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## Investigating the importance and causes of rheumatoid arthritis and its effective treatments: a review study

Investigación de la importancia y las causas de la artritis reumatoide y sus tratamientos efectivos: un estudio de revisión

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### ABSTRACT:

Rheumatoid arthritis (RA) is among the most important chronic diseases that can cause joint destruction and disability, especially in the adulthood. It is a progressive chronic autoimmune inflammatory disease with variable clinical symptoms, characterized by mild to severe inflammation of the joints that can result in pain, dryness and joint destruction along with joint malformations and disability. Besides its physical effects, it can also affect one's mental state and cause mental illnesses, such as depression, given its permanent changes in activity level and lifestyle. Therefore, due to the importance of this debilitating disease, the present study aimed to study the causes of RA and its effective treatments. The results showed that the most common cause of RA is genetic-related. However, genetic risk factor is not fully responsible for the disease and environmental factors have been reported to be effective. Although there has been a wide variety of studies on treatment of RA, no definitive treatments have been reported for the disease so far. The most commonly used treatment approaches for this disease are rest and general treatments, pharmacotherapy, hydrocortisone intra-articular injection, physiotherapy, occupational therapy and surgery. Rest is supposed to be effective, especially in the early stages of the disease and during the recurrence periods. Overall, the goal of non-pharmacological treatments is to reduce pressure on the joint. According to various studies, aspirin and non-steroidal anti-inflammatory drugs (indomethacin, ibuprofen, naproxen, and piroxicam) are the most commonly used drugs in the treatment of RA (especially in the early stages).

**KEYWORDS:** RA, genetics, environmental factors, treatment.

### RESUMEN:

La artritis reumatoide (AR) se encuentra entre las enfermedades crónicas más importantes que pueden causar destrucción articular y discapacidad, especialmente en la edad adulta. Es una enfermedad inflamatoria autoinmune crónica progresiva con síntomas clínicos variables, caracterizada por una inflamación leve a severa de las articulaciones que puede provocar dolor, sequedad y destrucción articular junto con malformaciones articulares y discapacidad. Además de sus efectos físicos, también puede afectar el estado mental y causar enfermedades mentales, como la depresión, dados sus cambios permanentes en el nivel de actividad y el estilo de vida. Por lo tanto, debido a la importancia de esta enfermedad debilitante, el presente estudio tuvo como objetivo estudiar las causas de la AR y sus tratamientos efectivos. Los resultados mostraron que la causa más común de AR está relacionada con la genética. Sin embargo, el factor de riesgo genético no es completamente responsable de la enfermedad y se ha informado que los factores ambientales son efectivos. Aunque ha habido una amplia variedad de estudios sobre el tratamiento de la AR, hasta ahora no se han informado tratamientos definitivos para la enfermedad. Los enfoques de tratamiento más utilizados para esta enfermedad son el descanso y los tratamientos generales, farmacoterapia, inyección intraarticular de hidrocortisona, fisioterapia, terapia ocupacional y cirugía. Se supone que el descanso es efectivo, especialmente en las primeras etapas de la enfermedad y durante los períodos de recurrencia. En general, el objetivo de los tratamientos no farmacológicos es reducir la presión sobre la articulación. Según diversos estudios, la aspirina y los medicamentos antiinflamatorios no esteroideos (indometacina, ibuprofeno, naproxeno y piroxicam) son los medicamentos más utilizados en el tratamiento de la AR (especialmente en las primeras etapas).

