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"RHEUMATOID ARTHRITIS: CURRENT INSIGHT INTO PATHOGENESIS, DIAGNOSIS AND THERAPEUTIC ADVANCES."

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Abstract
Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily targets the joints but also has systemic effects, significantly impacting overall health and quality of life. Research over the past decades has focused on its multifactorial etiology, involving genetic predisposition, environmental triggers, and immune system dysregulation. Abnormal cellular activity and changes within the synovial fluid contribute to persistent inflammation, joint destruction, and long-term disability. Globally, the burden of RA continues to rise, particularly among the elderly, highlighting its dual role as both a clinical challenge and a major public health concern. Advances in management have shifted therapeutic approaches from simple symptom relief to the use of disease-modifying antirheumatic drugs (DMARDs) and biologics, which effectively suppress disease activity and slow progression. More recently, small-molecule inhibitors and precision medicine strategies have expanded treatment options. Alongside pharmacological interventions, lifestyle modifications, physical therapy, and psychosocial support play crucial roles in improving patient outcomes. Despite these developments, many individuals continue to experience pain, reduced mobility, and impaired quality of life. Current challenges include treatment resistance, high costs, and limited access to advanced therapies in resource-constrained settings. Future research directions emphasize the integration of molecular discoveries, novel therapeutic targets, and epidemiological insights to design more effective, affordable, and globally accessible interventions. This review synthesizes the latest findings on the causes, immunopathology, treatment strategies, and global burden of RA, providing a comprehensive overview of the evolving research landscape.

Keywords
Rheumatoid arthritis, Autoimmune disease, Complement system, Synovial inflammation, Disease-Modifying Antirheumatic Drugs (DMARDs), Treatment strategies.

Introduction
RA affects up to 1–3% of the population, with a 3:1 female preponderance disappearing in older age. There is evidence of a genetic predisposition to the disease.
RA is characterized by progressive and irreversible damage of the synovial-lined joints causing loss of joint space, of bone and of function, as well as deformity. Extracellular matrix degradation is a hallmark of RA which is responsible for the typical destruction of cartilage, ligaments, tendons, and bone.

RA is characteristically a symmetric arthritis. Articular and periarticular manifestations include joint swelling and tenderness to palpation, with morning stiffness and severe motion impairment in the involved joints (1).

Early diagnosis and treatment of RA can avert or substantially slow progression of joint damage in up to 90% of patients, thereby preventing irreversible disability. The development of novel instruments to measure disease activity and identify the presence or absence of remission have facilitated new treatment strategies to arrest RA before joints are damaged irreversibly. Outcomes have been improved by recognizing the benefits of early diagnosis and early therapy with disease-modifying antirheumatic drugs (DMARDs). The treatment target is remission or a state of at least low disease activity, which should be attained within 6 months. Methotrexate is first-line therapy and should be prescribed at an optimal dose of 25 mg weekly and in combination with glucocorticoids; 40% to 50% of patients reach remission or at least low disease activity with this regimen. If this treatment fails, sequential application of targeted therapies, such as biologic agents (eg., tumor necrosis factor [TNF] inhibitors) or Janus kinase inhibitors in combination with methotrexate, have allowed up to 75% of these patients to reach the treatment target over time. New therapies have been developed in response to new pathogenetic findings. The costs of some therapies are considerable, but these costs are decreasing with the advent of biosimilar drugs (drugs essentially identical to the original biologic drugs but usually available at lower cost) (2).

T-cell-mediated antigen-specific responses, T-cell-independent cytokine networks, and aggressive tumour-like behaviour of rheumatoid synovium have also been implicated. More recently, the contribution of autoantibodies has returned to the forefront. Based on the pathogenic mechanisms, specific therapeutic interventions can be designed to suppress synovial inflammation and joint destruction in rheumatoid arthritis (3).

