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Rheumatoid Arthritis: A Comprehensive Review of Pathogenesis, Clinical Features and Management

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Abstract:

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by symmetric joint inflammation, leading to joint pain, swelling, and eventually joint damage and disability. This review aims to provide a comprehensive overview of the pathogenesis, clinical features, and management of RA. It covers the underlying mechanisms driving the disease, risk factors, and genetic predisposition. Additionally, the review explores the varied clinical manifestations of RA, from joint symptoms to systemic effects, and highlights the importance of early diagnosis and timely intervention. The various treatment approaches, including non-pharmacological strategies, conventional disease-modifying drugs, biologic agents, and targeted therapies, are discussed in detail, emphasizing their roles in symptom control, disease modification, and overall patient well-being. Moreover, recent research insights and future perspectives in the field of RA management are also explored.

Keywords: *Rheumatoid Arthritis, pathogenesis, clinical features, Joint Pain, Chronic Autoimmune Disease.*

Introduction:

A series of inflammatory joint illnesses known as arthritis are distinguished by joint pain, stiffness, swelling, and decreased mobility. People of all ages are affected, and it is one of the top causes of disability worldwide. This article offers a thorough analysis of arthritis joint pain, covering the many forms, causes, signs and symptoms, diagnostic procedures, and treatment options. An autoimmune illness that affects the joints and maybe other bodily parts, rheumatoid arthritis (RA) is a chronic condition. The cells and proteins in our bodies that fight infections make up the immune system. When a portion of our body is attacked by our immune system as if it were an outside invader like a virus or bacteria, it is known as an autoimmune disease. The immune system attacks the synovial membrane in rheumatoid arthritis. Synovial fluid is secreted into the joint by the synovial membrane. The joint fluid that lubricates and nourishes the joint is called synovial fluid. In rheumatoid arthritis, the immune system may also target other tissues, but the synovium, or synovial membrane, is typically the main target. Attacks on the synovial membrane cause inflammation (synovitis), which can thicken and destroy the membrane. Because it is not being secreted, synovial fluid is also eliminated along with the synovial membrane. The surrounding structures may also get affected, which might result in the joint abnormalities associated with rheumatoid arthritis [1-2].

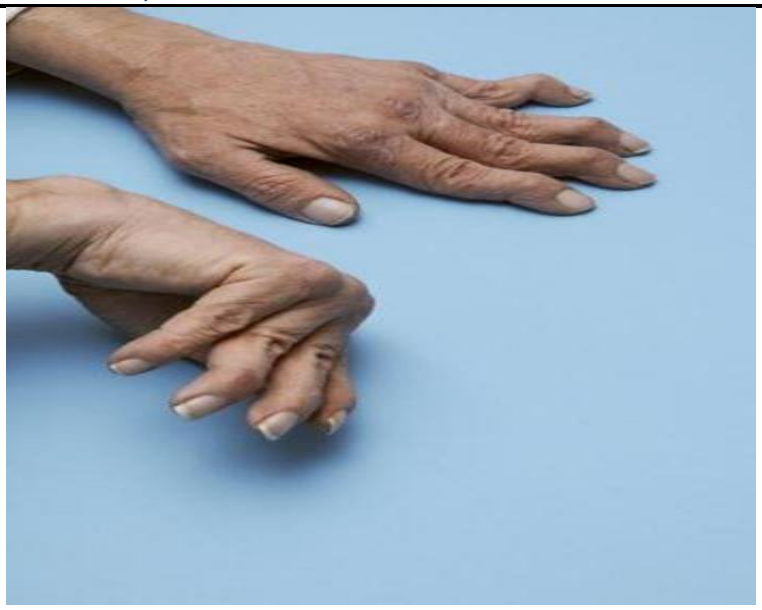

Fig.1: Rheumatoid Arthritis

Epidemiology of RA:

Rheumatoid Arthritis (RA) is a moderately prevalent chronic autoimmune disease that affects people of all ages and ethnic origins as of my most recent update in September 2021. The epidemiology of RA might range among various demographics and geographical areas, and continuing study may offer up-to-date statistics. Here are some significant RA epidemiology features:

Prevalence: Approximately 0.5% to 1% of adults globally are thought to have RA. Women are more frequently affected than men, and the prevalence tends to rise with age.