**PALABRAS CLAVE:** AR, genética, factores ambientales, tratamiento.

## INTRODUCTION:

Nowadays, the prevalence of chronic diseases is increasing given the lifestyle changes and is a major challenge in the medical world <sup>1</sup>. The 99 million patients with chronic diseases in the US in 1995 are predicted to reach 167 million by 2050 <sup>2</sup>. The cost of treatment, maintenance, equipment and services of these diseases are high and increasing due to their chronic nature <sup>1,2</sup>. These kinds of diseases can have effects on their work and family life due to their long-term and sometimes lifelong effects. Moreover, due to the need for prolonged care and frequent hospitalizations, financial strain and subsequent isolation are created <sup>3</sup>. Among the most important chronic diseases, RA can be cited. This disease can cause joint destruction and disability, especially in adulthood <sup>4</sup>. It is a progressive chronic autoimmune inflammatory disease with variable clinical symptoms, characterized by mild to severe inflammation of the joints that can result in pain, dryness and joint destruction along with joint malformations and disabilities. The total average of prevalence of the disease in the world is about 1%. It is more prevalent in women than men and is three to four times more common in men. The prevalence of the disease in the Mediterranean countries is 0.36% <sup>5</sup>. The prevalence of the disease is increasing, especially in the Western countries <sup>7, 6</sup>. According to the studies in Iran, the prevalence of RA in Iran is estimated to be 0.19% <sup>8</sup>. Besides its physical effects and permanent changes in activity and lifestyle, it can affect one's mental state and some mental illnesses such as depression <sup>(9)</sup>. Thus, given the significance of this debilitating disease, the study was conducted to examine the causes of RA and its effective treatments.

## RESULTS:

### RA

RA is a chronic systemic inflammatory disorder whose cause is not known. The disease is characterized by polyarticular joint pain and swelling, morning stiffness and fatigue <sup>10</sup>. RA is a chronic, systemic, and autoimmune disorder characterized by chronic, bilateral and degenerative synovial tissue inflammation <sup>11</sup>. A characteristic feature of this disease is persistent inflammatory synovitis that usually involves the peripheral joints symmetrically. Synovial inflammation is the major symptom of cartilage damage and bone destruction and subsequent changes in the articular structure <sup>12</sup>. RA is a chronic inflammatory disease of unknown etiology characterized by peripheral symmetric poly arthritis. It is the most prevalent form of chronic inflammatory arthritis and often causes arthritis and physical disability. As RA is a systemic disease, it can cause many extra-articular manifestations such as fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis and blood disorders <sup>13</sup>.

RA is one of the most common autoimmune diseases, with an estimated prevalence of 1% of the adult population and an annual prevalence of 0.03%. The prevalence of the disease has been lower than in Asia and Africa than in Europe and the United States<sup>31</sup>. Women are almost three times more likely to develop the disease than men, and the onset of the disease is often in the fourth and fifth decades of life, with 80% of patients from 35 to 50 years of age. The major cause of RA is genetic-related, and human leucocyte antigen (HLA) is one of the genetic risk factors <sup>10,11,13</sup>. However, genetic risk is not entirely responsible for the occurrence and environmental factors are involved in the etiology of the disease as well. This has been confirmed in epidemiological studies in Africa where the widespread effect of climate and urbanization on the incidence and severity of disease in similar genetic groups has been confirmed <sup>12</sup>.

### Etiology

The main cause of the disease is not known, and it is not yet clear how has this inflammatory disease been triggered and started. The multidimensional hypothesis for RA is that genetic, cognitive, and psychosocial

factors interact with each other in this disease<sup>14</sup>. The spread of the disease is an event mediated by the immune system. Indeed, RA is one of the autoimmune diseases in which the immune system attacks healthy tissue<sup>14</sup> and is also a mediating immune system between determinants of physiological, biochemical and endocrine pathology on the one hand, and psychosocial events on the other, processed by the central nervous system<sup>14</sup>.

Family studies show the genetic talent. For instance, in twins with one egg if one twin is affected, the second one's chance is 30%; whereas, this figure is 5% in twins with two eggs<sup>14</sup>. One of the causes of RA is joints poisoning. Even when a joint is injured by an accident, it is possible that a person develops arthritis because the injured joint is not properly healed and gets rigid and painful and eventually weak; accordingly, the person becomes crippled<sup>15</sup>.

#### **Psychosocial factors and RA**

A wide variety of studies has examined the relationship between this disease and psychological factors. Studies have shown that most patients have experienced significant stress prior to RA symptoms and disease recurrent periods<sup>14</sup>. The results of various studies have shown that some personality traits make a person susceptible to RA<sup>14,15</sup>. There is enough evidence of disturbed family relationships such as parental dispute, lack of parents due to death or divorce, stressful/strained marital relationships, and high rates of divorce in these patients<sup>14</sup>. Anxiety and stress are both involved in the occurrence and continuation of the disease. Patients at silent RA stage may experience relapse if they cannot control stress and anxiety<sup>16</sup>. Moreover, studies have indicated that depression is a common personality trait in all patients with RA. Continuous depression may affect the hypothalamic-pituitary-adrenal axis, weaken immune resistance, and cause pathologic changes in RA<sup>14</sup>.

