WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on Rheumatoid Arthritis

Galande Pooja Vinod[1], Kardile Divya Sunil[2], Pokale Gayatri Vilas[3], Apurva Gorakshnath Mhaske[4], Dr. Sanjay Ingale[5]

[1,2,3] Student, Guide[4], Principal[5]
Dharmaraj Shikashnik Pratishtha College of Pharmacy, Walki, Ahilyanagar (414006)

ABSTRACT :

An inflammatory disease that can cause severe joint destruction and disability, with subsequent high morbidity and mortality. Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by inflammation of the joints and surrounding tissues, leading to pain, swelling, stiffness, and progressive joint damage. It primarily affects the synovial joints, resulting in the destruction of cartilage and bone. RA is systemic and can also involve other organs such as the lungs, heart, and eyes. The exact cause of RA is unknown, but genetic and environmental factors play key roles in its development. The disease affects more women than men and typically manifests in middle age. Early diagnosis and treatment with disease-modifying antirheumatic drugs (DMARDs), biologics, and lifestyle modifications can help manage symptoms and slow disease progression.

Keywords: Rheumatoid Arthritis, incidence, prevalence, environmental factors, genetic factors.

Introduction :

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that causes joint inflammation and pain Rheumatoid arthritis (RA for short) is a sickness involving your immune system (body's natural defense against sickness) that leads to inflammation (painful swelling) in various organs. RA usually affects the joints and causes pain, swelling, and stiffness (hard to move). If RA is not treated well or on time, the inflammation can lead to joint damage and deformities (something that is not a normal shape**).**

Definition :

Rheumatoid arthritis is an autoimmune disease. Normally, your immune system helps protect your body from infection and disease. In rheumatoid arthritis, your immune system attacks healthy tissue in your joints. It can also cause medical problems with your heart, lungs, nerves, eyes and skin.

Symptoms :

Signs and symptoms of rheumatoid arthritis may include

- Tender, warm, swollen joints
- Joint stiffness that is usually worse in the mornings and after inactivity
- Fatigue, fever and loss of appetite

Rheumatoid arthritis (RA) is an autoimmune disease that is chronic (ongoing).

It occurs in the joints on both sides of your body, which makes it different from other types of arthritis. You may have symptoms of pain and inflammation in your:

- Fingers
- Hand's
- Wrists
- Knees
- Ankles
- Feet

Rheumatoid arthritis causes inflammation and pain in one or more joints. It can happen in most joints, but it's most common in the small joints of the hands, wrists and feet.

RA is chronic and may worsen over time without treatment. It can lead to severe damage to the joint and surrounding tissue. It can also affect the heart, lung and nervous systems.

Early signs and symptoms:

- Pain
- Stiffness
- Tenderness
- swelling or redness in one or more joints, usually in a symmetrical pattern (e.g., both hands or both feet).

Epidemiology :

Prevalence varies from 0.5% to 1.5% of the population.

• RA affects more women than men (ratio 3:1).

• The age of onset is between 30 and 55 years.

• RA results in progressive disability, with nearly half of all patients experiencing significant functional impairment within 10 years.

• RA shortens life expectancy by a number of years in both men and women.Epidemiology principles have been used to describe the distribution of RA in the population and to examine possible risk factors for disease occurrence and progression.

The Danish study also found a higher risk of RA among women with a history of preeclampsia, hyperemesis during pregnancy, or gestational hypertension.

Cause of Rheumatoid arthritis:

Researchers do not know what causes the immune system to turn against the body's joints and other tissues. Studies show that a combination of the following factors may lead to the disease:

- **Genes :** Certain genes that affect how the immune system works may lead to rheumatoid arthritis. However, some people who have these genes never develop the disease. This suggests that genes are not the only factor in the development of RA.
- **Environment :** Researchers continue to study how environmental factors such as cigarette smoke may trigger rheumatoid arthritis in people who have specific genes that also increase their risk. In addition, some factors such as inhalants, bacteria, viruses, gum disease, and lung disease may play a role in the development of RA.
- **Sex hormones :** Researchers think that sex hormones may play a role in the development of rheumatoid arthritis when genetic and environmental factors also are involved.
    - Women are more likely than men to develop rheumatoid arthritis.
    - The disease may improve during pregnancy and flare after pregnancy.

Rheumatoid arthritis is an autoimmune condition, which means it's caused by the immune system attacking healthy body tissue. However, it's not yet known what triggers this.