Epidemiology of RA

Between 1995 and 2007, rheumatoid arthritis (RA) was studied in 466 patients with an average age of 55.6 years, most of whom were women (69%) and rheumatoid factor positive (66%). The overall yearly incidence of RA was 40.9 cases per 100,000 people, with women having a higher rate (53.1 per 100,000) than men (27.7 per 100,000). Over this period, the incidence of RA increased moderately in women but not in men, and this rise was seen across all age groups. The total number of people living with RA also went up, from 0.62% of the population in 1995 (about 1.3 million US adults) to 0.72% in 2005 (about 1.5 million US adults), showing a clear increase over time (4).

Research shows that rheumatoid arthritis (RA) affects about 0.5% to 1% of the population. The number of new cases each year varies a lot (12 to 1200 per 100,000 people) depending on factors like gender, race/ethnicity, and the time period studied. Changes in RA rates over time suggest that both a person's genetic makeup and their environment play a role in causing the disease. People with RA also have a higher risk of dying earlier compared to people of the same age and sex who do not have RA (5).

The number of people with rheumatoid arthritis (RA) differs across regions, with higher rates usually seen in industrialized countries and cities. These differences are linked to genetics, environment, demographics, socioeconomic status, and how well the disease is reported.

Although more people are being diagnosed with RA, the severity, death rates, and related health problems are going down. The disease is thought to begin at mucosal sites (like the mouth, lungs, or gut) where genetic risk factors interact with environmental triggers. this is known as the "mucosal origin" hypothesis.

Some RA risk factors, such as diet and exposure to pollutants like tobacco smoke, can be changed, and these are now part of prevention strategies. (6).

Risk factor for RA[7]

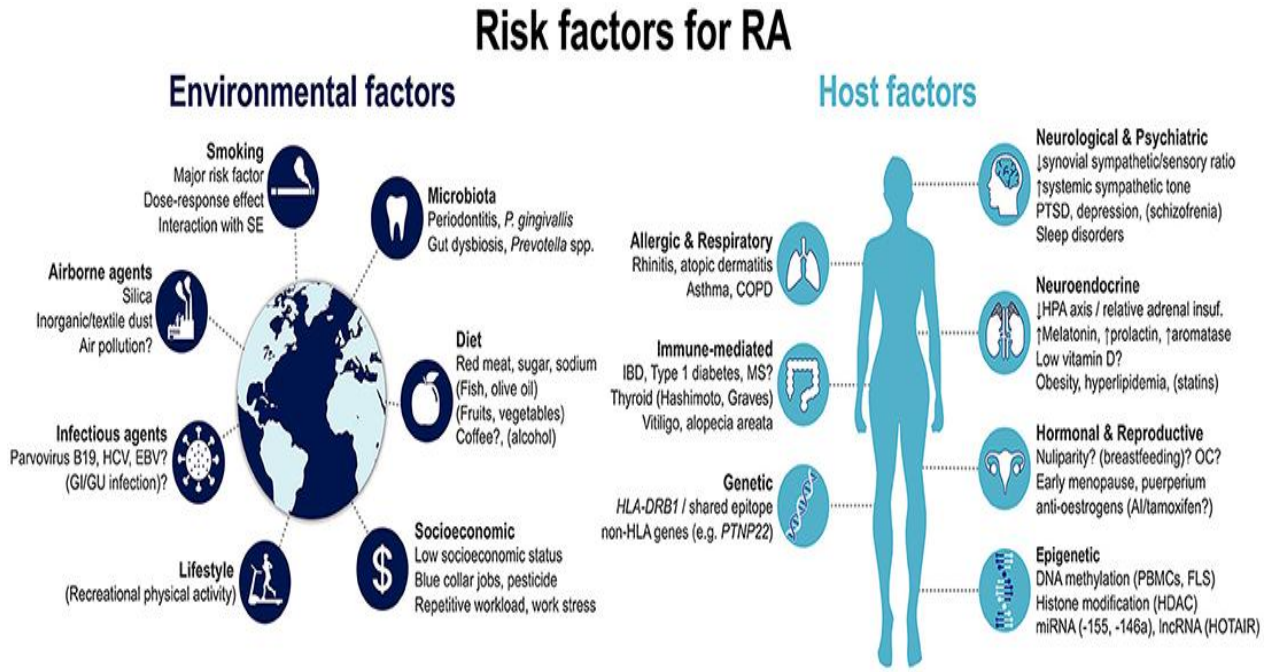

Fig.-1 Risk factor for RA.