#### **Pathology**

Symptoms are typical of synovial pannus involvement, which is synovial membrane thickening due to proliferation of membrane cells and mononuclear cell infiltration, especially monocytes and T lymphocytes. Pannus invades the joint surface of bone-cartilage-synovium and progressively damages the bone and joint. This process is seen in the radiography as peripheral bone erosions. Besides synovium in other tissues, rheumatoid nodules may be observed as well<sup>15</sup>.

#### **Clinical features**

The clinical manifestations of RA are highly various. In some patients, the disease starts quietly and with fatigue, anorexia, general malaise, and vague musculoskeletal symptoms until later synovitis. These early symptoms may persist for weeks or months, making it difficult to diagnose<sup>14</sup>. RA is a symmetric polyarthritis that primarily involves the small joints of the foot, wrist and ankle. Other joints that are most commonly involved are the cervical spine, shoulders, elbows, hip and knees<sup>14</sup>. In about 10% of the patients, the onset is more acute and polyarthritis develops rapidly accompanied by symptoms like fever, lymphadenopathy, and splenomegaly. In 1.3% of the patients the symptoms are initially confined to one or more joints. Although it may be possible for some patients to have unsymmetrical joint involvement, the symmetric involvement of the joints is typical<sup>14</sup>. Long morning stiffness usually takes more than an hour and often several hours, which is a classic feature of RA and other inflammatory arthropathies. Likewise, after prolonged inactivity, the joint stiffness increases and symptoms generally improve with moderate activity (Table 1). Over time, RA progresses towards joint destruction and deformity. Bone and cartilage degenerative lesions can be seen both on radiography and on the margins pathology<sup>15</sup>.

TABLE 1  
The clinical features of RA

| Articular                                                   | Non-articular                                                                      |
|-------------------------------------------------------------|------------------------------------------------------------------------------------|
| • Morning stiffness<br>“Dryness”                            | • Rheumatoid<br>Nodules:<br>subcutaneous,<br>pulmonary, scroll                     |
| • Symmetrical joint<br>swelling                             | • Lung disease                                                                     |
| • Articular<br>involvement and<br>deviation towards<br>Ulna | • Vasculitis,<br>especially in the<br>skin, peripheral<br>nerves and<br>intestines |
| • Inflammatory<br>joint fluid                               | • Episcleritis and<br>Scleritis                                                    |
| • Carpal tunnel<br>syndrome (CTS)                           | • Foot ulcers                                                                      |
| • Baker's cyst                                              | • Felty's<br>syndrome                                                              |

RA is a systemic disease and has various extra-articular symptoms, and although these are common, not all are of clinical significance<sup>14</sup>. Easily palpable subcutaneous rheumatoid nodules are usually found in the elbow area and to a lesser extent in the lungs and elsewhere, and rarely in the heart. The incidence of multiple pulmonary nodules in a patient with RA is called Caplan's syndrome. Pleuritis, pericarditis, and interstitial lung disease (ILD) are seen in a small number of patients. Felty's syndrome (spleen enlargement, leukopenia, and recurrent lung infections) is a rare complication and is usually seen with vasculitis<sup>15</sup>.

RA process is fully variable and difficult to predict in each patient<sup>14</sup>. Some patients have mild disease with slow progression with limited bone deformity and degenerative changes. At the end of this spectrum are the patients with rapidly progressive progression, who, if left untreated, develop disabilities and arthritis. Most patients are placed between these two poles and show varying degrees of disability. In some cases, the disease progresses over several years and is accompanied by acute periods of exacerbation of symptoms in one or more joints<sup>15</sup>.

## DIAGNOSIS

RA is a clinical diagnosis<sup>15</sup>. It is easy to diagnose RA in the presence of typical stabilized disease. In most of the patients, the disease shows its typical clinical symptoms within 1 to 2 years after onset<sup>14</sup>. Symmetrical synovitis of the small joints is a classic sign of the patient during admittance. About 20-30% of the patients are admitted with one joint involvement (usually in the knee joint)<sup>15</sup>. The temperamental symptoms that show the inflammatory nature of the disease like morning stiffness reinforce the diagnosis of RA. Subcutaneous nodules are a good diagnostic mark<sup>14</sup>).

