INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that induces inflammation, stiffness, rigidity, and lack of mobility in the joints and affects the peripheral joint synovial membrane. It has been characterized by erosive synovitis, penetration of inflammatory cells into the synovium or membrane existing in the synovial joints that line the joint capsules and produce synovial fluid for the joints in the hands and feet. The resulting inflammatory modifications occur in cartilage and bone loss and synovial hyperplasia eventually contributing to bone breakdown as well as articular cartilage and triggering neurological problems, like respiratory, pulmonary, psychiatric, and other skeletal disorders. The health-related quality of life in RA patients is substantially diminished by discomfort, exhaustion and pain. This is often known that mortality is elevated in patients with RA relative to the general population. RA impacts the joints of the shoulder, elbow, wrist, metacarpophalangeal, proximal interphalangeal, thigh, neck, ankle, and metatarsophalangeal. Prevalence is projected at 0.5 to 1% of the population, primarily of women, with a higher prevalence in the 30-50 year age range. It is distinguished by local and systemic inflammation with elevated plasma concentrations of proinflammatory cytokines, such as interleukin-6, interleukin 1β, tumour necrosis factor-α, and acute-phase proteins, which constitute an oxidative stress disorder. The major mechanism of cell membrane destruction and cell damage is considered to be lipid peroxidation mediated by free radicals. T-cells and cytokines play a significant role in the treatment of rheumatoid arthritis alongside oxygen radicals such as superoxide and hydrogen peroxide produced by activated macrophages. These reactive oxygen species (ROS) and thus reactive nitrogen species (RNS) have both beneficial and toxic effect. Oxidative stress is the state under which the ROS and RNS accumulation is deleterious and destroys the cells and biological macromolecules. Oxidative stress are...
triggered by the disrupted equilibrium between the anti-
oxidant processes of the body and the generation of oxida-
tive stress, which plays a significant role in the creation of
chronic diseases such as RA, cancer, etc.7,9
The term oxidative stress is defined as a pro-oxidant disorder
that results in cell damage. Various cells can withstand mod-
erate oxidative stress because they have an antioxidant pro-
tection mechanism and a repair program that identifies and
eliminates oxidation-damaged molecules like antioxidant
enzymes, which are the first safeguard against endogenous
reactive oxygen species (EROS) neutralization as well as an-
tioxidants nutrients.10 Antioxidant compounds are molecules
that postpone or reduce the degradation of oxidizable sub-
strates at low concentrations.11 Zinc, selenium, vitamin A, C,
and Ede serve particular consideration among the non-enzyme-
atic antioxidants responsible for lower molecular and cel-
lular oxidative stress.12 They are capable of destroying cell
membrane lipids, connective tissue, and nucleic acids. Free
radicals and their by-products are key inflammatory media-
tors. Because of the chemo-attractive properties of synovial
fluid, leukocytes accumulate in the synovial tissue triggering
a respiratory burst marked by elevated oxygen intake and an-
aerobic glycolysis contributing to superoxide, hydroxyl, hy-
pocalaric radicals, etc.13 It has been shown that neutrophils
are involved in the synovial fluid of RA patients, contrib-
uting to inflammation and damage.14,15 The free radicals are
produced in mammalian tissues in all physiological environ-
ments. A significant element in the tissue harm caused by
many pathophysologies is the unregulated development of
free radicals. The shift in the oxidant-antioxidant ratio identi-
fied in rheumatic diseases. Oxidant and antioxidant defi-
ciency due to enhanced chemical reaction or inadequate anti-
oxidant protection mechanism contribute to oxidant stress.16

**Inflammatory Mechanism in Rheumatoid Arthritis**

The swelling of the joints suggests the existence of an infec-
tion of the synovial membranes triggered by immune system
activation. Such infection is consistent with leucocyte prolif-
eration within the synovial cavity. The entire cycle involves
the intervention of both the adaptive immune system and the
innate immune system, which ultimately would end in the
joint destruction. Small joint biopsies along with extensive
molecular bases research have contributed to the conclu-
sion that there are many subtypes of synovial participation,
including lymphocytic-dominant, fibroid-dominant, and
myeloid-dominant. The precise type of detection will lead to
better management and treatment response.17 Advanced
mechanisms that involve cytokines and chemokines control
this inflammatory process in the joints. Those involve the
activating agent of the granulocyte-monocyte group, tumour
necrosis factor, and interleukin 6. Certain molecules may be
present such as interleukin 1, which are less essential in the
inflammatory cycle. The association between the preceding
molecules would induce endothelial cell proliferation and
aggregation of cells inside the joint to promote inflamma-
tion. Cell aggregation, coupled with fibroblast activity, may
contribute to the induction of osteoclast activity by activating
RANKL. The influence of cytokines on chondrocytes often
affects cartilage tissue. It would result in metalloproteinases
and other enzymes destroying the matrix.18