Your immune system normally makes antibodies that attack bacteria and viruses, helping to fight infection.

The following can play a part in why someone has rheumatoid arthritis**:**

1. **Age :** Rheumatoid arthritis affects adults of any age, although most people are diagnosed between the ages of 40 and 60
2. **Sex :** Rheumatoid arthritis is two to three times more common among women than men.
3. **Genetics :** Rheumatoid arthritis develops because of a combination of genetic and environmental factors, such as smoking and diet.
4. **Weight** : If you are overweight, you have a significantly greater chance of developing rheumatoid arthritis than if you are a healthy weight.

The body mass index (BMI) is a measure that calculates if your weight is healthy, using your height and weight.

For most adults, an ideal BMI is in the 18.5 to 24.9 range.

If your BMI is:

- below 18.5 – you're in the underweight range
- between 18.5 and 24.9 – you're in the healthy weight range
- between 25 and 29.9 – you're in the overweight range
- between 30 and 39.9 – you're in the obese range.

Risk factor :

There are several things that may increase your risk of developing rheumatoid arthritis, including:

- **your genes –** there's some evidence that rheumatoid arthritis can run in families, although the risk of inheriting it is thought to be low as genes are only thought to play a small role in the condition
- **hormones –** rheumatoid arthritis is more common in women than men, which may be because of the effects of the hormone oestrogen, although this link has not been proven
- **smoking –** some evidence suggests that people who smoke have an increased risk of developing rheumatoid arthritis.

Pathophysiology :

a chronic inflammatory disorder caused in many cases by the interaction between genes and environmental factors, including tobacco, that primarily involves synovial joints.

All elements of the immune system are involved, including innate immunity and adaptive immunity, which includes the cellular (T cell) immune response and the humeral (B cell) immune response.

The immune response in RA starts at sites distant from the synovial joints, such as the lung, gums, and GI tract. In these tissues, modified proteins are produced by biochemical reactions such as citrullination.

The mechanism behind environment-triggered RA is thought to be due to the repeated activation of innate immunity. Using the lungs as an example, cigarette smoking induces peptidyl arginine deiminase (PAD) expression in alveolar macrophages, which leads to the conversion of arginine to citrulline in the airway. This process creates a "neoantigen" that activates an immune response and leads to the formation of anti-citrullinated protein antibodies .

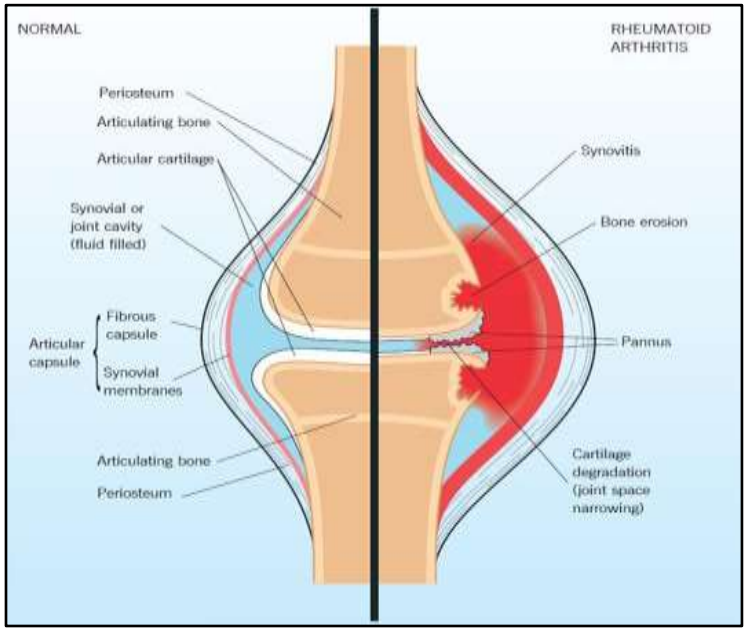


Fig: pathophysiology of Rheumatoid arthritis

Rheumatoid arthritis (RA) is an auto-immune disorder that progressively damages the joints and causes inflammation, pain, and deformities in extremities of the body such as fingers of upper and lower limbs, ankles, and wrist .

The exact reason behind the progression of RA is unknown . There are various characteristics of RA such as synovitis, hyperplasia, production of autoantibodies like anti-citrullinated protein antibody [ACPA], rheumatoid factor, and destruction of bone .