Age of Onset: Although RA can start at any age, it usually begins between the ages of 30 and 60. However, children and teenagers might be impacted by juvenile idiopathic arthritis (JIA), a group of RA-related arthritic diseases.

Gender: RA is two to three times more common in women than in men. Although the cause of this gender gap is not entirely known, hormonal and genetic variables may be at play.

Geographic Variation: variable locations and nations may have a variable prevalence of RA. In developed, temperate regions like North America, Northern Europe, and parts of Asia, higher rates are frequently seen.

Age of Onset: While RA can start to manifest at any age, it most frequently begins between the ages of 30 and 60. Juvenile idiopathic arthritis (JIA), a class of RA-related arthritis disorders, can, nonetheless, affect kids and teenagers.

Gender: Women have a two- to three-fold higher risk of developing RA than do men. Although the cause of this gender inequality is not entirely known, it may include hormonal and genetic components.

Geographic Variation: The incidence of RA varies between different nations and areas. Higher rates are frequently seen in developed, temperate regions like North America, Northern Europe, and parts of Asia.

Types of Arthritis:

Based on the causes of arthritis changes, several forms of arthritis can be named. A particular type of arthritis occurs in a particular age group and in a particular joint [39].

Table.1: Types of Arthritis

Arthritis	Age Group	Site
Osteoarthritis	Elderly	Knee, lower back, Fingers
Juvenile Rhumatoid Arthritis	Childhood	Knee, hip
Septic arthritis	Childhood	Knee, hip
Rhumatoid arthritis	Young adults	Hip, Knuckles, Knee
Ankylosing spondylitis	Young adults	Lower back, Cheast

Psoriatic arthritis	Young adults	Knee
Traumatic arthritis	Any	Any (Commonly knee, hip, ankle)
Gout	Young adults	Big toe, knee

Clinical Features:

Chronic autoimmune disease called rheumatoid arthritis (RA) primarily affects the joints but can also affect other body organs and tissues. Individuals with RA may exhibit a wide range of clinical symptoms, and the disease's progression could alternate between remissions and flare-ups. Here are a few typical rheumatoid arthritis clinical signs and symptoms: [3].

Joint Complaints:

On both sides of the body, various joints are frequently affected by RA. The joints that are most frequently affected include the knees, elbows, shoulders, hips, and hands (wrist, knuckle, and finger joints), foot (ankles and toes). Symptoms of the joints include:

Joint pain: Pain in the affected joints, frequently worse in the morning or following periods of inactivity.

Joint swelling: Inflammation causes swelling and a feeling of fullness in the affected joints.

Joint stiffness: Morning stiffness that lasts for over an hour, as well as stiffness that may follow extended periods of inactivity.

Reduced range of motion: As the condition worsens, damage to the joints may cause restrictions in movement and abnormalities.

Weariness: Even during times of low disease activity, many patients with RA experience weariness and an overall feeling of being sick. Rheumatoid nodules are tiny, solid lumps that can form beneath the skin, typically near pressure points or troubled joints. Although nodules do not always appear in RA patients, they are a hallmark of the condition [4].

Systemic symptoms:

Because RA is a systemic illness, the entire body may be affected. Some people may go through:

- Low-grade fever, appetite loss, and weight loss.
- Joint Damage and Deformities: Over time, persistent inflammation in the joints can cause cartilage loss, joint damage, and deformities.
- Anemia (low red blood cell count) is another factor.
- The form and alignment of the joints may alter as a result, which may influence how well the joints work.
- Extra-Articular Manifestations: Organs and tissues outside the joints may be impacted by RA, which can result in a number of difficulties, such as:
- Inflammation in the lungs from rheumatoid lung disease results in breathlessness and other respiratory symptoms.
- Rheumatoid nodules can appear in the lungs as well as other organs, as was previously described.
- Anemia and other disorders of the blood.