Examining the joint fluid is the most useful laboratory procedure. In RA, joint fluid has an inflammatory state and has more than 10,000 white blood cells. Rheumatoid factor is found in 80-90% of patients with RA. The presence of rheumatoid factor is neither a prerequisite for diagnosis nor a sufficient condition, but if the patient has it, it is called seropositive. The arthritis is more likely to develop, and nodules and extra-articular symptoms are more common in seropositive patients<sup>15, 16</sup>. The key to diagnose RA is the simultaneous involvement of several joints as erythrocyte sedimentation rate (ESR) increases. Serum rheumatoid factor

is strongly suggestive of this disease, although this test is not specific for RA and rheumatoid factor may be negative in 20% of patients with proven RA<sup>17,18</sup>. The radiographic features of the disease are such that initially no change in the natural state is seen. Then, a decrease in bone density is observed in the joint. Finally, the destruction of articular cartilage may reduce the space of articular cartilage and in severe cases, localized corrosion of the bones at the end of the bone, especially in the areas around the joint. In bone radioisotope scans, isotope reabsorption is increased in the affected joint<sup>17</sup>. In the advanced stages of the disease, bone corrosion is particularly marked and the joint space narrows<sup>18</sup>. The classification criteria for RA are presented in Table 2.

TABLE 2  
Classification criteria for RA<sup>14</sup>

- 1- Classification guides
  - a) Four symptoms out of seven are needed to place the patient in the classification of RA. b) Patients with two or more clinical diagnoses are not excluded.
2. Diagnostic symptoms
  - a) Morning stiffness sometimes and stiffness in and around the joint that lasts 1 hour before complete recovery
  - b) Arthritis in three or more articular areas: At least three joints, observed simultaneously by a physician, with soft tissue swelling or articular enlargement, not just over-growth of bone
  - c) Arthritis of the wrist: Wrist arthritis, metacarpophalangeal joint, or proximal interphalangeal joints
  - d) Systemic arthritis: concurrent similar joints affected on both sides of the body
  - e) Rheumatoid nodules: Subcutaneous nodules in the bony prominence and the extensor surfaces, or surrounding areas of the joint observed by the physician
  - f) Serum rheumatoid factor: Showing abnormal amounts of rheumatoid factor by any method that results in positive control in less than 5% of normal subjects
  - g) Radiographic changes: Typical changes in radiography of the upper back of the upper arm and wrist, which should include erosion or decalcification of the bone involved in the joint or near the joint more severe than other parts
- v Cases a-d should last at least 6 weeks; e-b should be seen by your doctor.

## Treatment

After the diagnosis of RA and initial evaluations, the treatment should be started. The patients with RA are treated in a variety of ways, whose purpose is to resolve the different problems that these patients have in terms of function and psychosis<sup>37</sup>. RA treatment is still on the progress, but no specific treatment has been

found yet<sup>39</sup>. The purpose of RA treatment is to reduce pain and discomfort, reduce inflammation, prevent deformity, and increase normal joints function to maintain normal physical, social, and mental performance and maintain working capacity<sup>10,18</sup>.

It is important to educate the patient and the family about the nature and course of the disease (the specific causes of the disease, the treatment goals, the problems, and the expectations). Presenting wrong information to the patient can lead to frustration, depression, and withdrawal from treatment. Treatment methods can be divided into rest and general treatment groups, pharmacotherapy, hydrocortisone intra-articular injection, physiotherapy, occupational therapy and surgery<sup>17</sup>. Rest is supposed to be useful, especially in the early stages of the disease and during the relapse periods. Generally, non-pharmacological treatments include reducing pressure on the joint<sup>10, 17</sup>.

Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) (indomethacin, ibuprofen, naproxen, and piroxicam) are probably the most commonly used drugs in RA treatment (especially in the early stages). These drugs reduce pain and inflammation and improve function, but they have no effect on the underlying course of the disease, especially preventing joint damage and corrosion, and when use is stopped, symptoms rapidly deteriorate. The main therapeutic effect of NSAIDs is related to their ability to stop the synthesis of prostaglandins. However, the side effects of these drugs should be considered. Gastric pain is common with most medications and more severe side effects such as gastric bleeding is sometimes seen<sup>11</sup>.