- Pathogenesis involves multiple factors, including both genetic and environmental influences.
- Immune cells and soluble inflammatory mediators play a crucial role in the pathogenesis, although therelative contribution of individual components remains uncertain.
- Proliferation of cells in the synovial layer of the joint, together with infiltration by various cell populations, as orchestrated by cytokines, chemokines, growth factors, and hormones, produces a locally invasive pannus that is capable of invading and ultimately destroying cartilage, bone, and surrounding soft tissues.

Diagnosis :

Differential Diagnosis :

- Osteoarthritis
- Psoriatic arthritis
- Systemic lupus erythematosus
- Sjogren syndrome
- Polymyalgia rheumatic
- Chronic gouty arthritis
- Calcium pyrophosphate deposition disease

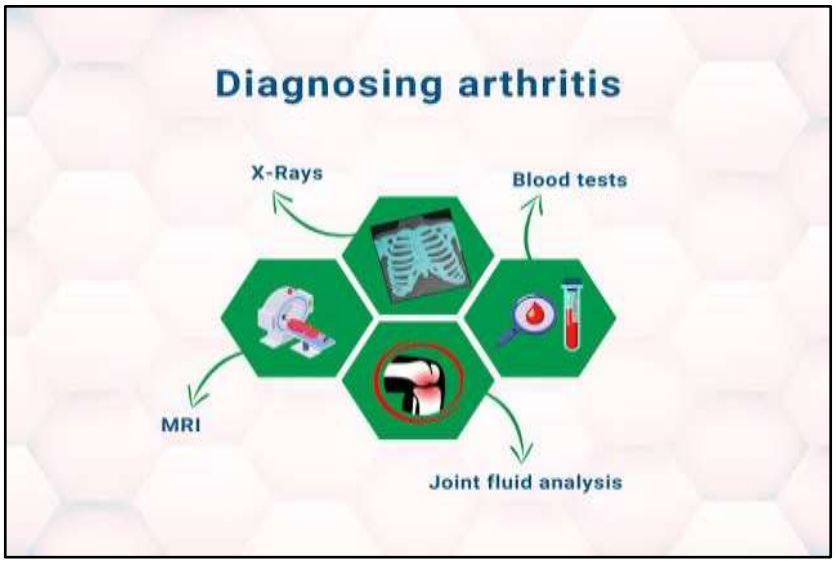


Fig: diagnosis of Rheumatoid arthritis

Your healthcare provider may refer you to a physician who specializes in arthritis (rheumatologist). Rheumatologists diagnose people with rheumatoid arthritis based on a combination of several factors. They'll do a physical exam and ask you about your medical history and symptoms. Your rheumatologist will order blood tests and imaging tests.

- Erythrocyte sedimentation rate (ESR) or "sed rate" confirms inflammation in your joints.
- C-reactive protein (CRP).
- About 80% of people with RA test positive for rheumatoid factor (RF).
- About 60% to 70% of people living with rheumatoid arthritis have antibodies to cyclic citrullinated peptides (CCP) (proteins).

Your rheumatologist may order imaging tests to look for signs that your joints are wearing away. Rheumatoid arthritis can cause the ends of the bones within your joints to wear down. The imaging tests may include:

- X-rays.
- Ultrasounds.
- Magnetic resonance imaging (MRI)

In some cases, your provider may watch how you do over time before making a definitive diagnosis of rheumatoid arthritis.

Diagnostic criteria :

- Inflammatory arthritis in two or more large Elevated levels of CRP or an elevated sed rate.
- Inflammatory arthritis in smaller joints.
- Positive biomarker tests like rheumatoid factor (RF) or CCP antibodies.
- Elevated levels of CRP or an elevated sed rate.