It's crucial to remember that every person with RA experiences the disease differently, both in terms of severity and specific symptoms. To control symptoms, avoid joint deterioration, and enhance overall quality of life for RA patients, early diagnosis and effective treatment are crucial. The need of getting a medical evaluation from a rheumatologist or other trained healthcare provider cannot be overstated if you think you may have rheumatoid arthritis or are experiencing joint pain and related symptoms. They are able to carry out a complete examination, offer a reliable diagnosis, and suggest a personalized treatment strategy based on your particular requirements [5].

Etiology for Arthritis:

The exact etiology or cause of Rheumatoid Arthritis (RA) is not fully understood, but it is believed to result from a complex interplay of genetic, environmental, and immune system factors.

Here are some key factors that contribute to the development of RA:

1. **Genetic Factors:** There is a strong genetic component to RA, as it tends to run in families. Certain genetic markers, such as specific variants of the human leukocyte antigen (HLA) genes (HLA-DRB1), are associated with an increased risk of developing RA. However, having these genetic markers does not guarantee that someone will develop the disease, as other factors are also involved.

2. **Autoimmune Response:** RA is classified as an autoimmune disease, which means the body's immune system mistakenly attacks its tissues. In the case of RA, the immune system targets the synovium, the lining of the membranes that surround the joints. This leads to chronic inflammation and damage to the joints.

3. **Environmental Triggers:** Various environmental factors may trigger the onset of RA in individuals with a genetic predisposition. Some potential triggers include smoking, exposure to certain infections (e.g., Epstein-Barr virus), and hormonal changes, particularly in women.

4. **Inflammatory Pathways:** Inflammation plays a crucial role in the development and progression of RA. The release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-alpha) and interleukins, contributes to joint inflammation and tissue damage.

5. **Abnormal Antibody Production:** In many people with RA, there is an abnormal production of antibodies, specifically rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. These antibodies target healthy joint tissues, leading to immune system attacks on the joints.

6. **Synovial Membrane Changes:** In RA, the synovial membrane that lines the joint becomes inflamed and thickened. This inflammation causes the release of enzymes that can break down cartilage and bone, leading to joint damage.

7. **Gut Microbiota:** Emerging research suggests a potential link between gut health and the development of autoimmune diseases like RA. Changes in the gut microbiota (the community of microorganisms living in the digestive tract) might influence the immune system and contribute to the development of RA [6].

Fig.2: Difference between Normal joints and Rheumatoid Arthritis joints

Inflammation is sustained by an interaction between fibroblasts and synovial macrophages. The study of synovium in established, rather than early, disease, where CD4 T-cells and monocytes-macrophages migrate into, and remain in the synovial interaction of cellular adhesion molecules with counterligands expressed on extracellular matrix molecules (e.g., collagen, fibronectin), provides the majority of our knowledge of the inflammatory process and cellular infiltrate in the rheumatoid joint. In contrast, neutrophils are almost exclusively found in the fluid of the synovial cavity and very infrequently in the synovial tissue. Their movement over the synovial lining and into the joint cavity through the synovial interstitium may be caused by the absence of particular adhesion molecules for extracellular matrix constituents [7].

