

Clinical advancement in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune disorder that mainly affects joints. The cause of RA is believed to be a combination of genetic and environmental factors. Family history of RA increases the risk around three to five times. Smoking, Caucasian populations, increasing risk of RA. Periodontal disease has been associated with RA. Disease progresses as phase 1, non-specific inflammation to phase 2, amplification in the synovium to phase 3 or chronic inflammation. RA primarily affects joint, rheumatoid nodule in the skin, lung fibrosis, atherosclerosis and risk of myocardial infarction. Diagnosis includes X-rays and imaging, laboratory tests, using diagnostic criteria, and excluding other medical conditions. There is no cure for RA, treatment can improve symptoms and slow the progress of the disease, change in lifestyle, regular exercise and use of disease modifying anti-rheumatic drugs (DMARDs). Surgery may be necessary for affected fingers, hands, and wrists, synovectomy may be needed to prevent pain or tendon rupture. A review of CAM (complimentary alternative medicine) (excluding fish oil), does not support their current use in the management of RA. Some evidence supports omega-3 fatty acids and gamma-linolenic acid in RA. Tai Chi improves joint motion, but acupuncture inconclusive. RA reduces lifespan from three to twelve years, and double risk of heart disease. There is no known prevention other than reduction of risk factors

Keywords: Rheumatoid arthritis, Risk factors, Inflammation, Pain medication Lifestyle.

Date of Submission: 05-02-2018

Date of acceptance: 19-02-2018

I Introduction

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints [1]. The term *rheumatoid arthritis* is based on the Greek for watery and inflamed joints [2]. RA affects about 24.5 million people as of 2015 [3]. This is between 0.5 and 1% of adults in the developed world with 5 and 50 per 100,000 newly developing the condition each year [4]. Onset is most frequent during middle age and women are affected 2.5 times frequently as men [1]. In 2013, it resulted in 38,000 deaths up from 30,000 in 1990 [5]. The cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints. This results in inflammation and thickening of joint capsule. It also affects the underlying bone and cartilage [1]. It typically results in warm, swollen, and painful joints [1]. The disease may affect other parts of the body. This may result in low red blood cell count, inflammation around lungs and the heart. Fever and low energy may also be present [1]. Often symptoms come on gradually over weeks to months [6]. The diagnosis is made mostly on the basis of person's signs and symptoms [6], X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms [1]. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others [6]. Treatment goals are to reduce pain and inflammation, and improve a person's overall functioning [7]. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. Disease modifying anti-rheumatic drugs (DMARD), such as hydroxychloroquine and methotrexate, may also be used, to try to slow progression of disease [1]. Biological DMARDs may be used when disease does not respond to other treatment [8]. However, they have greater rate of adverse effects [9]. Surgery to repair, replace, or fuse joints may help in certain situations [1]. Most alternative medicine treatments are not supported by evidence [10]. The paper reviews the risk factor, clinical manifestation and management of Rheumatoid arthritis.

II. Historical perspective

Rheumatoid arthritis is derived from the Greek word "flow current". The suffix-*oid* ("resembling") gives the translation as *joint inflammation that resembles rheumatic fever*. Rhuma which means watery

discharge might refer to the fact that the joints are swollen or that the disease may be made worse by wet weather [2]. The first known traces of arthritis date back at least as far as 4500 BC. A text dated 123 AD first describes symptoms very similar to RA. It was noted in skeletal remains of Native Americans found in Tennessee [11]. In Europe, the disease is vanishingly rare before the 17th century [12]. The first recognized description of RA in modern medicine was in 1800 by the French physician Dr Augustin Jacob Landre-Beauvais (1772-1840) who was based in the famed Salpetriere Hospital in Paris [13]. The name "rheumatoid arthritis" itself was coined in 1850 by British rheumatologist Dr Alfred Haring Garrod [14].

An anomaly has been noticed from the investigation of Pre-Columbian bones. The bones from the Tennessee site show no signs of tuberculosis even though it was prevalent at that time throughout Americas [15].

