ABSTRACT

Rheumatoid arthritis is a severe autoimmune disease causes the inflammation, swelling, joint pain and stiffness leads to imbalance of protective role. During the inflammation process several inflammatory cells get released causes joint inflammation. Rheumatoid arthritis can affects the hands, wrists, knees, nerves and damage the vital organs. It is strongly associated with genes of HLA-DR 4 which is the major genetic factor causes arthritis. Primarily it starts with rapid cellular activation leads to damage of protective cells and formation of immune complexes in both joints and other organs where it multiplies rapidly. The initial stage has no inflammation after the severity of disease condition release of various inflammatory cells causes joint destruction. The environmental factors, smoking, allergens, genetics, insecticides and occupational exposure contributes the arthritis development. The B-cells, T-cells, major histocompatibility cells, CD4 cells having significant role in arthritis development. Treatment strategy depends on providing symptomatic relief and early diagnosis, effective implementation of therapeutic plan that impact treatment outcomes and improves the quality of life and rapidly arrest the structural joint damage. Methotrexate is the initial drug of choice in most patients with rheumatoid arthritis. The combination regimens includes methotrexate and other conventional disease modifying anti rheumatoid arthritis drugs may an effective approach to the treatment. The non pharmacological interventions includes reducing pain, inflammation, free joint movement and improvement in patient's health related quality of life. The regular monitoring of balanced rest, proper sleep, stress reduction, exercise, use of splints and braces, Pain relieving medications, corticosteroids provides many beneficial effects which will reduce the joint complications in clinical practice.

KEYWORDS: Allergens, Genetics, HLA-DR4, Inflammation, Joint stiffness.
INTRODUCTION

It is the most common form of autoimmune disease and inflammatory condition of arthritis. About 75% of rheumatoid arthritis patients are women. The disease most often begins at the ages of 30 and 50. However rheumatoid arthritis occurs at any age. It attacks healthy cells in body by mistake, causing inflammation in the affected parts of the body. Rheumatoid arthritis mainly attacks the joints, usually many joints at once. It commonly affects the joints in the hands, wrists and knees. This tissue damage can cause long-lasting or chronic pain, unsteadiness and deformity. The severe progress of arthritis can affect other tissues through out the body and cause problems in organs such as the lungs, heart and eyes.\[1,2\]

The inflammation is associated with rheumatoid arthritis can damage other parts of the body as well.\[3,4\] It is associated with autoimmune disease in which its body’s immune system normally protects health by attacking foreign substances like bacteria and viruses mistakenly attacks the joints.\[4,5\] This creates inflammation that causes the tissue that lines the inside of joints to thicken, resulting in swelling and pain in and around the joints.

Rheumatoid arthritis most commonly affects the joints of the hands, feet, wrists, elbows, knees and ankles. The infected blood circulated through out the body and affects vital organs functions.

The inflammation process associated with rheumatoid arthritis can damage other parts of the body as well. While new types of medications have improved treatment options for severe rheumatoid arthritis.\[5,6\]

The joint stiffness in active rheumatoid arthritis is often the worst in the morning. It may last one to two hours. It generally improves with movement of the joints. Stiffness for a long time in the morning is a identification fact for rheumatoid arthritis.\[6,7\]

The disease often affects the wrist joints and the finger joints closest to the hand. It can also affect other parts of the body besides the joints. In addition, people with rheumatoid arthritis may have fatigue and, fever.\[8,9\]

The ends of bones are covered by elastic tissue called cartilage to support and protect it during movements. The synovium, which produces synovial fluid that acts as a lubricant and nourishment to the cartilage. The people with rheumatoid arthritis, white blood cells cause
inflammation in the synovium. This causes the tissue that lines the walls of the joints to thicken and become swollen and painful when moved.\textsuperscript{[10,11]}

Fig 1: Rheumatoid arthritis process

It can affects the multiple vital organ functions in the body known as systemic disease. The cause of rheumatoid arthritis includes an abnormal response of the immune system plays a leading role in the inflammation and joint damage that occurs.\textsuperscript{[12,13,14,15]}