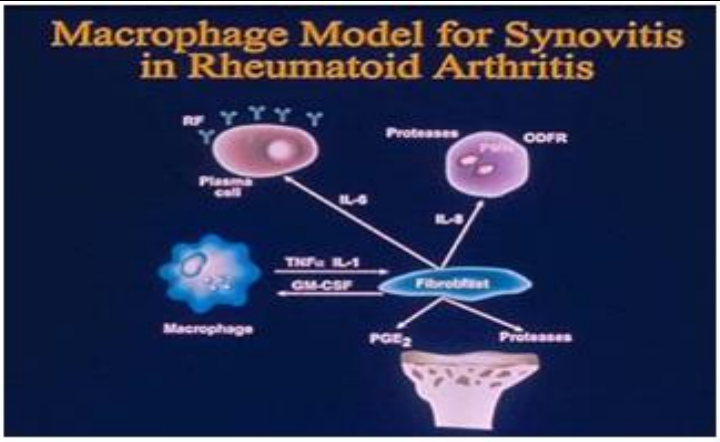

Fig.3: Pathogenesis of Rheumatoid Arthritis

The "T cell centric" theory of RA postulates that CD4 cell activation would start and maintain the inflammatory response in the rheumatoid joint. It's interesting to note that although remaining in high numbers in the synovium during the whole duration of the disease, CD4 cells seem dormant throughout the chronic stage of the illness. For instance, there is relatively little secretion of certain cytokines (such as IL2, IL4 and g-IFN) and expression of surface antigens (such IL2 and transferring receptors) that are linked to an activated T cell state [8].

Table.2: Cellular sources of synovial cytokines in RA

Products of T cells	IL-2
	IL-3
	IL-4
	IL-6
	IFNg
	TNFb
	GM-CSF

Contrarily, RNA synovium and synovial fluid have high levels of expression of cytokines that are known to be largely produced by "effectors" cells (macrophages) and connective tissue cells (fibroblasts), as determined by ELISA or mRNA studies. These cytokines consist of GM-CSF, IL1, IL6, and IL8. The "macrophage-fibroblast theory" of RA claims that these two cell types are primarily in charge of producing a chronic inflammatory state that is self-perpetuating and in which T cell involvement may no longer be essential. In this case, the synovial fibroblast is continuously kept in an activated state by the secretion of IL-1 and TNF by the activated macrophage [9].

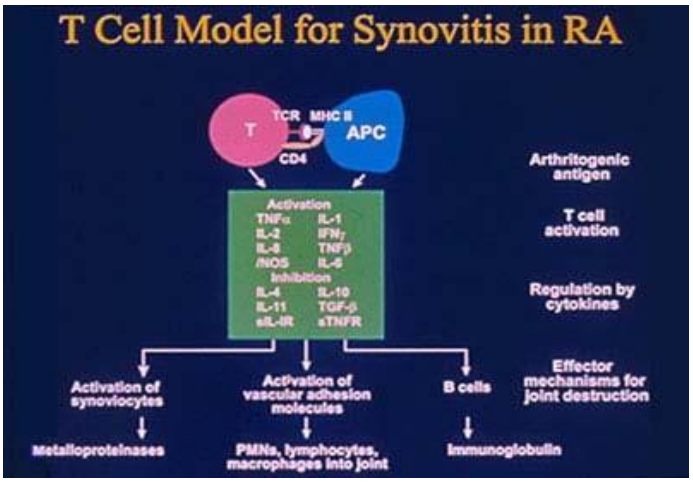

Fig.4: Synovitis in RA patients

The fibroblast, in turn, secretes large amounts of: a) cytokines – IL6, IL8 and GM-CSF; b) prostaglandins; c) protease enzymes. GM-CSF feeds back to promote the maturation of newly recruited monocytes to macrophages.IL-8 and IL-6 contribute to the recruitment and/or activation of yet other cell populations, while the prostaglandins and proteases act directly to erode and destroy nearby connective tissues such as bone and cartilage [10].

Inflammatory Mediators in RA:

IL-1 and TNF have significant systemic effects in addition to stimulating synovial cells to release inflammatory mediators.

Table.3: Mediators in RA

Cellular	Systemic
• Upregulation of adhesion molecules • Costimulant for T cells • Induction of prostanoid synthesis • Induction of cytokine synthesis (IL-6, IL-8, GMCSF)	• Fever • Decreased appetite • Muscle wasting

The elevation of IL-6 production serves as a mediator for some of these systemic effects. Another important biological element of the rheumatoid synovium is mature plasma cells that release rheumatoid factor. CD4 T cells have traditionally been thought to be the stimulus for B cells to mature into immunoglobulin-secreting plasma cells, however as has already been mentioned, CD4 T cells are not activated in the chronic phase of rheumatoid arthritis. However, IL-6 is a strong stimulant for the development of B cells into plasma cells. The "T cell independent" signal for ongoing plasma cell activation and rheumatoid factor generation is thus presumably being provided by synovial fibroblasts. Additionally, IL-6 increases the production of acute phase proteins and inhibits albumin synthesis by the liver. Therefore, IL-6 plays a major role in the elevation of ESR [11].