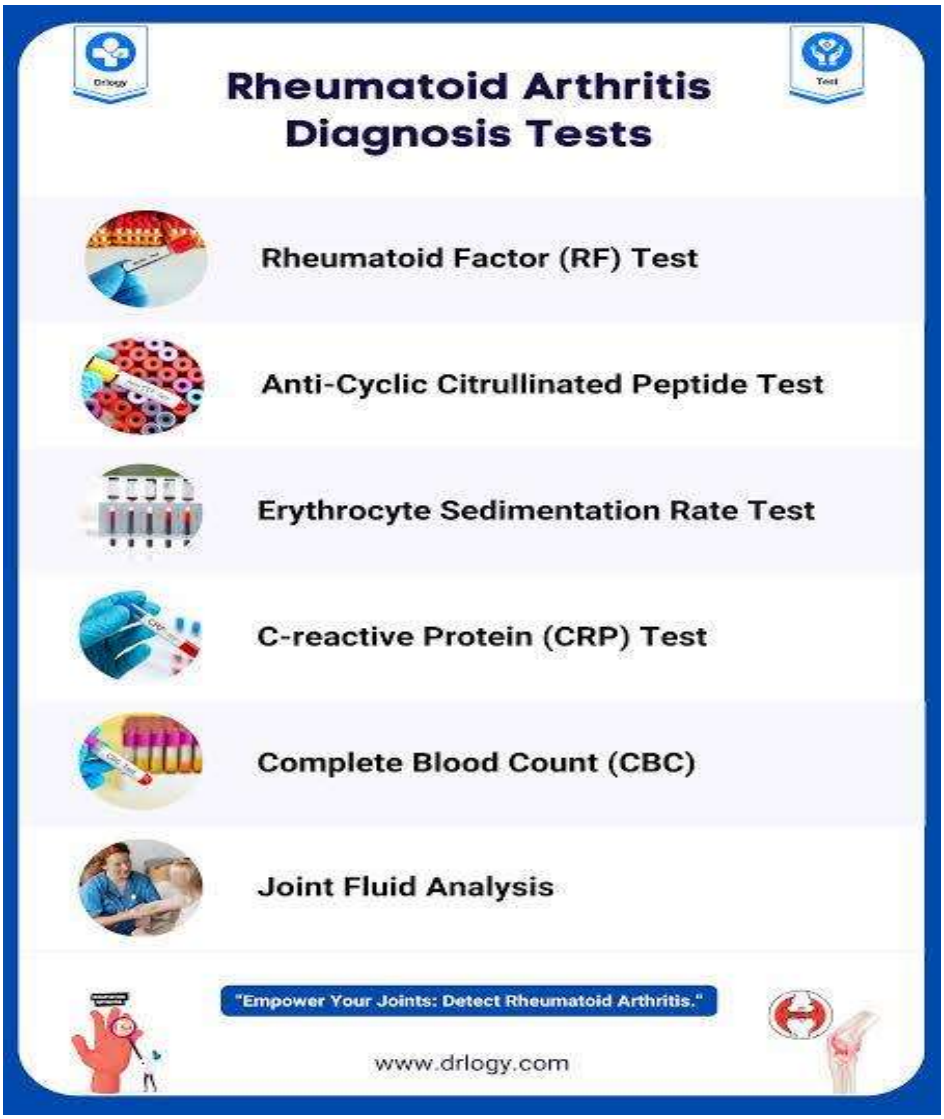


Fig: diagnosis test of RA

Diagnosis test of Rheumatoid arthritis:

1 . Rheumatoid factor (RF) Test :

This blood test checks for RF, an antibody that many people with rheumatoid arthritis can eventually have in their blood. An antibody is a special protein made by the immune system that normally helps fight invaders in the body. Not all people with RA test positive for RF; some people test positive for RF but never develop the disease; and some people test positive but have another disease. However, doctors can use this test, along with other test results and evaluations, to diagnose rheumatoid arthritis.

2 .Anti-cyclic citrullinated peptide Test (anti-CCP):

This blood test checks for anti-CCP antibodies, which appear in many people with rheumatoid arthritis. In addition, anti-CCP can appear before RA symptoms develop, which can help doctors diagnose the disease early. This test's results, along with the results from RF blood tests, are very useful in confirming a rheumatoid arthritis diagnosis.

3 .Erythrocyte sedimentation rate Test :

This test measures inflammation in the body and monitors disease activity and response to treatments.C-reactive protein.

4 .C-reactive protein :

This is another common test for inflammation that can help diagnose rheumatoid arthritis and monitor disease activity and response to treatments.

5 .Complete blood count :

This blood test measures different blood cell counts and can help diagnose anemia, which is common in people with RA.

6 .Joint fluid analysis :

- To check for joint damage, doctors may use imaging tests such as:X-rays help check for RA; however, they are not generally abnormal in the early stages of rheumatoid arthritis, before joint damage occurs. Doctors may use x-rays to monitor the progression of the disease or to rule out other causes for the joint pain.
- Magnetic resonance imaging (MRI) and ultrasound may help diagnose rheumatoid arthritis in the early stages of the disease. In addition, these imaging tests can help evaluate the amount of damage in the joints and the severity of the disease.
- Other imaging tests sometimes considered for rheumatoid arthritis include computed tomography (CT) scanning, positron emission tomography (PET) scan, bone scan, and dual-energy X-ray absorptiometry (DEXA).