The art of Peter Paul Rubens may possibly depict the effects of RA. In his later paintings, his rendered hands show, in opinion of some physicians, increasing deformity consistent with the symptoms of the disease [16]. RA appears to some have been depicted in 16th century paintings [17]. However, it is generally recognized in art historical circles that painting of hands in the 16th and 17th century followed certain stylized conventions, most clearly seen in mannerist movement. It was conventional, for instance, to show the upheld right hand of Christ in what now appears a deformed posture. The conventions are easily misinterpreted as portrayals of disease. Historical treatment for RA have also included rest, ice, compression, and elevation, apple diet, nutmeg, some light exercise every now and then, nettles, bee venom, copper bracelets, rhubarb diet, extraction of teeth, fasting, honey, vitamins, magnet, and electro convulsion therapy (ECT) [18]. Onset is uncommon under the age of 15 and from then on the incidence rises with age of 80. Women are affected three to five times as often as men [19]. The age at which the disease starts in women between 40 and 50 years of age and for men somewhat later [20]. In 2010 it resulted in about 49,000 deaths globally [21].

III. Contributory factors

3.1. Genetic: A family history of RA increases the risk around three to five times, as of 2016 it was estimated genetics may account for between 40 and 65% of cases of seropositive RA, but only 20% for seronegative RA [4]. RA is strongly associated with genes of the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DR4 is the major genetic factor implicated—the relative importance varies across ethnic groups [22]. Genome-wide association studies examining single nucleotide polymorphism have found around one hundred genes associated with RA risk, with most of them involving the HLA system (particularly HLA-DRB1) which controls recognition of self-versus non-self molecules, other mutations affecting co-stimulatory immune pathways, for example CD28 and CD40, cytokine signaling lymphocyte receptor activation threshold (e.g. PTPN22), and innate immune activation appear to have less influence than HLA mutations [4].

3.2. Lifestyle and environmental factor: There are epigenetic and environmental risk factors [4]. Smoking is an established risk factor for RA in Caucasian populations, increasing the risk three times compared to non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive [23]. Modest alcohol consumption may be protective [24]. Silica exposure has been linked to RA [25].

3.3. Inconclusive or negative tests: No infectious agents has been linked with RA and there is no evidence of disease clustering to indicate its infectious cause [22], but periodontal disease has been consistently associated with RA [4]. As of 1999, there was no evidence that physical and emotional effects or stress could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might, in fact, be a chance event inherent with the immune response [26, 37].

IV. Pathognomonic

RA primarily starts as a state of persistent cellular activation leading to autoimmunity and immune complexes in both joints and other organs where it manifests. The initial site of disease is synovial membrane, where swelling and congestion leads to infiltration by immune cells. Three phases of progression of RA are an initiation phase, due to non-specific inflammation, an amplification phase, due to T cell activation and chronic inflammation phase with tissue injury, due to cytokines IL-1, TNF-alpha and IL-6 [19].

4.1. Phase 1 or non-specific inflammation: Factors allowing an abnormal immune response once initiated to become permanent and chronic are genetic mutations for example, which change regulation of the adaptive immune response [4]. Genetic factors interact with environmental risk factor for RA, the most clearly defined being cigarette smoking [23]. Other environmental and hormonal factors in an individual may explain the higher risk in women, onset after child birth, and (slight) modulation of disease risk by hormonal medications. Exactly how altered regulatory thresholds allow triggering of a specific autoimmune response remains uncertain. One possibility is that negative feedback mechanism, which normally maintain tolerance of the self are overtaken by positive feedback mechanisms for certain antigens, such as IgG Fc bound by Rheumatoid Factor and citrullinated fibrinogen bound by antibodies to citrullinated peptides (ACPA). A debate on the relative roles of B-cell produced immune complexes and T cell products in inflammation in RA has continued for 30 years, but, neither cell is

necessary at the site of inflammation, only autoantibodies to IgG known as rheumatoid factors (RF) and (ACPA). As with other autoimmune diseases, people with RA have abnormally glycosylated antibodies, which are believed to promote joint inflammation [27].

4.2. Phase 2 or amplification in the synovium: Once the generalized abnormal immune response has become established which may take several years before any symptoms occur, plasma cells derived from B lymphocytes produce rheumatoid factors and ACPA of IgG and IgM classes in large quantities. These activate macrophages through Fc receptor and complement binding which is part of intense inflammation in RA [28]. Binding of autoreactive antibody to Fc receptors is mediated through the antibody's N-glycans, which are adhered to promote inflammation in people with RA [27]. This contributes to total inflammation in a joint, specifically the synovium with edema, vasodilation and entry of activated T-cells, mainly CD4 microscopically nodular aggregates and CD8 in microscopically diffuse infiltrates. Synovial macrophages and dendritic cells function as antigen-presenting cells by expressing MHC class II molecules, which establishes the immune reaction in the tissue [27].