Fig.-1 Shows that rheumatoid arthritis (RA) is caused by a mix of environmental factors(like smoking, infections, pollution, diet, and lifestyle) and host factors (like genes, hormones, immunity, and other health conditions). Together, these triggers disturb the immune system and increase the risk of developing RA.

Etiology of RA[8]

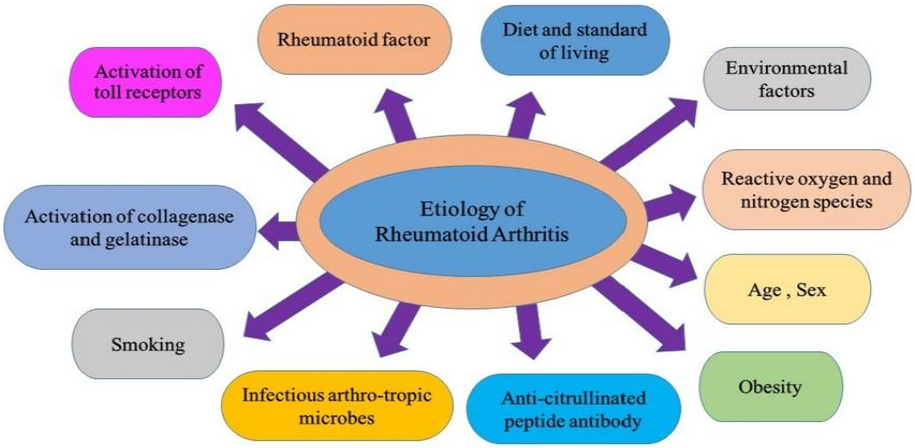

Fig.-2 Etiology of RA.

Pathophysiology of RA[9]

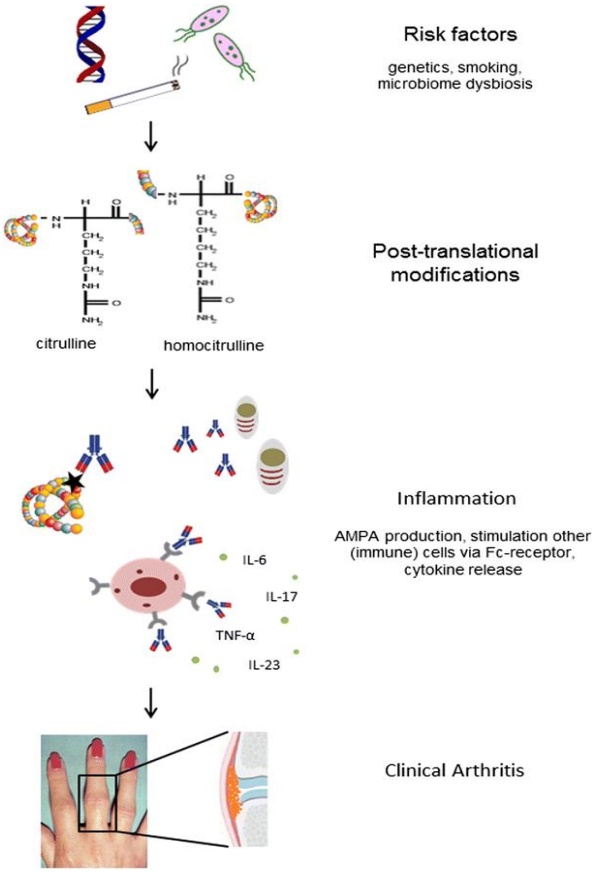

Fig.3- Final Common Inflammatory Pathway of Autoantibodies in RA.