Evaluation parameters :

- Laboratory testing often reveals anemia of chronic disease and thrombocytosis.
- Neutropenia may be present if Felty syndrome is present (rare).
- RF is present in 80-90% of patients with RA, with a sensitivity of 69% and a specificity of 85%. ACPA is present in 70-80% of patients, with a sensitivity of 67% and a specificity of 95%. Patients with RA with RF, ACPA, or both are designated as having seropositive RA.
- About 10% of RA patients are seronegative, meaning they do not have RF or ACPA.
- The presence of rheumatoid factor is not diagnostic of rheumatoid arthritis.
- It may be present in other connective tissue diseases such as systemic lupus erythematosus, Sjogren syndrome, scleroderma, and granulomatosis with polyangiitis.
- RF may also be found in patients with chronic infections and healthy individuals, albeit in low titers; if both RF and ACPA are positive, the sensitivity and specificity of the diagnosis increase substantially.
- RF and ACPA are present for months to years before the onset of clinical arthritis.

Classification of criteria :

- Number and size of involved joints.
    - 2 to 10 large joints = 1 point (shoulders, elbows, hips, knees, and ankles)
    - 1 to 3 small joints = 2 points (metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists)
    - 4 to 10 small joints = 3 points
    - Greater than 10 joints (including at least 1 small joint) = 5 points
- Serological testing for rheumatoid factor or anti-citrullinated peptide/protein antibody.
    - Low positive = 2 points
    - High positive = 3 points
- Elevated acute phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) = 1 point

- Symptom duration of at least six weeks = 1 point

Treatment :

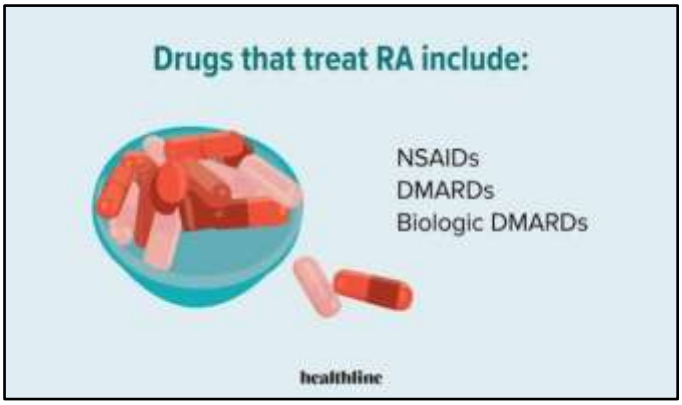
Once you have been diagnosed, you will be seen at a rheumatology clinic in a hospital. You'll usually see a specialist doctor, known as a rheumatologist, and a rheumatology nurse specialist.

There are three main ways to treat rheumatoid arthritis:

• drugs

• physical therapies

• surgery.



- **Drugs :**

Drugs used to treat rheumatoid arthritis include:

• painkillers

• non-steroidal anti-inflammatory drugs (NSAIDs)

• conventional disease-modifying anti-rheumatic drugs (DMARDs)

• biological treatments

• janus kinase inhibitors (JAK inhibitors)

• steroid treatments, as needed.

Disease-modifying anti-rheumatic drugs (DMARDs) :

Disease-modifying anti-rheumatic drugs (DMARDs) change the way a condition progresses, rather than just treating symptoms.

They're not painkillers, but they'll reduce pain, swelling and stiffness by slowing down the condition and its effects on the joints.

There are two types of DMARDs: conventional DMARDs and biological therapies.

Conventional DMARDS include drugs such as:

• hydroxychloroquine

• leflunomide

• methotrexate

• mycophenolate

• sulfasalazine.

Biologics include drugs such as:

• abatacept

• rituximab

• tocilizumab.

Janus kinase inhibitors (JAK inhibitors)

Janus kinase inhibitors (JAK inhibitors) are newer types of drugs. They are usually offered to people who can't take DMARDs or biologics, or people who haven' benefitted from them.

JAK inhibitors include:

• tofacitinib

• baricitinib.

Painkillers

Painkillers can help to relieve the pain caused by rheumatoid arthritis. But they shouldn't be the only treatment you receive. There are many types and strengths of painkillers available.

Some painkillers, such as paracetamol, can be bought over the

counter from a pharmacy or supermarket. Other painkillers, such as

codeine, are only available on prescription.