**Pathogenesis of Rheumatoid Arthritis**

RA pathogenesis includes invasion and activation of dif-
f erent communities of cells, and the release of several in-
flammatory and harmful mediators, including cytokines,
prostaglandins, and metalloproteinase. RA pathology has
been reported to consist of (i) acute and chronic inflamma-
tion, (ii) proliferation of cells, and (iii) destruction/fibrosis of
tissues. Natural synovium is a fragile tissue that covers the
joint capsule but, in RA, the synovium turns into a violent,
tumour-like organ called pannus that invades and erodes the
joint.19 Based on the existence or absence of anti-citrullinat-
ed protein antibodies (ACPAs) two main subtypes of RA
occur. The calcium-dependent enzyme peptidyl arginine-
deiminase (PAD) catalyze citrullination, converting a posi-
tively charged arginine into polar yet neutral citrulline as a
consequence of a post-translational change. ACPAs can be
found in around 67% of RA patients and act as a valuable
diagnostic guideline for patients with early, undifferentiated
arthritis and as an indicator of the possible development of
disease via RA.20,21 RA’s ACPA-positive subset has a more
reactive clinical phenotype relative to RA’s ACPA-negative
subset.22 It is stated that ACPA-negative RA has distinct pat-
terns of genetic interaction23 and differentiated responses of
the immune cells to citrullinated antigens24 from those of the
ACP A-positive subset. In medication terms,25–27 less success-
ful methotrexate (MTX) or rituximab therapy reaction has
been reported in the ACPA-negative group. This indicates a
need for future research on the apparent disparity in patho-
physiology between these two subsets. While T cells and
macrophage populations dominate the existing pathogenesis
hypotheses of RA, there is evidence that B cells and their RF
development could also be intrinsic to RA.28 The proba-
bility that RF is involved in disease pathogenesis is increased
by the clear finding that 80 % of RA patients have elevated
autoantibody serum rates that correlate rheumatoid element
is an antibody aimed against the IgG molecule Fc fragment
of RF. RF can be among all subclasses in RA, but is mainly an
IgG antibody that has a strong affinity to macrophage and
neutrophil receptors, fixes complement, and may migrate
into extravascular space.

RF also demonstrates a large degree of replacement mutations
in RA patients suggesting maturation of the affinity.29 This in-
dicates that RF in patients with RA is generated in response to
a somatic mutation mechanism of the immunoglobulin
gene sequence powered by T cells. In comparison, the RF produced by normal individuals in response to infection or immunization is typically IgM, transient, with low affinity, and of the germline, origin indicating that it is part of the innate immune response. Because RF is different in RA patients, it was necessary to figure out how it will lead to inflammation to continue in RA patients.