Table.4: Effects of IL-6

Effects of IL-6	
B cell maturation	Ig, rheumatoid factor , hypergammaglobulemia
Hepatocyte stimulus	Acute phase proteins (high ESR) Decreased albumin synthesis

Neutrophils can be aspirated in the synovial fluid after being drawn in significant quantities to the rheumatic cavity. Complement activation is not one of the main characteristics of RA. C5a is therefore not anticipated

to have a major impact on the recruitment of neutrophils to the joint. But IL-8 also acts as a strong and targeted chemotactic stimulation for neutrophils. Since synovial fibroblasts border the joint cavity, their production of this cytokine there is likely what causes neutrophils to be specifically required in the synovial cavity. The synovial fluid contains active neutrophils that release oxygen-derived free radicals that depolymerize hyaluronic acid and inactivate endogenous protease inhibitors, causing joint injury. As the pannus invades adjacent bone and cartilage, synovial fibroblasts also release prostaglandins and proteases. PGE2 promotes bone resorption and is a factor in the radiographically visible erosions at the synovial bone attachment site. The collagen and proteoglycan matrix of bone and cartilage is broken down enzymatically by the proteases (collagenase, stromelysin, and gelatinase). The fact that IL1 (and TNF) inhibit the formation of these matrix molecules adds to this damaging effect. As a result, IL1 causes a "double insult" to connective tissue by both promoting its breakdown (by increasing the production of proteases) and impeding its repair (by inhibiting the production of collagen and proteoglycans) [12].

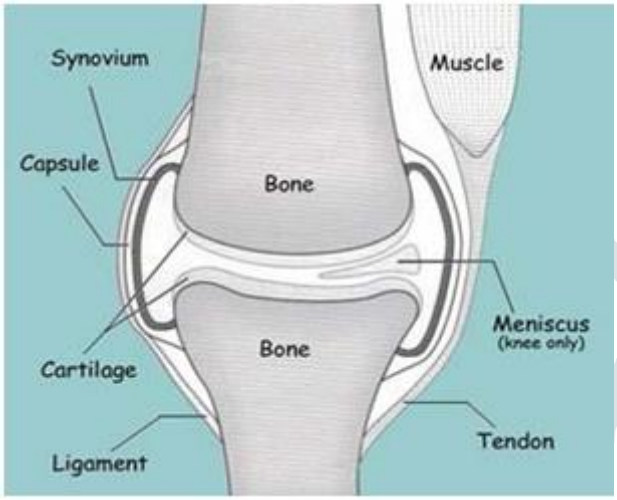

Fig.5: Normal view joint

A joint afflicted by arthritis loses its capacity to allow for easy bone-to-bone motion. this is as a result of the following changes occurring gradually over time.

- A reduction in synovial fluid volume.
- Articular cartilage deterioration.
- The synovium's thickness and stiffness, as well as the joint capsule's stiffness.
- Ageing, autoimmune diseases (when the immune system attacks the body), hereditary problems, traumatic events (accidents, falls, blunt injuries), infections, and other factors can all contribute to these changes.
- After some time, the arthritic changes are usually irreversible and cannot be stopped. Therefore, the only way to stop more harm is by early detection and treatment [13].

Symptoms of Rheumatoid Arthritis:

(Stiffness from osteoarthritis, for instance , usually clears up within half an hour).even after remaining motionless for a few moments , the body can stiffen. Movement becomes easier again after loosening up.