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are used to relieve pain and reduce inflammation. But they will not stop your rheumatoid arthritis from getting worse over time.

NSAIDs start working within a few hours, and the effects can be felt for up to a whole day.

Some can be bought from supermarkets or chemists, but others are only available on prescription. They're available as tablets, creams and gels, injections and patches.

NSAIDs include aspirin, ibuprofen and naproxen. You can take them along with painkillers.

Steroids

Steroids help to ease symptoms such as swelling, pain and stiffness. They are usually given to provide short-term relief.

Steroids are also sometimes known as corticosteroids. These are different to the anabolic steroids that bodybuilders and athletes use.

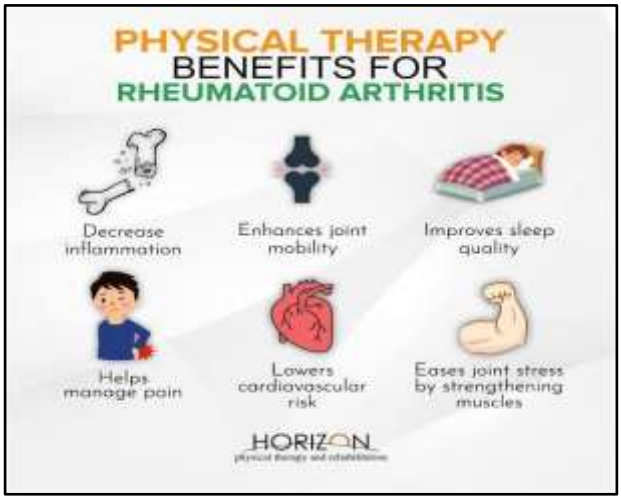
Steroids can be used as:

• a tablet or liquid you drink

• an injection directly into a joint

• an injection into a muscle.

- **Physical therapies**



You might also be offered physical therapies to ease your symptoms and improve your mobility.

- **Physiotherapy**

Physiotherapy is given by trained specialists, known as physiotherapists, to help people with an injury or long-term health condition be active and independent.

It involves movement, exercise, manual therapy, education and advice to help ease your pain and help your muscles and joints move more easily.

- **Hydrotherapy**

Hydrotherapy, also known as aquatic therapy, is exercise that takes place in a warm water swimming pool, with a physiotherapist. It normally takes place in a physiotherapy department at a hospital.

Occupational therapy

Occupational therapy provides practical support to help you keep your independence and carry on doing everyday activities. An occupational therapist can look at your work, home or school and other suggestions to make tasks easier.

Surgery

Not everyone with rheumatoid arthritis will need surgery, but sometimes it can help to reduce pain, correct the shape of your joint or improve your mobility.

Foot surgery :

Examples of this type of surgery include:

• removal of inflamed tissues from the forefoot (the front of your foot)

• removal of the small joints in theball of the foot

• straightening of toes

• fixing of joints.

Finger, hand and wrist surgery

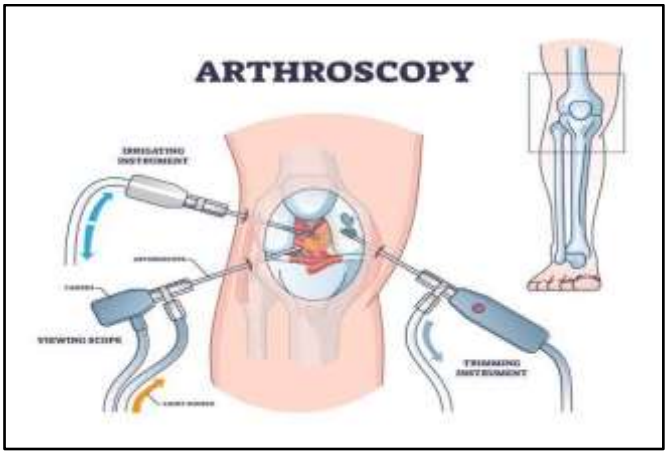
Examples of this type of surgery include:

• carpal tunnel release (used to treat carpal tunnel syndrome)

• removal of inflamed tissue in the finger joints

• release of tendons in the fingers.

Arthroscopy



Arthroscopy is a type of keyhole surgery that's used to diagnose and treat joint problems. It's often used to repair damaged cartilage, drainexcess fluid or remove bits of loose bone or cartilage.

The equipment is very small, so only small cuts are needed. Because of this, it has a faster healing time and a lower risk of infection.