**Rheumatoid arthritis affects the most important joints in the body includes**
- Hands
- Feet
- Wrists
- Elbows
- Knees
- Ankles

**Risk factors**

**Factors that increase the risk of rheumatoid arthritis include**
- **Gender:** Women are more likely than men to develop rheumatoid arthritis.
- **Age:** Rheumatoid arthritis can occur at any age, but it most commonly begins between the ages of 40 and 60.
- **Family history:** The family history is one of the risk factor for developing arthritis.
- **Smoking:** Cigarette smoking increases risk of abnormalities in blood vessels and also causing several inflammatory reactions in the body.
• **Environmental exposure:** The exposure to environmental factors such as asbestos or silica may increase the risk for developing rheumatoid arthritis.

• **Obesity.** People who are overweight or obese appear to be at some what higher risk of developing rheumatoid arthritis, especially in women diagnosed with the disease when they were 55 or younger.\(^{[16,17]}\)

**Complications of rheumatoid arthritis**

Rheumatoid arthritis increases the risk of developing:

• **Osteoporosis:** Rheumatoid arthritis itself, along with some medications used for treating rheumatoid arthritis, can increase risk.

• **Rheumatoid nodules:** These firm bumps of tissue most commonly form around pressure points, such as the elbows.\(^{[18,19]}\)

• **Infections.** The disease itself and many of the medications used to combat rheumatoid arthritis can impair the immune system, leading to increased infections.

• **Abnormal body composition:** The proportion of fat compared to lean mass is often higher in people who have rheumatoid arthritis, even in people who have a normal body mass index.

• **Carpal tunnel syndrome:** If rheumatoid arthritis affects wrists, the inflammation can compress the nerve.

• **Heart problems:** Rheumatoid arthritis can increase the risk of hardened and blocked arteries, as well as inflammation of the sac that encloses the heart.

• **Lung disease:** People with rheumatoid arthritis have an increased risk of inflammation and scarring of the lung tissues, which can lead to progressive shortness of breath.

• **Lymphoma:** Rheumatoid arthritis increases the risk of lymphoma, a group of blood cancers that develop in the lymph system.\(^{[20,21]}\)

**Carpal tunnel syndrome**

Carpal tunnel syndrome is a common condition in people with rheumatoid arthritis. The result of compression of the nerve that controls sensation and movement in the hands and can cause symptoms such as:

• aching

• numbness

• Tingling in your thumb, fingers and part of the hand
Wide spread inflammation

Rheumatoid arthritis is an inflammatory condition which can cause inflammation to develop in other parts of your body, such as the:

- Lungs: Inflammation of the lungs or lung lining can lead to pleurisy or pulmonary fibrosis, which can cause chest pain, a persistent cough and shortness of breath.
- Heart: Inflammation of the tissue around the heart can lead to pericarditis, which causes chest pain.\textsuperscript{22,23}
- Eyes: Inflammation of the eyes can lead to scleritis or Sjogren’s syndrome. Scleritis can cause eye redness and pain.

Problems that can affect the joints include

- Damage to near by bone and cartilage.
- Damage to nearby tendons which could cause them to break.
- Joint deformities\textsuperscript{24,25}

Cardiovascular disease

Cardio vascular disease is a general term that describes conditions affecting the heart or blood vessels, it includes life threatening problems such as heart attacks and strokes.\textsuperscript{25,26}

The risk is well controlled by reducing the impact of other factors that contribute to cardiovascular disease such as:

- Stopping smoking
- Eating healthily
- Exercising regularly

Cervical myelopathy

The patient suffering with rheumatoid arthritis some time with increased risk of developing cervical myelopathy disorder.\textsuperscript{27,28}

Etiology of Rheumatoid Arthritis

The immune system is supposed to attack foreign particles like bacteria and viruses, by creating inflammation. In an autoimmune disease, the immune system mistakenly sends inflammation to own healthy tissue. The immune system creates a lot of inflammation that causing joint pain and swelling carring rheumatoid arthritis.\textsuperscript{29,30}
Genetic Factors
There are certain genes that may play a small role in the development of rheumatoid arthritis, although not directly.\textsuperscript{[31,32]}

Environmental Factors
There are several environmental factors that, combined with a genetic predisposition, give people a greater risk to develop rheumatoid arthritis.\textsuperscript{[33,34]}

These include
- Bacteria and viruses
- Exposure to secondhand smoke
- Air pollution
- Insecticides
- Mineral oils
- Silica mineral

Personal Factors
Gender: It affects both men and women are susceptible to rheumatoid arthritis, but the disease is far more common in women.\textsuperscript{[35,36]}

Age: It can affect at any age, but it typically presents in those between the ages of 40-60.