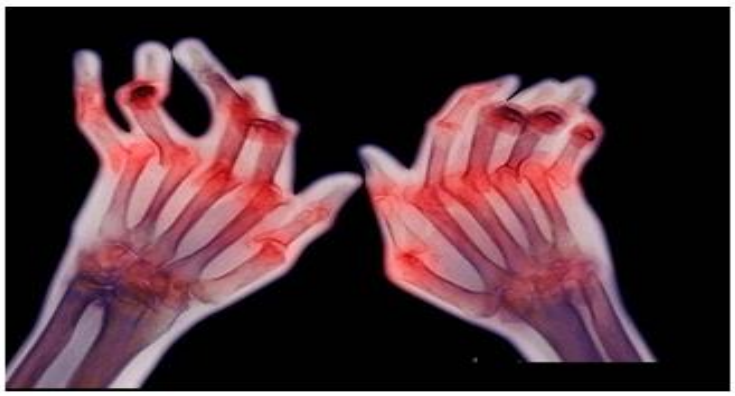

Fig.6: Symptoms of RA

Swelling and Pain:

Joint pain and swelling must last for at least six weeks before a RA diagnosis is made. Inflamed joints are typically swollen and frequently feel warm and "boggy" to the touch. Depending on which hand the person uses most frequently, the discomfort is frequently symmetrical but may be more intense on one side of the body (Fig. 6).

Particular Joints Affected:

Although RA generally always starts in the wrists and knuckles, it can also affect the knees and the joints in the ball of the foot. The cervical spine, shoulders, elbows, fingers, temperomandibular joint (mouth), and even joints between incredibly small bones in the inner ear may all be affected. Although osteoarthritis is common in the fingertips, where RA is less common, the joints at the base of the fingers are frequently uncomfortable.

Nodules: Nodules might develop at any time during the progression of the illness. Rarely, nodules may become painful and infected, especially if they are in areas that experience stress, like the ankles. Rheumatoid vasculitis, a disorder that can affect the blood vessels in the lungs, kidneys, or other organs, can occasionally be indicated by nodules.

Fluid Accumulation:

Fluid may build up, especially in the ankles. A Baker cyst is created when fluid builds up in the joint sac behind the knee. This cyst, which occasionally stretches down the back of the calf and causes agony, feels like a tumour. Baker cysts frequently form in persons without RA [14].

Symptoms of the flu:

Early RA symptoms might include exhaustion, weight loss, and fever. Some individuals compare these symptoms to those of the flu or a cold, although RA symptoms can linger for years.

Children's Symptoms:

Juvenile RA in children, commonly known as Still's disease, is typically accompanied by a high fever, shivering chills and joint discomfort and swelling. It's possible to have a pink skin rash [15].

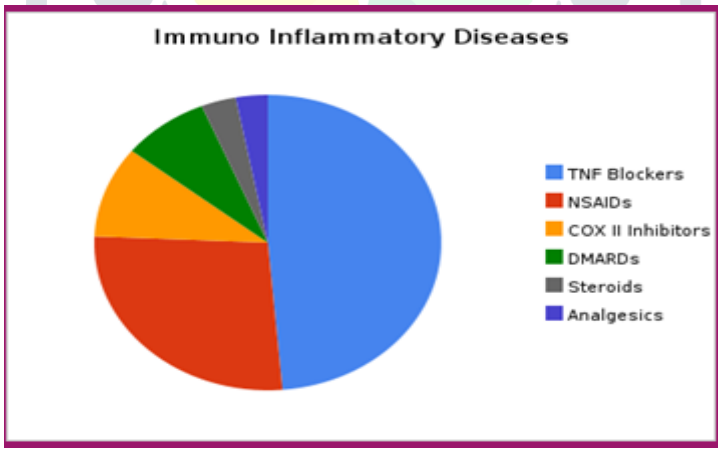

Fig.7: Medication of RA

Medications:

Many medications used to treat rheumatoid arthritis have adverse effects that could be life-threatening. Typically, drugs with the fewest side effects are first prescribed by doctors. As your illness worsens, you might require stronger medications or a mix of medications. Rheumatoid Arthritis (RA) treatment seeks to lessen inflammation, control symptoms, avoid joint damage, and enhance overall quality of life for those who have the condition. The choice of treatment for RA relies on the severity of the condition, the patient's reaction to therapy, and other medical factors. There are various categories of drugs that are used to treat RA. The following are some typical drugs for RA:

NSAIDs Non-steroidal anti-inflammatory drugs:

NSAIDs are used to treat RA inflammation and discomfort. Although they assist in reducing joint discomfort and stiffness, they do not halt the disease's course or stop joint destruction. Ibuprofen, naproxen, and Diclofenac are among NSAIDs.