Joint replacement

Some people with rheumatoid arthritis might need surgery to replace part, or all, of a joint. This is known as a joint replacement, or arthroplasty. Common joint replacements include the hip, knee and shoulder.

Thousands of people have joint replacement surgeries each year. But, as with any surgery, it's important to think about the possible risks and to discuss them with your surgeon before you decide

Complications :

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily affects the joints but can lead to various systemic complications due to inflammation. Some of the key complications include:

1. Joint Damage and Deformities :

Erosions and joint deformities: Prolonged inflammation leads to joint damage, erosion of cartilage and bone, and eventual deformities like swan neck and boutonnière deformities.

Loss of mobility: Severe joint damage can lead to reduced mobility, stiffness, and functional impairment.

2. Cardiovascular Complications

Increased risk of heart disease: RA is associated with a higher risk of cardiovascular diseases such as heart attacks, strokes, and atherosclerosis (hardening of the arteries).

Pericarditis: Inflammation of the pericardium (the lining around the heart).

Myocarditis: Inflammation of the heart muscle.

3. Lung Complications

Interstitial lung disease (ILD): RA can cause scarring of the lung tissue, leading to breathing difficulties.

Pleuritis: Inflammation of the pleura (the lining around the lungs), causing chest pain and breathing issues.

Pulmonary nodules: Small, round growths that can appear in the lungs.

4. Osteoporosis

Bone weakening: RA and the use of corticosteroids can lead to osteoporosis, increasing the risk of fractures.

5. Rheumatoid Nodules

These are firm lumps of tissue that form under the skin, often near pressure points like the elbows. They can also develop in the lungs and other organs.

6. Infections

RA and its treatments (especially immunosuppressive drugs like biologics and corticosteroids) can increase the risk of infections, including respiratory and urinary tract infections.

7. Eye Problems

Dry eyes (Sjögren's syndrome): Inflammation of the tear glands can cause dry eyes.

Scleritis: Inflammation of the sclera (the white part of the eye) that can lead to pain and vision problems.

Uveitis: Inflammation of the middle layer of the eye.

8. Vasculitis

Inflammation of blood vessels: This can affect blood flow to organs and tissues, causing skin ulcers, nerve damage, or more serious organ damage.

9. Anemia and Blood Disorders

Anemia of chronic disease: Inflammation can reduce red blood cell production, leading to fatigue and weakness.

Thrombocytosis: Elevated platelet levels can occur due to inflammation.

Felty's syndrome: A rare complication involving an enlarged spleen and low white blood cell count, increasing infection risk.

10. Neurological Issues

Carpal tunnel syndrome: Inflammation around the wrist can compress the median nerve, causing pain, tingling, and numbness in the hand.

Cervical spine issues: RA can affect the cervical vertebrae, leading to neck pain, and in severe cases, spinal cord compression.

11. Kidney Problems

Amyloidosis: This occurs when inflammatory proteins (amyloid) accumulate in the kidneys, impairing kidney function.

Nephropathy: Certain medications used to treat RA, like NSAIDs, can contribute to kidney damage over time.

12. Mental Health Concerns

Depression and anxiety: The chronic pain and disability associated with RA can lead to mood disorders, including depression and anxiety.

13. Gastrointestinal Issues

Medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the risk of stomach ulcers and gastrointestinal bleeding.

These complications highlight the importance of managing RA effectively with proper medication, regular monitoring, and lifestyle adjustments to prevent or mitigate the impact on overall health.

Conclusion :

RA is a chronic disease that requires interventions to modify disease progression. While initial presentations are related to joint inflammation, long-term sequelae can include extra-skeletal manifestations.

Rheumatoid arthritis (RA) is a chronic, autoimmune disorder primarily affecting the joints, causing inflammation, pain, stiffness, and potential joint damage over time. Although there is no cure, early diagnosis and treatment are crucial for managing the disease and slowing its progression. Medications like disease-modifying antirheumatic drugs (DMARDs), biologics, and lifestyle modifications, such as regular exercise and a balanced diet, play a key role in controlling symptoms. Collaborative care between healthcare providers and patients can significantly improve quality of life by reducing flare-ups, managing pain, and maintaining joint function.

Reference :

1. American College of Rheumatology ad hoc Committee on Clinical Guidelines. Guidelines for the management of rheumatoid arthritis. Arthritis Rheum 2002;46:328–46.