Family History: Those who have a family history of rheumatoid arthritis may have a higher chance of developing the disease.\textsuperscript{[37,38]}

Incidence
Rheumatoid Arthritis affects about 0.5 to 1 per cent of adults in developed countries. About 50 individuals in every 100000 people develop the disease annually. The incidence of rheumatoid arthritis increases with the age of an individual until the age of 80 years. Women are the most affected as compared to men.\textsuperscript{[39-40]}

Rheumatoid arthritis symptoms
In the early stages, people with Rheumatoid arthritis may not initially see redness or swelling in the joints, but they may experience tenderness and pain.\textsuperscript{[41,42]}

The following joint symptoms are findings to rheumatoid arthritis:
• Joint pain, tenderness, swelling or stiffness for six weeks or longer.
• Morning stiffness for longer.
• More than one joint is affected.\cite{43,44}
• Small joints like wrists, certain joints of the hands and feet are affected.
• The same joints on both sides of the body are affected.\cite{45,46}

**Physical symptoms include**

• Fatigue
• Minor fever
• Loss of appetite
• Muscle aches
• Weight loss

**There are similar symptoms that appear in specific locations in the body**

• Shortness of breath can come from inflammation and scarring of the lungs.
• Rheumatoid nodules are small lumps that form under the skin over bony areas that have been eroded away.
• Currently, approximately 20\% of rheumatoid arthritis patients have developed these nodules.
• Inflamed blood vessels from rheumatoid arthritis can lead to damage in nerves and skin resulting in numbness, tingling and burning.
• Anemia conditions the decrease in production of red blood cells, it is one of the identified common symptom of rheumatoid arthritis.\cite{47,48}
• Progressive articular deterioration.
• Extra articular involvement.\cite{49-50}
• Difficulty performing activities of daily living.

**The physical examination should address the following symptoms in patients**

• Upper extremities symptoms in meta carpophalangeal joints, wrists, elbows, shoulders.
• Lower extremities symptoms in ankles, feet, knees, hips.
• Cervical spine.\cite{51,52}

**During the physical examination, it is important to assess the following**

• Stiffness
• Tenderness
Some ways rheumatoid arthritis can affect body systems like

- **Eyes:** The patient may suffer from Dryness, pain, redness, sensitivity to light and impaired vision in retina of the eyes.
- **Mouth:** In this condition mouth causes dryness and gum irritation or infections may present.
- **Skin:** Rheumatoid arthritis condition it forms nodules small lumps under the skin over bony areas get affected.
- **Lungs:** The Inflammation and scarring that can lead to shortness of breath conditions.
- **Blood Vessels:** The complete Inflammation of blood vessels that can lead to damage in the nerves, skin and other organs.[54-55]
- **Blood:** A lower than normal number of red blood cells causes the anemia.

The most common symptoms are

- **Swelling:** Synovial tissue in the caps of joints becomes damaged in rheumatoid arthritis sufferers, causing the tissue to thicken and swell.
- **Stiffness:** Inflamed joints tend to stiffen and are difficult to move correctly. People who have rheumatoid arthritis experience stiff joints, especially in the mornings or after long periods of rest.[56-57]
- **Pain:** Cartilage and bone within the joints will wear down over time. Joints are supported by surrounding muscles, ligaments and tendons, but these will weaken and no longer stabilize joints. This causes intense pain and joint damage.[58-60]
- **Redness:** Joints can be warm and may appear pink, or even red, on the outside during a flare or when inflamed.
- It is most commonly affects in the hands, but can happen in any joint, including knees, wrists, neck, shoulders, elbows, feet, hips, and even the jaw.[61-62]

**Diagnosis of rheumatoid arthritis**

The diagnosis of the rheumatoid arthritis depends on following test:
Medical history: The physician interacts with patient and look for clinical findings includes asking the patient to describe the symptoms and when and how the condition started, as well as how the symptoms have changed over time.