4.3. Phase 3 or chronic inflammation: The disease progresses by forming granulation at the edges of the synovial lining, pannus with extensive angiogenesis and enzymes causing tissue damage. The synovium thickens, cartilage and underlying bone begin to disintegrate and joint is getting destroyed. Cytokines and chemokines attract and accumulate immune cells, i.e. activated T- and B cells, monocytes and macrophages from activated fibroblasts, in the joint space. By signaling through RANKL, and RANK they eventually trigger osteoclast production, which degrades bone tissue [4].

Tumor necrosis factors (TNF alpha) plays a major role and several theories exist how TNF release happens in RA. If TNF release is stimulated by B cell products in the form of RF or ACPA-containing immune complexes, through activation of immunoglobulin Fc receptors, then RA can be seen as a form of Type III hypersensitivity [29]. If TNF release is stimulated by T cell product such as interleukin-17 it might be closer to type IV hypersensitivity although this terminology may be getting somewhat dated and unhelpful [30]. Although TNF appears to be the dominant chemical mediator other cytokines are involved in inflammation. Erythrocyte sedimentation rate (ESR) blocking TNF does not benefit all persons and all tissues, particularly lung disease and nodules may get worse. Blocking IL-1, IL-15 and IL-6 have beneficial effects and IL-17 may be important [31].

V. Clinical Manifestation

RA primarily affects joints, but it also affects other organs in more than 15-25% of individuals [32].

5.1. Joints: Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender and warm, stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved [33]. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function [6]. The pain associated with RA is induced at the site of inflammation and classified as nociceptive as opposed to neuropathic [34]. The joints are often affected in a fairly symmetrical fashion, although this is not specific, and the initial presentation may be asymmetrical [33].

As the pathology progresses the inflammatory activity leads to tendon tethering and erosion and destruction of the joint surface, which impairs range of movement and leads to deformity. The fingers may suffer from almost any deformity depending on which joints are most involved. Specific deformities, which also occur in osteoarthritis, include ulnar deviation, boutonniere deformity (also: buttonhole deformity “flexion of proximal interphalangeal joint and extension of distal interphalangeal joint of the hand”), swan neck deformity (hyperextension at proximal interphalangeal joint and flexion at distal interphalangeal joint) and “Z-thumb” “Z-thumb” or “Z-deformity” “consists of the interphalangeal joint, fixed flexion and subluxation of the metacarpophalangeal joint and gives” appearance to the thumb [33]. The hammer toe deformity may be seen. In worst case joints are known as arthritis mutilans due to the mutilating nature of the deformities [19].

5.2. Involvement of skin: The rheumatoid nodule, which is sometimes in the skin, is most common non-joint feature and occurs in 30% of people who have RA [35]. It is a type of inflammatory reaction known to pathologists as a “necrotizing granuloma”. The initial pathologic process in nodule formation is unknown but may be essentially the same as the synovitis, since similar structural features occur in both. The nodule has a central area of fibrinoid necrosis that may be fissured and which corresponds to the fibrin-rich necrotic material found in and around an affected synovial space. Surrounding the necrosis is a layer of palisading macrophages and fibroblasts, corresponding to the intimal layer in synovium and a cuff of connective tissue containing clusters of lymphocytes and plasma cells, corresponding to the sub-intimal zone synovitis. The typical rheumatoid nodule may be few millimeter to a few centimeters in diameter and usually found over bony prominences, such as the elbow, the heel, the knuckles, or other areas that sustain repeated mechanical stress. Nodules are associated with a positive RF (rheumatoid factor) titer, ACPA, and severe erosive arthritis. Rarely these can occur in internal organs or at diverse sites on the body [35].

Several form of vasculitis occurs in RA, but are mostly seen with long-standing and untreated disease. The common presentation is due to involvement of small-and medium-sized vessels. Rheumatoid vasculitis can thus commonly present with skin ulceration and vasculitis nerve infarction known as mononeuritis multiplex [36].