The earliest in RA pathogenesis is the stimulation of the innate immune response, including the recruitment of dendritic cells by exogenous content and autologous antigens. Antigen-presenting cells, including dendritic cells, macrophages, and activated B cells, present antigens to T cells consistent with arthritis. Concurrently, the synovial membrane is invaded by CD4+ T cells which secrete IL-2 and IFN-g, most RA patients bear the HLA-DRB1 cluster epitope. While prevalent associations with the HLA-DRB1 locus were established decades ago, recent research provided new insights into the possible causative variants within both HLA-DRB1 and other HLA loci that lead to the risk of disease. Such alleles share a homologous sequence of amino acids on the HLA-DR b-chain that links different peptides and influences the appearance of antigens in TCRs. HLA-DR alleles associated with the disease can pose arthritis-related peptides, contributing to the activation and expansion of autoantigen-specific T cells in joints and lymph nodes. In addition to the HLA-DRB1 alleles, genomic stratification through an expression of HLA-DRB4 alleles contributed to the discovery of distinct innate and adaptive immune transcription trends that could anticipate an early RA response, namely methotrexate (MTX). Many important findings on the relationship of HLA loci polymorphisms with RA initiation or therapy reaction have come from research performed in animal models of RA. In collagen-induced arthritis (CIA), the HLA-G2 protein, which is implicated in maternal-fetal immune tolerance, is a valuable mechanism for the treatment of RA, explicitly binding paired Ig-like receptor, expressed only by cells presenting an antigen (APC). B cells lead to RA pathogenesis not only by transmitting antigens but also by developing antibodies, autoantibodies, and cytokines. RF and autoantibodies to the anti-CCP are normal in RA patients. B lymphocytes release proteins of the cell membrane, including immunoglobulin and antigens of differentiation such as CD20 and CD22. More than 100 specific variants of non-HLA loci have been implicated of RA susceptibility, in addition to the HLA loci. For example, in PSORS1C1, PTPN2 and MIR146A genes, polymorphisms in the signalling transducers and transcription activators- STAT-4 and interleukin- (IL)-10 genes were associated with a severe disease phenotype in terms of autoantibody status and radiographic damage. Autoantibodies can form broader immune complexes which can further promote the development of pro-inflammatory cytokines, including TNF-α, by supplementing and stimulating Fc-receptors. T- and B-cell activation contributes to enhanced cytokine and chemokine output, resulting in a feedback loop for additional T-cell, macrophage, and B-cell interactions. Macrophages are active in osteoclastogenesis in addition to receptor presentation and a significant source of cytokines, including TNF-α, IL-1, and IL-6. There is a significant rise in active fibroblast-like synoviocytes inside the synovial membrane, which often releases inflammatory cytokines, PGs and MMPs. Synoviocytes lead to cartilage and bone degradation by secreting MMPs into the SF and by the overt invasion of certain tissues.

Macrophages in RA
Macrophages tend to play a crucial role in RA since they are abundant in the inflamed synovial membrane and at the junction of cartilage – pannus. It gives strong signs of activation, such as overexpression of large class II complex histocompatibility molecules, tumour necrosis factor (TNF)-α proinflammatory or regulatory cytokines, and growth factors [eg IL-1, IL-6, IL-10, IL-13, IL-15, IL-18, and granulocyte-macrophage colony-stimulating factor (GM-CSF)], chemokines and chemoattractants [eg IL-8, inflammatory protein macrophage (MIP)-1 and monocyte chemoattractant protein (MCP)-1], metalloproteinases and neopterin. Macrophages are unlikely to play a causal role in the pathogenesis of RA other than their work as antigen-presenting cells in the primary autoimmune disease hypothesis.

Factors of tumour necrosis
TNF is a rational part of the immune response of the body to tumour cells, bacteria and viruses. It plays role in both acute and chronic inflammation. Cells release it as they sense a certain compound (an antigen) they have been sensitized to.

Tumour necrosis factor-α
TNF-α arises mainly from monocytes and macrophages, but also B-cells, T-cells, and fibroblasts. This is one of the main cytokine molecules that induce inflammation in RA. It is also an autocrine stimulator and a potent paracrine inducer of certain inflammatory cytokines, namely interleukin-1 (IL-1), IL-6, IL-8, and a granulocyte-monocyte-colony stimulating factor (GM-CSF). TNF-α is also considered to activate fibroblasts to release molecules of adhesion such as intracellular adhesion molecule (ICAM-1). TNF-α is a pleiotropic cytokine, which enhances the synovial cells’ production of cytokines, adhesion proteins, prostaglandin E2, collagenase, and collagen. In RA, TNF-α is mainly developed by macrophages in the synovial membrane and at the junction of cartilage – pannus and is assumed to be a proximal cytokine in the inflammatory cascade. Although an average of around 5% of synovial cells expresses TNF-α mRNA in vivo, the degree of TNF-α expression in synovial tissue tends to be based on the predominant histological configuration. TNF-α is a potent cytokine consistent with natural im-
mune and inflammatory response. Individuals with RA have elevated rates of TNF-α in the synovial fluid and it plays a major role in inflammation and joint damage, which are RA hallmarks. Anti-TNF-α therapy induces a cytokine balance change which generates more anti-inflammatory cytokines. Studies have demonstrated a significant increase in synovial inflammation in RA patients after treatment with neutralizing anti-TNF-α Abs or soluble TNF receptors and reduced joint damage after IL-1Ra therapy. Throughout RA synovitis, immunosuppressive and anti-inflammatory cytokines like TGFβ, IL-10, and IL-1Ra are released strongly and stably. Such cytokines have been suggested to indicate attempts by the patient to suppress or regulate inflammation and maintain homeostasis.52