Disease-Modifying Antirheumatic Drugs (DMARDs):

DMARDs are a group of medications that help slow down the progression of RA and prevent joint damage. They work by targeting the underlying autoimmune process that causes inflammation. Some commonly used DMARDs for RA include:

- Methotrexate: One of the most commonly prescribed DMARDs for RA. It helps reduce joint inflammation and prevent joint damage.
- Sulfasalazine.
- Hydroxychloroquine.
- Leflunomide.
- Azathioprine.

Biologic Response Modifiers (Biologics):

Biologics are a type of DMARD that target specific components of the immune system involved in RA. They are often used when conventional DMARDs are not effective. Biologics are administered by injection or infusion and include:

Tumor Necrosis Factor (TNF) Inhibitors:

- Examples include adalimumab, etanercept, and infliximab.
- Interleukin-6 (IL-6) Inhibitors: Tocilizumab is an example.
- Interleukin-1 (IL-1) Inhibitors: Anakinra is an example.
- B-cell Inhibitors: Rituximab and ocrelizumab target B-cells involved in the immune response.
- T-cell Co-stimulation Inhibitors: Abatacept is an example.

Janus Kinase (JAK) Inhibitors:

JAK inhibitors are a newer class of medications that target specific enzymes involved in the immune response. They help reduce inflammation and slow the progression of RA. Examples include tofacitinib and baricitinib.

Glucocorticoids (Steroids):

Short-term use of oral or injected Glucocorticoids, such as prednisone, can help quickly reduce inflammation and provide symptom relief during disease flares. However, their long-term use is generally avoided due to potential side effects.

Analgesics:

These are pain-relieving medications, such as acetaminophen, that can be used to manage pain in RA. The choice of medications and treatment approach should be individualized based on factors such as disease severity, response to therapy, presence of other medical conditions, and patient preferences. Treatment plans often involve a combination of medications to achieve optimal control of RA symptoms and prevent joint damage [16].

Mechanism of Action:

By inhibiting fatty acid COX enzyme, trolamine salicylate inhibits the production of prostaglandins and thromboxanes in inflammatory cells involved in generating pain and inflammation [17].

Inflammation:

Inflammation (Latin, inflammo, "I ignite, set alight") is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants (Fig.8).Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

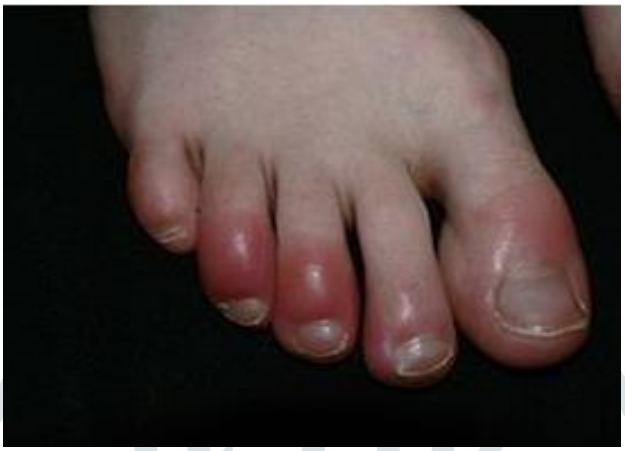

Fig.8: Inflammation

Classification of Inflammation:

Inflammation can be classified as either *acute* or *chronic*. *Acute inflammation* is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as *chronic inflammation*, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process [18].