5.3. Miscellaneous RA complication: Lung fibrosis is a recognized complication of rheumatoid arthritis. It is also a rare a rare but well-recognized consequence of therapy (for example with methotrexate and leflunomide). Caplan's syndrome describes lung nodules in individuals with RA and additional exposure to coal dust. Exudative pleural effusions are also associated with RA [37].

People with RA are more prone atherosclerosis and risk of myocardial infarction (heart attack) and stroke is markedly increased [38]. Other complication that may arise include: pericarditis, endocarditis, left ventricular failure, valvulitis and fibrosis [39]. Many people with RA do not experience the same chest pain that others feel when they have angina or myocardial infarction. To reduce cardiovascular risk, it is crucial to maintain optimal control of the inflammation caused by RA (which may be involved in causing the cardiovascular risk), and to use exercise and medications appropriately to reduce other cardiovascular risk factors such as blood lipids and blood pressure. Doctors who treat people with RA should be sensitive to cardiovascular risk when prescribing anti-inflammatory medications, and may want to consider prescribing routine use of low doses of aspirin if the gastrointestinal effects are tolerable [39].

Anemia is far more common abnormality of the blood cells which can be caused by variety of mechanism. The chronic inflammation caused by RA leads to raised hepcidin levels, leading to anemia of chronic disease where iron is poorly absorbed and also sequestered into macrophages. A may also cause a warm autoimmune hemolytic anemia [40]. Renal amyloidosis occur as a consequence of untreated chronic inflammation. Treatment with penicillamine and gold salts are recognized causes of membranous nephropathy [41]. The incidence of lymphoma is increased, although it is uncommon and associated with the chronic inflammation, not the treatment of RA [42]. More than 75% of women with rheumatoid arthritis have symptoms improve during pregnancy but might have symptoms worsen after pregnancy [19].

VI. Diagnosis

6.1. X-rays and Imaging: X-rays of hands and feet are generally performed when many joints affected. In RA, there may be no changes in the early stages of the disease or x-rays may show osteopenia near the joint, soft tissue swelling and a smaller than normal joint space. As the disease advances, there may be bony erosions and subluxation. Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA [19].

6.2. Laboratory tests: When RA is suspected, a physician may test for rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs measured as anti-CCP antibodies) [43]. It is positive in 75-85%, but a negative RF or CCP antibody does not rule out RA, rather the arthritis is called 'seronegative', which is in about 15-25% of people with RA [44]. During the first year of illness, rheumatoid factor is more likely to be negative with some individuals becoming seropositive over time RF is a non-specific antibody test and seen in about 10% of healthy people, in many other chronic infection like hepatitis C, and chronic autoimmune diseases such as Sjogren's syndromes and systemic lupus erythematosus (SLE). Therefore test is not specific for RA [19]. New serological tests check for anti-cyclic citrullinated peptide (anti CCP-ACPA). These tests are again positive in 61-75% of all RA cases, but with specificity of around 95% [45]. In 2008 a serological point-of-care test for the early detection of RA combined the detection of RF and anti-MCV with a sensitivity of 72% and specificity of 99.7% [46]. Other diagnostic tests include: full blood count, renal profile, liver function test (LFT), ESR (erythrocyte sedimentation rate) and other specialized tests.

6.3. Diagnostic classification criteria: In 2010 the 2010 ACR/EULAR Rheumatoid arthritis Classification Criteria were introduced [47]. The new criteria is not a diagnostic criterion but a classification criterion to identify the disease with high likely hood of developing a chronic form [19]. The new classification criteria overruled the "old" ACR criteria of 1987. The "new" classification criteria jointly published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) established a point value between 0 and 10. Four areas are covered in the diagnosis: [47].

a). Joint involvement, designating the metacarpophalangeal joints, proximal interphalangeal joints, the interphalangeal joint of the thumb, second through fifth metatarsophalangeal joint and wrist as small joint, and shoulders, elbows, hip joint, knee and ankles as large joints'). serological parameters-including the rheumatoid factor as well as ACPA. A negative RF and negative ACPA gives, low positive RF or low positive ACPA gives 2 points, high positive RF or high positive ACPA gives 3 points'). acute phase reactants: 1 point for elevated ESR, or elevated CRP value (c-reactive protein). d). duration of arthritis: 1 point for symptoms lasting six weeks or longer.

