

Rheumatoid Arthritis

Introduction

Definition and Overview:

Rheumatoid arthritis (RA) is a chronic noninfectious disorder involving your immune system, which normally defend against infection and disease to help protect the body. RA occur when the immune system attacks the body's own tissues. It mostly affects the joints and causes pain, swelling, stiffness (hard to move), and loss of function in joints. Additionally, it leads to inflammation (painful swelling) in various organs which can bring about joint damage and malformations (something that is abnormal shape) if it not treated well or on time.

Historical Context:

RA has a long history. There are clues on its pathogeny provided by historical research. The ancient pathological evidence indicates the entity of RA in America since 8000 BC and in Europe since the 7th century. The symmetric chronic polyarthritis producing characteristic deformities representations and descriptions can be found in Rome since 100 BC and in India since 500 BC. In 1578 in Mexico, the first difference between RA and gout was published. The lack of recognition of RA by official medicine before 1800 was because different historical conditions. In the 19th century, the socioeconomic situations influenced the recognition of RA as a distinct existence.

Epidemiology:

Environmental factors such as microbial infections and smoking strongly interact to influence RA onset and progression, in addition to, susceptibility across population, although their precise mechanisms are not fully understood.

Etiology

Causes and Risk Factors:

Multiple gene polymorphisms have been identified and established to increase the risk of developing rheumatoid arthritis and, with reference to their function, the vast majority are associated with immunity. The most important are associated with the HLA genes; more specifically, HLA-DRB1 genes involved in the differentiation of the immune system between the body's own proteins and the proteins of the foreign invaders. The alterations in other genes have a comparatively lesser contribution towards the condition of rheumatoid arthritis. Some other factors can also non-genetic son predispose the patient to developing the condition although the way this happens is not well understood. Possible causes include fluctuations in estrogen/progesterone levels (in women), dust/fibers exposure, viral-bacterial infection.

Chronic smoking is a confirmed risk-indicator; it aggravates the condition and may produce more severe symptoms in patients with the disease. Moreover, it is well understood that their risk of the disease rises if a close relative already has it.

Genetic and environmental influences:

Rheumatoid arthritis (RA) results from a combination of genetic and environmental factors. Genetic predisposition, particularly markers like HLA-DRB1 alleles such as DRB104, increases susceptibility to RA. Meanwhile, factors such as smoking, infections, and hormonal fluctuations can trigger or worsen the condition. The interaction between genetics and the environment contributes to the diverse causes and symptoms of RA across different individuals.

Clinical Features

Signs and Symptoms:

The development of RA differs in every person, beginning with the signs of milder to moderate inflammation in several joints and if the inflammation progresses it involves all the other joints in the body. Symptoms include: Any Joint pain, Stiffness, Swelling, Tenderness and any form of pain that lasts more than half an hour in the morning or after a period of inactivity. Moreover, RA mostly impacts the fingers, wrists, ankles, and toes of the people suffering from it. It can also, affect daily activities like gripping or bending elbows and knees. Feeling tired or loss of energy, fatigue, occasional fever, and loss of appetite are common. Moreover, RA may lead to complications such as rheumatoid nodules (lumps on the skin), anemia, neck pain, dry eyes, and inflammation of blood vessels or lung tissue.

Disease Stages and Progression:

RA symptoms and progression can vary widely from person to another, and can change over time. Here, what can happen at each stage of the disease:

The early stage: In the early stages, RA often causes joint swelling, pain, stiffness and fatigue.

The moderate-stage: The moderate stage of RA is when damage to cartilage can begin to appear, resulting in loss of mobility and range of movement. Fatigue can also become a big problem.

The severe stage: RA's severe stage means that synovial inflammation has eroded the cartilage of the joint and has moved on to eroding the bone. This stage can mean more pain and swelling; less mobility and muscle strength; and the beginning of visible joint deformities.

The end stage: The end stage of RA means that most of the tissue that was formerly inflamed has been destroyed, and bone erosion has occurred. The affected joints stop functioning and patients experience pain and severe loss of mobility.