Physical examination: The physician will examine each joint, looking for tenderness, swelling, warmth and painful or limited movement. The number and pattern of joints affected can also indicate the presence of rheumatoid arthritis.

Laboratory tests: A number of lab tests may be useful in confirming a diagnosis of rheumatoid arthritis.

Following are some of the more common ones
- Rheumatoid factor: Rheumatoid factor is an antibody that is present eventually in the blood of most people with rheumatoid arthritis.
- Anti-CCP antibodies: This blood test detects antibodies to cyclic citrullinated peptide. This test is positive in most people with rheumatoid arthritis and can even be positive and indicates the rheumatoid arthritis.[63]
- Other common tests includes: The other laboratory tests include a white blood cell count, a blood test for anemia, erythrocyte sedimentation rate, which measures inflammation in the body, C-reactive protein, another common test for inflammation that is useful both in making a diagnosis and monitoring disease.[64]
- X rays: X rays are used to determine the degree of joint destruction.

Blood Tests
The blood tests will measure inflammation levels and look for biomarkers such as antibodies attached with arthritis.

Inflammation: It diagnosis depends upon erythrocyte sedimentation rate and C-reactive protein levels are used to identify and diagnosis the inflammation.

Pathogenesis: Both genetic as well as environmental factors, are implicated in the disease progressing. It primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in both joints where it proliferates. The Initial site of disease is the synovial membrane, where swelling and congestion leads to infiltration.
Fig 2: Pathophysiology of Rheumatoid arthritis

The genetic association with HLA-DR4, as well as associations with the gene PTPN22 implicate altered thresholds in regulation of the adaptive immune response. The B and T cells are essential to the disease. This tends to favor immune complexes as the initiators. The presence of auto antibodies to IgGFc, known as rheumatoid factors and antibodies to citrullinated peptides (ACPA) is an integral part of rheumatoid arthritis disease process. Once the abnormal immune response has become established plasma cells derived from B lymphocytes produce rheumatoid factors, IgG and IgM, activation of macrophages through Fc receptor and complement binding, which seems to play an important role in the intense inflammatory response. Auto reactive antibody binds to the Fc receptors is mediated through the antibody's N-glycans, which are altered to promote inflammation of the synovium, in the form of edema, vasodilation and infiltration by activated T-cells. Synovial macrophages and dendritic cells further function as antigen presenting cells by expressing MHC class II molecules, leading to an established local immune reaction in the tissue. The disease progresses in concern with the formation of granulation tissue at the edges of the synovial lining with extensive angiogenesis and production of enzymes that cause tissue damage.

Figure 3 comparison between normal and rheumatoid arthritis joint
Epidemiology
Rheumatoid arthritis has a worldwide distribution with an estimated prevalence of 1 to 2%. Prevalence may increases with age, gender, area wise approaching 5% in women over age 55. Both incidence and prevalence of rheumatoid arthritis are two to three times greater in women than in men.[64]

Non pharmacological and nonsurgical therapies include the following:
- Heat and cold therapies
- Orthotics and splints
- Therapeutic exercise
- Occupational therapy
- Adaptive equipment

Non biological disease modifying anti rheumatoid drugs
- Hydroxychloroquine
- Azathioprine
- Sulfasalazine
- Methotrexate
- Leflunomide
- Cyclosporine
- Gold salts
- D-penicillamine
- Minocycline

Biological Tumour necrosis factor alpha-inhibitors include the following
- Etanercept
- Infliximab
- Adalimumab
- Certolizumab
- Golimumab

Adverse effects
- Sore Throat, Mouth Ulcers
- Nausea
- Vomiting
• Abdominal Discomfort
• Jaundice

**Interleukin receptor antagonist**

Interleukin inhibitors are immunosuppressive agents which inhibit the action of interleukins. It includes:
• Rituximab
• Anakinra

**Adverse effects**
- Fever or chills
- Headache
- Itching, pain, redness, swelling
- Joint pain
- Muscle aches and pains

**Biologic non-TNF DMARDs include the following**
• Abatacept
• Tocilizumab
• Tofacitinib

**Adverse effects**
It develops the Injection site reactions, severe allergic reaction, infections, hematological effects.

