting with undifferentiated inflammatory arthritis, factors that best discriminate between those who were and those who were not at high risk for persistent and/or erosive disease – this being the appropriate current paradigm underlying the disease construct RA ***(Aletaha et al., 2010).***