Complications:

Complications and associated conditions due to uncontrolled systemic inflammation in rheumatoid arthritis (RA) include:

1. **Chronic joint inflammation:** leads to X-ray damage, progressive deformity, and reduced function.
2. **Anemia of chronic disease and Felty's syndrome:** are common in seropositive RA.
3. **Secondary Sjögren's syndrome:** linked to RA, affects up to **10%** of patients and can cause lung issues.
4. **Rheumatoid vasculitis:** is a rare but serious complication, ranging from finger involvement to symptoms similar to polyarteritis nodosa.
5. **Pulmonary issues:** such as pleuritis, bronchiolitis, and interstitial lung disease (ILD) affect **5-16%** of RA patients, often tied to specific antibodies and higher mortality.

Cardiovascular Disease: RA increases the incidence of CAD and peripheral vascular disease because the arteries become hardened at a faster pace; it adds to insulin resistance and diabetes.

Lymphoma: RA patients are at a higher risk of developing non-Hodgkin lymphoma particularly when they are still having active disease.

Various emphases concerning comorbidity associated with RA and its management include the occurrence of early mortality, predisposition to severe infections, and promotion of bone thinning and osteoporosis due to the use of glucocorticoids as well as higher risk of venous thromboembolic disease. This risk may be affected more by disease activity than directly by specific RA treatments such as TNF inhibitors and JAK inhibitors. Effective management involves precise monitoring and personalized treatment plans suited to each patient's requirements.

Others: Depression is a significant comorbidity of RA, with many of the affected patients exposed to chronic disease activity and severe functional limitation. Thus, the analysis of numerous papers from 2013 states that depression is found in RA patients with a frequency of 17-39%.

Diagnosis

Diagnostic Criteria:

Diagnostic criteria are particular indicators such as symptoms, signs, and test result that used to determine if someone suffers from rheumatoid arthritis (RA). These criteria are established through clinical experience and extensive investigation. Not all individuals with RA will display every criterion. Generally, the diagnostic criteria for RA include:

1. Inflammation affecting two or more large joints (such as shoulders, elbows, hips, knees, and ankles).
2. Inflammation affecting smaller joints.
3. Positive biomarker tests like rheumatoid factor (RF) or CCP antibodies.
4. Elevated levels of CRP (C-reactive protein) or an elevated sedimentation rate (sed rate).
5. Symptoms persisting for more than six weeks.

Diagnostic Tests and Procedures:

The diagnosis of Rheumatoid arthritis (RA) is not thus a single or a unique affair because of this and because the disease manifests in so many ways and in so many parts. Initially, the doctor including the General Practitioner, assesses for clinical signs of joint inflammatory changes and reduced range of movement NOT limited to evaluation of all the symptoms for diagnosis. Some of the blood tests include: data such as Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and full blood count to assess the level of inflammation and to rule out other causes of the symptoms. Rheumatoid factor and anti cyclic citrullinated peptide check or anti-CCP is suggestive for RA but not all RA patients are positive for both. Diagnostic examinations, such as X-ray or MRI, show inflammation and the harm done to the tissues in order properly to develop the treatment strategy and prevent the further growth of pathology. Outcome measures record daily functional capacity, and grip strength to try and capture treatment input's ability to manage RA as the condition evolves over time.

Differential Diagnosis:

The following are other possibilities to address when distinguishing the Diagnosis of RA; The other forms of arthritis that need to be compared and contrasted include the psoriatic arthritis, haemochromatosis, sarcoidosis, and some of the other types of polyarthritis that accompany most connective tissue diseases, such as lupus erythematosus or the first symptoms of Sjogren's syndrome, among others. Polyarthritis was listed as resulting from rubella, parvovirus B-19, Lyme disease, and reactive arthritis associated with infection of the GI or GU tracts. In addition, its diagnosis in elderly is always complicated because PPHEA can also occur in the polyarticular chronic form.

Pathophysiology

Mechanisms of Disease Development:

Rheumatoid Arthritis (RA) can be classified into two main subtypes based on the presence or absence of anti-citrullinated protein antibodies (ACPAs). Citrullination, a process mediated by the enzyme peptidyl-arginine-deiminase (PAD), converts positively charged arginine to neutral citrulline through post-translational modification. ACPAs are found in about 67% of RA patients and are valuable for diagnosing early, undifferentiated arthritis, predicting progression to RA. The ACPA-positive RA subtype tends to exhibit a more aggressive clinical course compared to ACPA-negative RA.