**The Drugs used therapeutically include the following**

**Corticosteroids**
• Prednisone
• methylprednisolone
• Triamcinolone

**Adverse effects:** It develops pain and discomfort, flushing, infection, causing redness, swelling and pain, fluid retension, high blood pressure, physical stress, gastrointestinal ulcers, weight gain, insomnia.
Table 1: Non steroidal anti inflammatory drugs

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<table>
<thead>
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<tbody>
<tr>
<td>Aspirin</td>
<td>Fenoprofen</td>
<td>Ketoprofen</td>
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<tr>
<td>Celecoxib</td>
<td>Flurbiprofen</td>
<td>Ketorolac</td>
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<tr>
<td>Diclofenac</td>
<td>Ibuprofen</td>
<td>Meloxicam</td>
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<tr>
<td>Etodolac</td>
<td>Indomethacin</td>
<td>Nabumetone</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Piroxicam</td>
<td>Sulindac</td>
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</tbody>
</table>

Adverse effects
The most common side effects are
- constipation
- diarrhea
- reduced appetite
- headache
- dizziness
- rashes
- swelling of the arms and legs
- ulcers, bleeding, kidney failure, liver failure

Surgical treatments include the following
- Synovectomy
- Tenosynovectomy
- Tendon realignment
- Reconstructive surgery
- Arthrodesis

Disease modifying anti rheumatoid drugs

Gold: Route of administration: Intramuscular injection as sodium aurothiomalate.

Penicillamine: It is a chelating agent licensed for the treatment of severe active rheumatoid arthritis, including juvenile forms.

Sulfasalazine: It is used for the treatment of rheumatoid arthritis which has failed to respond to non-steroidal anti-inflammatory drugs.

Drugs which affect the Immune process
- Chloroquine and Hydroxy chloroquine: Hydroxy chloroquine is an antimalarial agent used for the treatment of rheumatoid arthritis.
- **Methotrexate**: It may be used in the treatment of rheumatoid arthritis and psoriatic arthritis.

- **Azathioprine**: It is a cytotoxic drug and a pro drug of mercaptopurine.

- **Ciclosporin**: It acts as a powerful immune suppressant that appears to act specifically on lymphocytes.

- **Leflunomide**: It is a category under high disease modifying anti rheumatoid arthritis drugs and having anti proliferative properties.

**Contraindications of anti rheumatic drugs**: The choice of first choice of drug or combination of agents should be based on a risk and pharmacoeconomic needs for individual patients.

**Table 2: Contra indications of Anti rheumatic drugs**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold Sodium Aurothiomalate, Leflunomide</td>
<td>Severe liver, kidney damage</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>kidney disease</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Liver impairment</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Liver impairment</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td>Infliximab, Ciclosporin[65]</td>
<td>Abnormal infections</td>
</tr>
</tbody>
</table>

**CONCLUSION**

It is a chronic systemic inflammatory disease results in complete destruction and loss of joint function. Treatment guidelines should meet the national and International standards may depends upon the early diagnosis and treatment. The better treatment depends upon the disease modifying anti rheumatoid drugs and biological therapies. The exact outcomes depends upon the greater understanding the etiological and pathological mechanisms and dietary modifications plays a key role in management of disease.[65] It is a chronic auto immune disease with unknown aetiology and it is characterized by a deforming and multiple systemic manifestations. The management of rheumatoid arthritis is a complex process related with patient lifestyle and disease factors but also it is linked with the health care system functions. Reaching the healthy practices well balanced nutritional diet reduce the joint complications clinically.

The treatment option may associated to the pharmacologic treatment options reducing the pain, swelling, inflammation, supporting physical exercise as well as surgical interventions which are important elements of care for rheumatoid arthritis patients and several clinical and
social interventions that are especially important for patient satisfaction and compliance which are beneficial for managing the disease in the clinical practice.

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REFERENCES