**Interleukin-6**

IL-6 is the most remarkably elevated cytokine in RA, especially in the acute disease synovial fluid.53 While IL-6 levels in the synovial fluid correlate with the degree of radiological joint injury, and IL-6 and soluble IL-6 receptors promote the production of osteoclasts54, this cytokine may also protect cartilage in acute disease but also promote excessive bone formation in chronic disease55. IL-6 is mainly developed by synovial fibroblasts and only partly by macrophages56; two results indicate that the striking growth of IL-6 is a prominent consequence of macrophage activation and the morphological similarity of IL-6-expressing fibroblasts with CD14 + macrophages in RA synovial tissue.57

**Matrix metalloproteinases**

An essential feature of RA synovial fibroblasts and macrophages in the enhanced development of the matrix-degrading enzyme family MMPs. MMPs are a family of zinc-dependent endopeptidases, capable of degrading all major extracellular matrix components. A variety of studies have shown that MMPs are effective mediators in inflammatory tissue and connective diseases such as RA. The gelatinase subfamily of MMPs composed of MMP-2 (gelatinase A) and MMP-9 (gelatinase B) is of great significance in arthritis.58-60

**Chemokines**

Chemokines are chemotactic cytokines, which control immune cell migration in various physiological and pathological processes. We play a key role in homeostasis, in the production of cellular and humoral immune responses, and the involvement of pathologic immune in different diseases. Chemokines consist of a wide family of more than 50 chemokine ligands and receptors, listed in their primary amino acid sequence based on the assembly of cysteine residues.61

Chemokine receptors are expressed on all leukocytes and can be divided into two groups:

1. Protein serpentine G – generalized chemokine receptors (GPCRs)
2. Atypical receptors to the chemokine.62

Many chemokine ligands may attach to several receptors, whereas some receptors have more ligands, including those involving chemokines in inflammatory processes. Chemokine receptors and ligands were involved in different RA development processes including inflammation and angiogenesis.63,64 Chemokine activity was documented to differ at various stages of RA. CCL4, CXCL4, CXCL7, and CXCL13 were articulated at an early level, while CCL3 and CCL9 were published at later stages.65,66 Other chemokines, including CXCL1 and CXCL5, foster inflammation and hence tend to raise their rates by constant inflammation.67 This should be remembered that citrullination of chemokines (e.g. CXCL5 and CCL2) exists in RA and has been found in RA patients with synovial fluid. Citrulline chemokines have a change in their function that contributes to a decrease in chemotaxis.68 RA patients have elevated plasma and synovial fluid amounts of CCL2, CCL3, CCL4, and CXCL10. CCL5, on the other hand, indicated a raised plasma volume but a decrease in RA patients’ synovial fluid.69

**Figure 1:** Mechanism of initiation, inflammation and destruction of bone in RA70

Different cells including lymphocytes, innate immune cells, osteoclast and synovial fibroblast plays role in the development of RA, through the production of autoantibodies as well as the activation of innate immunity and synovial fibroblast, ultimately leading to bone destruction.70

**CONCLUSION**

RA is a disabling, chronic, inflammatory condition that can cause both joint injury and long-term impairment. The disorder has predominance in women, despite large numbers possessing a healthy family history. To avoid permanent injury
and impairment of vital bodily functions, early detection and action are necessary. The prescribing practitioner will consider adhering to guidelines for the treatment-to-target. Medications such as NSAIDs, opioids, DMARDS, and biological reaction modifications, these medications can target parts of the immune system that trigger inflammation that causes joint and tissue damage. Lifestyle modification is really important for RA patients by performing daily workouts and discovering ways to deal with pain by minimizing tension in life.

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Butola et al.: Endogenous Factor and Pathophysiology of Rheumatoid Arthritis: An Autoimmune Disease from Decades

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