ACPA-negative RA shows distinct genetic associations and immune cell responses to citrullinated antigens from the ACPA-positive subset. Treatment responses to medications like methotrexate (MTX) or rituximab are generally less effective in ACPA-negative RA, suggesting a need for further research into potential pathophysiological differences between these subtypes. This review focuses on the ACPA-positive subset of RA, discussing its progression through various stages, which may occur concurrently or sequentially.

Cellular and Molecular Changes:

Thus, in rheumatoid arthritis (RA), changes are not only systemic, but also cellular and molecular as well. This entails chronic inflammation that entails infiltration of leukocytes including T cells, B cells and macrophages which results in synovial membrane hyperplasia and joint destruction. On the cellular level intervening proteins like TNF-alpha and IL-6 are used in maintaining inflammation and resulting in damage of the joints. Also, derangements in signaling cascades such as the NF-kB and MAPK have been implicated in the onset of RA, thus, depicting the complexity of cellular and molecular events of the disease.

Impact on Body Systems:

RA and the Musculoskeletal System: The main effect of this illness on your body relates to the musculoskeletal system of the body. This system consists of muscles and the support structures including bones that makes the body to move. When rheumatoid arthritis affects a patient musculoskeletal system, it becomes impossible for the patient to perform simple physical activities. This condition impacts on various elements of this system in different ways. It is now time to focus on the specifics of these.

The Skeletal System: The part of the human body that makes up the skeletal system is bones, tendons, cartilage, ligaments and joints. Besides supporting the body structure, other functions include protecting other organs in the body, enable movement and also has the function of manufacturing blood in the bone marrow. It also belongs to the places where primary

symptoms of RA can be also observed to the greatest extent. It was also confirmed that many people start experiencing rheumatoid arthritis with such an early morning joint stiffness that lasts an hour or more. As for symptoms, for Dr. Chu morning stiffness is a serious feature of RA.

The Muscular System: Muscular system factor comprises of muscles and the tissues that give body support. Studies indicate that disabled adults with Rheumatoid Arthritis (RA) had lesser lean muscle mass and strength than non-disabled adults, which difference is evident at the early stages of the disease. Several researches prove earlier that the muscular strength in RA patients may reduce by 25-70%. This may not necessarily be due to a direct inflammation by RA and targeting of muscles but due to reduced physical activity precipitated by manifestations of RA. However, RA leads to the inflammation of tendons known as tenosynovitis that connect muscles to bones which is very painful.

Management and Treatment

Medical and Surgical Treatments:

management of rheumatoid arthritis (RA) is based on improving patient's quality of life through reduction of discomfort and protection of the affected joints. Options include:

NSAIDs: Ibuprofen for example and naproxen- these are pain relievers that also work to ease inflammation – but might lead to irritation of the stomach lining or even damage to the kidneys.

Steroids: Steroids such as prednisone bring about a speedy settlement of inflammation and pain but when taken in the long term, could cause osteoporosis amongst other complications.

Conventional DMARDs: Others, such as methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine help to reduce disease progression and defend the joints at the cost of possibly harming the liver.

Biologic agents: More recent drugs include adalimumab and rituximab; these are directed at various components of the immune system and lessen inflammation – an advantage of these drugs is that they are associated with an increased risk of infections.

Targeted synthetic DMARDs: Tofacitinib and baricitinib are used when other treatments fail, but these have side effects like blood clots and heart problems Too often, very old people with covid-19 face tough choices between their life and being sore.

Choosing a treatment regimen depends on the severity of the symptoms and the duration of RA and used to control the symptoms and prevent destructive changes in the joints.

As for the medical treatment for rheumatoid arthritis if medications do not work well to prevent or to delay the structural alterations in joints, surgery can be done in such case. Surgical options include:

Synovectomy: Synovectomy to reduce pain and to improve joint flexibility by stripping off of the wet working lining of the joint.

Tendon repair: Fixing tendons around the joint that may have become loose or ruptured due to inflammation and damage.

1. **Joint fusion:** Joining a joint surgically to stabilize or realign it, offering pain relief when joint replacement is not suitable.
2. **Total joint replacement:** Surgery where damaged parts of the joint are replaced with a metal and plastic prosthesis.

Surgery carries risks such as bleeding, infection, and pain. It's essential to discuss the potential benefits and risks with your doctor before proceeding.