Pathophysiology of RA

- Before RA begins, the immune system produces autoantibodies like ACPA and RF, which are linked to severe disease and joint damage.
- Genetic and environmental risk factors cause abnormal protein changes (citrullination), leading the immune system to create autoantibodies.
- ACPA immune complexes bind to Fcγ receptors on macrophages, releasing TNF, while RF strengthens this response and increases complement activation.
- ACPA activate the classical and alternative complement pathways, driving opsonisation, membrane attack complex formation, and chemotaxis in joints.
- Neutrophils release NETs that expose citrullinated proteins, fueling more ACPA production, while ACPA also stimulate NETosis, worsening inflammation.
- ACPA bind directly to osteoclasts, making them more active and causing bone erosion, with IL-8 acting as a key mediator of this process.
- Even without visible inflammation, ACPA-activated osteoclasts release CXCL1(like
- IL-8) which sensitizes nerves and causes joint pain before arthritis fully develops (9).

Diagnosis and Treatments of RA

A problem in the diagnostic research of RA is the lack of an independent gold standard. RA has no disease-specific clinical, radiological or immunological features.

In most studies, either the physician's clinical diagnosis or the disease classification according to the 1987 American College of Rheumatology (ACR) classification criteria has been used as the gold standard. A drawback of these gold standards is that they are dependent on the diagnostic tests that are evaluated. (10)

1. **Acute-Phase Reactants (ESR, CRP):** These markers indicate systemic inflammation but lack specificity for RA and have limited value in predicting erosive disease.

2. **Rheumatoid Factor (RF):** RF is a key serological marker included in ACR criteria, strongly linked to diagnosis and prognosis, with positivity suggesting more severe outcomes.
3. **Conventional Radiography (X-rays):** X-rays of hands and wrists can reveal early erosions or periarticular osteopenia, though only a minority of patients show changes at initial presentation.
4. **Synovial Histopathology:** Biopsy findings reveal subtle alterations in cytokine patterns and cell activity, offering research potential but no current role in routine diagnosis (10).

Treatments for RA

RA is a chronic inflammatory disease characterized by a heterogeneous clinical response to the different treatments. Some patients are difficult to treat and do not reach the treatment targets as clinical remission or low disease activity. Known negative prognostic factors, such as the presence of auto-antiantibodies and joint erosion, the presence of genetic profile, comorbidities and extra-articular manifestations, pregnancy or a pregnancy wish may concur to the treatment failure (11).

Disease Modifying Anti-Rheumatic Drugs (DMARDs) became the mainstay of RA treatment in the 1970s. As a group, they have been shown to decrease inflammation and slow radiographic progression, but the degree to which this is accomplished is variable. The timing of DMARD initiation has been debated, but current consensus suggests that the earlier treatment can be initiated, the better the overall outcome for clinical improvement and prevention of erosive disease. The initial 15 months of RA are critical for initiation and escalation of DMARD therapy, in order to achieve acceptable outcomes long-term. A major difficulty in treating patients with RA is that it is currently impossible to predict which patients will respond to which medication regimen. Current research is ongoing to develop patient-specific disease signatures via genetic and proteomic approaches; however, the practical application of such advances has not been achieved. Thus, practice guidelines typically recommend starting with conventional DMARD treatment before addition or substitution of biologic DMARD medications. Importantly, the use of DMARDs in combination rather than monotherapy is more effective in achieving improved clinical outcomes as well as slowing radiographic progression. Conventional DMARDs can be combined with each other and/or with biologic DMARDs (12).

First-Line Management: NSAIDS and Corticosteroids

The overall goal of first-line treatment is to relieve pain and decrease inflammation. Medications, considered to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an effective anti-inflammatory for RA when used at high doses, due to the inhibition of prostaglandins. It is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at high doses include tinnitus, hearing loss, and gastric intolerance. There are other NSAIDs that are newer on the market than aspirin and just as effective. In addition, these drugs require fewer doses per day. NSAIDs work by inhibiting cyclo-oxygenase to prevent the synthesis of prostaglandins, prostacyclin, and thromboxanes. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding. These symptoms can be reduced if taken with food, antacids, proton pump inhibitors, or misoprostol (Cytotec), An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects (13).

Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation (14). They work by preventing the release of phospholipids and decreasing the actions of eosinophils, thereby decreasing inflammation. Their side effects include bone-thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of the bone. Side effects can be reduced by gradually tapering doses as a patient's condition improves. It is important to not abruptly discontinue injected or oral corticosteroids as this can lead to suppression of the hypothalamic-pituitary-adrenal axis (HPA) or flares of RA (15).