Glucocorticoids have maintained their importance in RA treatment, especially in acute cases. Many patients need long-term use of low doses of these drugs for optimal control of disease activity. The side effects of long-term glucocorticoid use in diseases such as RA, which cause partial immobility, can be significant and very debilitating. These side effects include osteoporosis and pathological fractures, avascular necrosis of the bone, obesity and glucose intolerance. Intra-articular glucocorticoids are highly effective in acute attacks that involve only a few joints, and the intra-articular distribution of these drugs has almost no side effects. Although non-steroidal anti-inflammatory drugs and glucocorticoids are an important part of RA treatment, in most patients they do not control the symptoms and do not alter the course of the disease<sup>10</sup>.

Corticosteroid (usually hydrocortisone) injection into the affected joint improves symptoms and is helpful in exacerbated disease and does not have the systemic effects of oral corticosteroids. However, the widespread use of this treatment is limited due to its disadvantages. The main disadvantages of this treatment are the risk of infection, especially with repeated injections, the risk of accelerating joint damage (the mechanism of this effect is still unclear), and the short duration of symptom recovery. Repeated injections in different joints can be so annoying and, thus, unacceptable to the patient. Overall, it is reasonable to avoid repeated injections<sup>17</sup>. Most patients are prescribed disease modifying antirheumatic drugs (DMARDs) nowadays. Using these medications at the right time can prevent the progression of the disease and damage and corrosion of the joints. Among the drugs in this group are gold compounds, chloroquine, sulfasalazine, methotrexate, cyclosporine, mycophenolate and leflunomide. Methotrexate is still the most widely used DMARD for RA treatment. Hydroxychloroquine, minocycline and sulfasalazine are commonly prescribed for patients with mild to moderate disease or in combination with other medications. Cyclophosphamide is used almost exclusively in very severe cases of the disease, especially in the presence of extra-articular manifestations such as vasculitis. Leflunomide is a relatively new immunosuppressive drug that is widely used in moderate to severe RA<sup>10</sup>. Surgery may be done to reduce pain and improve joint function. Surgery in some cases can slow the progress of destruction for a while. This is done to remove the invasive tissue within the joint, clear the articular capsule from fine particles, smooth the rough cartilage, correct the angle of contact in a torn knee, and immobilize painful and unstable joints<sup>19</sup>. Physiotherapy and occupation therapy have a significant role in many patients. Physiotherapy increases muscle strength and status and maintains joint mobility<sup>15</sup>.

Newer methods of drug production have focused on the production of biomolecules by genetic engineering to inhibit or reduce the production of cytokines and degradative enzymes released from synovial

cells in RA. The first drug of this group is tumor necrosis factor (TNF) (entacept and influx Infiliximab), which has had promising results in patients but no long-term result of this medicine is available <sup>10</sup>.

### Prognosis

Several symptoms are valuable regarding prognostic in patients with RA. Disease activity is more likely to decrease in the first year. Those with high titers of rheumatoid factor and patients with subcutaneous nodules have worse prognosis at primary evaluation. Although continuous activity of the disease over a period of more than one year has an unpleasant outcome, it is not as fast as the progression of fixed articular lesions, and mostly progression occurs within the first 6 months of the disease and then much slower <sup>14</sup>. The available data shows that 50% of the patients becomes disabled within 5 years <sup>14</sup>. The average life expectancy of the patients with RA has been estimated to be 3-7 years <sup>14</sup>. The overall mortality rate has increased at least in severe cases of RA. Increased mortality happens due to infection, kidney and lung disease, and gastrointestinal bleeding, some of which may be due to therapeutic interventions <sup>15, 20-25</sup>.

### CONCLUSION:

RA is a chronic systemic inflammatory disorder whose cause is unknown. The symptoms of the disease are pain and symmetric polyarticular swelling, morning stiffness and fatigue. Examining various results showed that the most common cause of RA is genetic. However, genetic risk factors were not fully responsible for the disease and environmental factors were reported to be effective as well. Despite a wide variety of studies conducted to treat RA, no definitive cures have been found so far. The major used treatment approaches are rest and general treatment, pharmacotherapy, hydrocortisone intra-articular injection, physiotherapy, occupational therapy and surgery. Rest is supposed to be effective, especially in the early stages of the disease and during the recurrence periods. Overall, the goal of non-pharmacological treatments is to reduce pressure on the joint. According to various studies, aspirin and NSAIDs (indomethacin, ibuprofen, naproxen, and piroxicam) are the main used drugs in the treatment of RA (especially in the early stages)

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