Pharmacological Therapies:

Pharmacological treatments for rheumatoid arthritis (RA) involve using medications to manage symptoms, slow down disease progression, and decrease inflammation. These include NSAIDs to alleviate pain and inflammation, corticosteroids for short-term symptom relief, and different types of DMARDs (conventional, biologic, and targeted synthetic) that suppress the immune system to protect joints from damage. Treatment plans are customized according to the severity of RA and the specific needs of each patient, often combining multiple medications to achieve the best results with minimal side effects. Regular monitoring and adjustments are essential for successfully managing RA.

Lifestyle and Dietary Modifications:

Lifestyle and dietary modifications for rheumatoid arthritis (RA) include regular exercise to maintain joint flexibility and strength, protecting joints from strain, managing stress through techniques like yoga, maintaining a balanced diet rich in anti-inflammatory foods, managing weight, quitting smoking, and ensuring consistent medication management and medical monitoring. These adjustments aim to alleviate symptoms, improve joint health, and enhance overall well-being for individuals with RA.

Rehabilitation and Supportive Care:

RA rehabilitation and supportive care encompass a range of strategies to improve mobility, manage pain, and enhance quality of life for those with rheumatoid arthritis. These include physical and occupational therapy for joint function and daily tasks, pain management techniques, psychological support, education on self-management, support groups, and nutritional counseling. Individualized approaches aim to alleviate symptoms and optimize well-being despite the challenges of RA.

Prevention and Control

Primary, Secondary, and Tertiary Prevention Strategies:

The prevention strategies for rheumatoid arthritis (RA) can be categorized into primary, secondary, and tertiary levels. Primary prevention focuses on lifestyle changes and early management of risk factors to prevent the onset of RA. Secondary prevention involves early detection and prompt treatment upon initial symptoms or risk indicators to minimize joint damage. Tertiary prevention aims at managing diagnosed RA through comprehensive care, rehabilitation, and ongoing support to enhance quality of life and prevent disability progression. These strategies collectively aim to improve outcomes and mitigate the impact of RA on affected individuals.

Public Health Interventions:

Public health interventions for rheumatoid arthritis (RA) encompass strategies aimed at reducing its impact at a population level. These include health promotion campaigns, primary prevention efforts promoting healthy lifestyles, screening programs for early detection, ensuring access to healthcare, advocating for supportive policies, and conducting research and surveillance. These measures collectively aim to improve RA awareness, prevention, early diagnosis, and management across communities.

Vaccination and Screening Programs:

Vaccination and screening programs for rheumatoid arthritis (RA) are designed to prevent complications and enhance management. Vaccinations prevent infections that can exacerbate RA symptoms or interfere with treatments, while screening initiatives detect RA in its early

stages, facilitating prompt intervention. These efforts play a critical role in minimizing the impact of RA and improving the well-being of those affected.

Prognosis

Disease Outcomes and Survival Rates:

The outcomes of rheumatoid arthritis (RA) can vary widely among individuals but commonly include joint pain, stiffness, swelling, and reduced mobility. Over time, RA can lead to joint deformities and damage, affecting daily activities and quality of life. Beyond joint symptoms, RA may also impact organs such as the heart, lungs, and eyes, increasing the risk of cardiovascular disease, respiratory issues, and eye complications. Early diagnosis and effective management are crucial to slowing disease progression, minimizing joint damage, and improving long-term outcomes for individuals with RA.

Patients with rheumatoid arthritis (RA) exhibited a lower overall survival rate compared to control subjects. Specifically, the 5-year survival rate **was 80% (95% CI 78–81%)** for RA patients, whereas it was **88% (95% CI 88–89%)** for control subjects. Throughout the study period, the survival rate for RA patients consistently lagged behind that of control subjects by approximately **10%**. By the 12-year mark, the probability of survival dropped to **61% (95% CI 61–63%)** for RA patients and was **74% (95% CI 74–75%)** for control subjects. Additionally, the hazard ratio of **0.59** indicated that controls had a **41%** lower risk of mortality compared to RA patients.

Factors Influencing Prognosis:

Factors influencing the prognosis of rheumatoid arthritis (RA) include:

1. **Disease Severity:** The extent of joint inflammation and damage.
2. **Early Diagnosis and Treatment:** Prompt intervention can slow disease progression.
3. **Response to Medications:** Effective management with DMARDs and biologics.
4. **Presence of Comorbidities:** Conditions like cardiovascular disease can worsen outcomes.
5. **Lifestyle Factors:** Diet, exercise, and smoking habits can impact disease severity.
6. **Genetic Factors:** Genetic predisposition may influence disease progression.
7. **Joint Damage:** The extent of irreversible joint damage affects long-term prognosis.