Opioid Analgesics

Whittle et al (16). addressed the question of the use of opioid analgesics for patients with pain due to RA. From their conclusions, weak opioids such as codeine, dextropropoxyphene, and tramadol may play an effective role in the short-term management of pain caused by RA, but the adverse effects outweigh the benefits. They recommend that other analgesics be considered first (17).

Second-Line Management: Disease-Modifying Antirheumatic Drugs

The overall goal of second-line treatment is to promote remission by slowing or stopping the progression of joint destruction and deformity. Medications are considered to be slow-acting because they take from weeks to months to be effective. Disease-modifying antirheumatic drugs (DMARDs) can also reduce the risk of developing lymphoma that can be associated with RA (18).

Methotrexate (MTX) is the initial second-line drug (also considered an anchor drug). It is an analog to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, the metabolism of purine and pyrimidine is impaired, and the synthesis of amino acids and polyamine is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects, i.e., liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has a lower incidence of side effects than other DMARDs, and has dosage flexibility, meaning that doses can be adjusted as needed (19).

Until now, there is convincing data showing the benefits of combinations of conventional synthetic DMARDs over MTX monotherapy. However, biological and synthetic DMARDs in combination are reported to be better than MTX but with more side effects and greater costs. (20).

Hydroxychloroqyine (Plaquenil) is an antimalarial drug and can be used for long-term treatment of RA. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the GI tract, skin, and central nervous system. The eyes, in particular, can be affected when this drug is taken at high doses. Patients on this medication require routine consultation with an ophthalmologist (21).

Sulfasalazine (Azulfidine) is a DMARD typically used in the treatment of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be used to treat RA. The mechanism of action of this drug in the treatment of RA has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin (IL)-8 and monocyte chemoattractant protein (MCP). This drug has side effects of GI and central nervous system symptoms as well as rash. It is usually well-tolerated among patients, but should be avoided in patients with sulfa allergies since it contains sulfa and salicylate compounds (22).

Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen and Cuprimine) have been used frequently in the treatment of RA. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and kidneys. They have not been used recently due to the more effective treatments, particularly MTX. Other immunosuppressive medications like azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune) can be employed but are typically reserved for patients with very aggressive RA or complications of the disease. (23,24).

Newer Medications

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine. It relieves symptoms and retards the progression of RA. It is recommended to be used in combination with MTX but can constitute a monotherapy if patients do not respond to MTX. Side effects include hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow damage (24,25).

Biologics, also known as biological DMARDs, are rapidly effective in retarding the progression of the joint damage caused by RA. They are considered to be a more "direct, defined and targeted" method of treatment (26). Nonetheless, biologics pose the problem of serious side effects, such as increased risk of infections. Other common side effects include neurologic diseases like multiple sclerosis and lymphoma (27-29).

Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are recommended if other second-line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of RA and with various mechanisms of action is a matter of continuous investigation. They are often used in combination with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic medication has a different mode of administration (30-32).

Anakinra (Kineret) is a drug that is injected subcutaneously daily. It works by binding to IL-1, a chemical messenger of inflammation. It can be used in combination with other DMARDs or as a monotherapy, but due its low response rate compared to other biologics, it is not used as frequently (33-34). Rituximab (Rituxan) is useful in RA because it depletes the B cells responsible for inflammation and the production of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in cases of RA where TNF inhibitors have failed. In addition, rituximab has shown benefits in treating the complications of RA, such as vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in 2 doses, 2 weeks apart, every 6 months (35-36). Abatacept (Orencia) is a biologic medication that works by blocking T cell activation. This is given as an intravenous infusion once a month or subcutaneously once a week. It is used in patients who have not been effectively treated with traditional DMARDs (37).