2. Lee JE, Kim IJ, Cho MS, Lee J. A Case of Rheumatoid Vasculitis Involving Hepatic Artery in Early Rheumatoid Arthritis. J Korean Med Sci. 2017 Jul;32((7)):1207–10. [PMC free article] [PubMed] [Google Scholar]

3. Fox CQ, Ahmed SS. Physician Assistant's Clinical Review Cards. Philadelphia: F. A. Davis Company; 2002. pp. . pp. 138–139. [Google Scholar]

4. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of rheumatoid arthritis in Sweden: a nationwide population-based assessment of incidence, its determinants, and treatment penetration. Arthritis Care Res (Hoboken). 2013 Jun;65(6):870-8. [PubMed]

5. Safiri S, Kolahi AA, Hoy D, Smith E, Bettampadi D, Mansournia MA, Almasi-Hashiani A, Ashrafi-Asgarabad A, Moradi-Lakeh M, Qorbani M, Collins G, Woolf AD, March L, Cross M. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. Ann Rheum Dis. 2019 Nov;78(11):1463-1471.. [PubMed]

6. Makrygiannakis D, Hermansson M, Ulfgren AK, Nicholas AP, Zendman AJ, Eklund A, Grunewald J, Skold CM, Klareskog L, Catrina AI. Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells. Ann Rheum Dis. 2008 Oct;67(10):1488-92.

7. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011 Dec 08;365(23):2205-19.

8. Long H, Liu Q, Yin H, Diao N, Zhang Y, Lin J et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: Findings from the global burden of disease study 2019. Arthritis Rheumatol 2022; 74(7): 1172-83.

9. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St Clair EW, Tindall E, Miller AS, McAlindon T. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. [PubMed]

10. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010 Jan;69(1):70-81. [PubMed]

11. Derksen VFAM, Huizinga TWJ, van der Woude D. The role of autoantibodies in the pathophysiology of rheumatoid arthritis. Semin Immunopathol. 2017 Jun;39(4):437-446. [PMC free article] [PubMed]

12. Cross M, Smith E, Hoy D, Carmona L, Wolfe F, Vos T, Williams B, Gabriel S, Lassere M, Johns N, Buchbinder R, Woolf A, March L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul;73(7):1316-22. [PubMed]

13. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, Saigo K, Morinobu A, Koshiba M, Kuntz KM, Kamae I, Kumagai S. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2007 Jun 05;146(11):797-808. [PubMed]

14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010 Sep;62(9):2569-81. [PubMed]

15. Rheumatoid arthritis: In depth. National Center for Complementary and Integrative Health. https://www.nccih.nih.gov/health/rheumatoid-arthritis-in-depth. Accessed Feb. 23, 2021.

16. Xeljanz, Xeljanz XR (tofacitinib): Drug safety communication — Initial safety trial results find increased risk of serious heart-related problems and cancer with arthritis and ulcerative colitis medicine. https://www.fda.gov/safety/medical-product-safety-information/xeljanz-xeljanz-xr-tofacitinib-drug-safety-communication-initial-safety-trial-results-find-increased. Accessed Feb. 23, 2021.

17. Bemis EA, Demoruelle MK, Seifert JA, Polinski KJ, Weisman MH, Buckner JH, Gregersen PK, Mikuls TR, ODell JR, Keating RM, Deane KD, Holers VM, Norris JM. Factors associated with progression to inflammatory arthritis in first-degree relatives of individuals with RA following autoantibody positive screening in a non-clinical setting. Ann Rheum Dis. 2021 Feb;80(2):154-161. [PMC free article] [PubMed]

18. Kortekangas P, Aro HT, Tuominen J, Toivanen A. Synovial fluid leukocytosis in bacterial arthritis vs. reactive arthritis and rheumatoid arthritis in the adult knee. Scand J Rheumatol. 1992;21(6):283-8. [PubMed]

19. Anderson J, Caplan L, Yazdany J, Robbins ML, Neogi T, Michaud K, Saag KG, O'Dell JR, Kazi S. Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. Arthritis Care Res (Hoboken). 2012 May;64(5):640-7. [PMC free article] [PubMed

20. England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR, O'Dell JR, Ranganath VK, Limanni A, Suter LG, Michaud K. 2019 Update of the American College of Rheumatology Recommended Rheumatoid Arthritis Disease Activity Measures. Arthritis Care Res (Hoboken). 2019 Dec;71(12):1540-1555. [PMC free article]

21. 15. American College of Rheumatology. Updated guideline for the management of rheumatoid arthritis. Project plan—October 2018. Accessed January 13, 2019.