Quality of Life:

Rheumatoid arthritis (RA) significantly affects the quality of life for people who suffer from it by chronic pain, joint stiffness, and reduced mobility. This can affect emotional well-being and restrain daily activities. The validation of treatment such as disease control and pain management have a necessary role in the quality of life improving. Additionally, physical therapy, psychological support, and lifestyle adjustments are also essential in managing RA symptoms and enhancing overall well-being.

Current Research and Future Directions

Recent Advances and Discoveries:

1. **RvT4 Molecule:** Researchers at Queen Mary University of London have identified that Resolvin T4 (RvT4) can remove arterial blockages in patients with rheumatoid arthritis (RA) and soothe inflammation. Reprogramming macrophages help to operate this molecule to release stored lipids, reducing inflammation, and enhancing vascular health. This penetration offers possible new treatment options for RA and associated cardiovascular conditions.
2. **Biologic and Targeted Synthetic Therapies:** *The KURAMA cohort's long-term data study represents that biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) have notably developed clinical outcomes for RA patients. Over a ten-year period, treatments such as IL-6 receptor inhibitors and JAK inhibitors have effectively achieved low disease activity and remission in many patients.*
3. **ELMO1 Gene:** It is found that deleting the ELMO1 gene in mice unexpectedly modified arthritis symptoms by researchers at the University of Virginia. ELMO1 develops inflammation through its activity in neutrophils, which are crucial white blood cells in the body's defense but can cause tissue damage when overactive. This discovery suggests the possibility to develop drugs that specifically inhibit ELMO1, offering a new treatment approach for rheumatoid arthritis without affecting other cellular functions.

These penetrations represent significant steps forward in treating and understanding RA, offering hope for more effective and targeted therapies for patients.

Ongoing Clinical Trials:

1. **MYMD-1 Phase 2 Trial:** MYMD-1 is a drug designed to treat inflammation by specifically targeting and preventing swelling necrosis factor-alpha (TNF- α). MyMD Pharmaceuticals is running a Phase 2 clinical trial for it. This trial includes nearly 60 patients with active rheumatoid arthritis (RA) and is aimed at estimate the drug's validation in reducing

inflammation without causing the immunosuppressive side effects typically linked to traditional treatments.

2. **R-2487 Phase 1 Trial by Rise Therapeutics:** R-2487 is an oral immunotherapy aimed at promoting bystander tolerance by encouraging the evolution of T regulatory cells (Treg cells). Rise Therapeutics has started a Phase 1 trial for it. This study will include up to 36 participants and will assess the drug's safety, pharmacodynamics, and clinical activity in patients with rheumatoid arthritis (RA).

3. **Bioelectronic Device Trial:** For inhibiting the production of inflammatory cytokines such as TNF, SetPoint Medical is conducting an attempt on an implantable bioelectronic device designed to catalyze the vagus nerve. This method offers an innovative way to managing RA by leveraging the body's electrical signals to adjust inflammation. Early results from this trial have noted an improvement in symptoms for participants with rheumatoid arthritis.

These trials represent advanced efforts to explore new treatments for RA, focusing on innovative methods like selective inhibition of inflammatory cytokines, synthetic biology-based immunotherapies, and bioelectronic devices.

Future Research Needs:

Enhancing particular treatment strategies, exploring long-term effectiveness and safety of innovative therapies, looking for biomarkers for early exposure and prediction, and progression understanding of the disease's underlying mechanisms to promote targeted interventions should be prioritized by the future research in rheumatoid arthritis (RA).

Case Studies

Example Cases:

A 60-year-old woman called JC encounters rheumatoid arthritis (RA) two years ago. She visits the clinic due to worsening disease symptoms. During the previous two months, she has suffered from increased joint pain and inflammation, which lead to limiting her daily activities. JC has been managing her symptoms with naproxen for relief and is presently on a weekly conservation dose of methotrexate 15 mg. Given the decadence in her disease activity, the physician searches recommendations on regulating or changing her disease-modifying antirheumatic drugs (DMARDs).