Tocilizumab (Actemra) is a biologic that works by blocking IL-6, a chemical messenger of inflammation. It is administered via intravenous infusion given monthly or via weekly subcutaneous injections. It is also used for patients who have not been effectively treated with traditional DMARDs (38). Lastly, tofacitinib (Xeljanz) has a different mechanism of action and works by blocking Janus kinases within cells, which are enzymes of inflammation. For this reason, it is known as a JAK inhibitor. This medication is used for patients who have not been effectively treated with MTX. Tofacitinib is taken orally twice daily, alone or in combination with MTX. It should not be used in combination with traditional biologic medications or other potent immunosuppressants (39,40).

Surgery

Joint surgery in patients with RA reached a peak in the 1990s. However, a 2010 study showed decreased rates of joint surgery in RA patients 40–59 years of age. In contrast, patients older than 60 years had increased rates of surgery (41). Surgery is a last resort for the treatment of RA. Indications include intractable joint pain or functional decline due to joint destruction after all nonsurgical approaches have failed. At this point, the disease is considered "end-stage." The goal of surgical management is to relieve pain for the patient and restore the function of the joints. A patient needing surgical treatment should be evaluated based on their customized needs because there are many different types of surgery.

A tenosynovectomy involves the excision of inflamed tendon sheaths or repairing a recent tendon rupture, most commonly in the hand (42). Radiosynovectomy is an alternative to surgical synovectomy; it involves intra-articular injection of small radioactive particles, is cost-effective, and can treat multiple joints simultaneously (43). Repair of ruptured tendons can also be done through arthroscopy, most commonly in the rotator cuff of the shoulder. Excision of an inflamed synovium via arthroscopy or open synovectomy is no longer commonly used due to the availability of more effective options. Another surgical option is osteotomy. In this procedure, weight-bearing bones are realigned to correct valgus or varus deformities, most commonly in the knee (44). Joint fusion can be done to stabilize joints that are not easily replaceable such as the ankle, wrist, thumb, and cervical

spine. A procedure for soft-tissue release can be done to correct severe contractures around joints causing decreased range of motion; this is an older procedure that is not commonly utilized (45). Small-joint implant arthroplasty can be done to reduce pain and improve hand function, most commonly in the metacarpophalangeal joints. Metatarsal-head excision arthroplasty is done to alleviate severe forefoot pain. Lastly, a total joint replacement involves removing the damaged joint and replacing it with a metallic, plastic, or ceramic prosthesis. This is most commonly done in the shoulder, elbow, wrist, hip, knee, and ankle (46,47). The major contraindication for surgical joint replacements is the presence of active systemic articular infection.

Other Therapies

It has been found that, in contrast to suggestions in the past, there are no specific foods that patients with RA should avoid. The idea that diet can "aggravate" symptoms is no longer accepted as true (48). Home remedies have been proven to be helpful for patients suffering from RA, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements are beneficial for the short-term symptoms of RA. Cumin has been shown to have anti-inflammatory effects in patients with this disease. Calcium and vitamin D supplementation can be helpful in preventing osteoporosis. Lastly, folic acid can help to prevent the side effects of MTX (49).

Patients with RA also benefit from physical and occupational therapy. It is recommended that they perform exercise regularly to maintain joint mobility and strengthen the muscles around the joints. Movement exercises that are less traumatic for joints but good for muscle strength include swimming, yoga, and tai chi. Applying heat- and cold-packs before and after exercise minimizes painful symptoms. Studies are being done on different types of connective tissue collagen, to better understand and reduce RA disease activity. Lastly, with the scientific advancements and enhanced understanding of the molecular mechanisms, newer and better treatment options should become available in the near future (50-55).

Conclusion

RA is a debilitating, chronic, inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. The treating physician should consider adhering to treat-to-target (T2T) recommendations (56), by first outlining the aims and then implementing the protocols to achieve and assess them. Furthermore, early referral to a specialist can help to ensure better treatment outcomes. With advances in the field of molecular medicine, we have a better understanding of disease mechanisms which can aid in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. Gene array analysis is proving beneficial in finding out which patients will be more responsive to specific medications. This customization will allow for more rapid treatment as well as decrease the likelihood of disease progression during the experimental phase to seek an appropriate treatment for a particular patient. Gene array analysis is also being used to determine which patients are at greater risk for more aggressive forms of RA. It is foreseen that treatment methods will face tremendous improvements in the management of RA.

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