Symptoms of Inflammation:

- Redness.
- Swollen joint that's tender and warm to the touch.
- Joint pain.
- Joint stiffness.
- Loss of joint function.

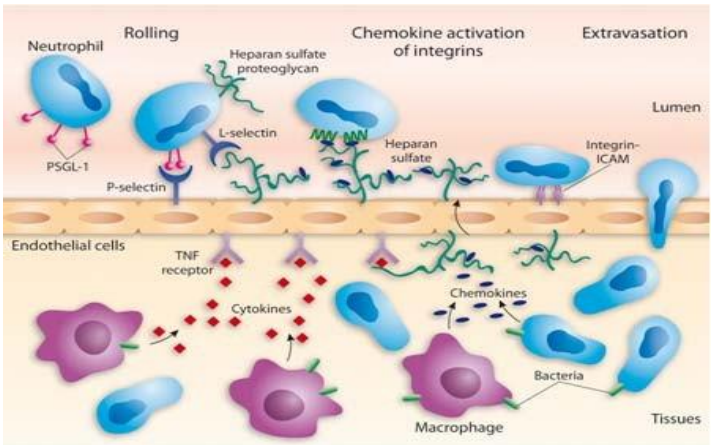

Fig.9: Mechanism of Inflammation

Anti- inflammatory Effects:

Many mediators coordinate inflammatory and allergic reaction. While some are produced in response to specific stimuli (e.g. Histamine in allergic inflammation) there is considerable redundancy, and each facet of response – vasodilatation, increased vascular permeability, cell accumulation, etc-can be produced by several separate mechanisms. The NSAIDS reduce mainly those component of the inflammatory and immune response in which prostaglandin, mainly derived from COX-2, play a significant part .These include:

- Vasodilatation.
- Oedema (by an indirect action; the vasodilatation facilities and potentiating the action of mediators such as histamine that increase the permeability of post capillary venules.
- Pain again potentiating other mediators, such as bradykinin.

The NSAIDs suppress the pain, swelling and increasing blood flow associated with inflammation but have little or no action on the actual progress of the underlying chronic disease itself. As a class, they are generally without effect on other aspects of inflammation, such as leucocytes migration, lysosomal enzyme release and toxic oxygen radical production that contribute to tissue damage in chronic inflammatory conditions such as rheumatoid arthritis, vasculitis and nephritis [19].

Conclusion:

In conclusion, Rheumatoid Arthritis (RA) is a chronic autoimmune disorder that primarily affects the joints, causing inflammation, pain, and joint damage. It is characterized by an abnormal immune response that leads to the attack of the synovial membrane, resulting in chronic joint inflammation. While the exact cause of RA remains unclear, a combination of genetic, environmental, and immune system factors is believed to contribute to its development. RA can affect people of all ages and genders, but it is more common in women and tends to start between the ages of 30 and 60. The disease often presents with symmetrical joint involvement, joint pain, swelling, stiffness, and reduced range of motion. In addition to joint symptoms, RA can have systemic effects, causing fatigue, low-grade fever, and other systemic manifestations. If left untreated, RA can lead to joint damage, deformities, and disability, significantly impacting a person's quality of life. Early diagnosis and prompt treatment are essential to manage symptoms, slow down disease progression, and prevent joint damage. Treatment for RA typically involves a combination of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom relief, disease-modifying Antirheumatic drugs (DMARDs) to slow down disease progression, biologics that target specific components of the immune system, and Janus Kinase (JAK) inhibitors. Glucocorticoids may also be used for short-term symptom relief during flares. In addition to medications, lifestyle changes, physical therapy, and regular exercise can play a crucial role in managing RA and maintaining joint function and mobility. Regular monitoring and follow-up with a rheumatologist or qualified healthcare professional are essential to assess the disease's progression, adjust treatment as needed, and optimize outcomes for individuals living with Rheumatoid Arthritis. Research and advancements in understanding the disease continue to improve management and treatment options available, providing hope for better outcomes and a higher quality of life for those affected by RA.

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