6.4. Exclusion of other medical conditions: Several other medical conditions can resemble RA, and need to be distinguished from it at time of diagnosis includes: [48].

i) Crystal induced arthritis(gout,andpseudo gout).ii)Oseoarthritis-distinguished with X-rays of affected joints.iii)SLE-distinguished by specific clinical symptoms and blood tests(antibodies against double –stranded DNA).iv) Psoriatic arthritis resembles RA.v)Lyme disease causes erosive arthritis and may closely arthritis.vi).Reactive arthritis(previously Reiter’s disease).vi).Axial spondyloarthritis (including ankylosing spondylitis)-this involves spine,although an RA-like symmetrical small- joint polyarthritis may occur in the context of this condition.vii).Hepatitis C-RA-like symmetrical polyarthritis may occur in the context of this condition.Hepatitis C may also induce Rheumatoid Factor auto-antibodies.

6.5.Monitoringtherapy:*Disease Activity Score of 28 points(DAS28)* is widely used as an indicator of RA disease activity and response to treatment. Joint included are (bilaterally)proximal interphrangeal joint(10joints)metacarpophangeal joints(10 joints),wrists(2),elbows(2),shoulders(2),and knees(2).When looking at these joints,both the number of joints with tenderness upon touching(TEN28) and swelling(SW2*) are counted.The ESR is measured and the affected person makes a subjective assessment(SA) of disease activity during the preceding 7 days on a scale between 0 and 100,where 0 is “no activity” and 100 is “highest activity possible”. With these parameters,DAS28 is calculated[49].

VII.Treatment

There is no cure for RA, but treatments can improve symptoms and slow the progress of the disease. Disease –modifying treatment has best results when it is started early and aggressively[50].The goal of the treatment is to minimize symptoms such as pain swelling, to prevent deformity(e.g.,bone erosions visible in X-rays),and to main day-to-day functioning[51].This is primarily addressed with disease modifying anti-rheumatic drugs(DMARDs),analgesics may be used to help manage pain[[7].RA should generally be treated with at least one specific anti-rheumatic medication[8].The use of benzodiazepines (such as diazepam) to treat the pain is not recommended as it does not appear to help and is associated with risks[52].

7.1.Change in lifestyle and choice of drugs: Regular exercise is recommended as both safe and useful to maintain muscle strength and overall physical function[53].It is uncertain if specific dietary measures have an effect [54].Occupation therapy has a positive role in improving functional ability of persons with RA[55].The drugs that are considered as DMARDs:merthotrezate,hydroxychloroquine,sulfasalazine,leflunomide,TNF-alpha inhibitors(cecalizumab),infiximab and etanercept),abatacept,andanakinraRituximb and tocilizumb are monoclonal and also DMARDs[8]Antiinflammatory and analgesic drugs,like Glucocorticoids can be used in the short term and at the lowest dose possible[8],and Non-NSAID drugs reduce pain[4].Methotrexate and leflunomide are teratogenic (harmful to foetus) and not used in pregnancy[51].

7.2. Surgery and Alternative medicine: Especially for affected fingers, hands, andwrists, synovectomy may be needed to prevent pain or tendon rupture when drug treatment has failed. Severely affected joints may require joint replacement surgery, such as knee replacement. Postoperatively, physiotherapy is always necessary [33].In general, there is not enough evidence to support and complementary health approaches for RA,with safety concerns for some of them[56].A systematic review of CAM(complimentary alternative medicine) modalities(excluding fish oil) found that “available evidence does not support their current use in the management of RA”[57].There is some evidence that Tai Chi improves the range of motion of a joint in persons with RA[58].The evidence of acupuncture is inconclusive[59].Some evidence supports omega-3 fatty acids and gamma-linolenic acid in RA[60].Gamma- linolenic acid which may reduce pain, tender joint count and stiffness, is generally safe[61].*There is no scientific evidence that herbal supplements advertised as “natural” are safe for use than conventional medications as both are chemicals. Herbal medications, although labelled “natural” may be toxic or fatal if consumed [62].*

VIII. Mortality and Prevention

8.1. Mortality:RA reduces lifespan on average from three to twelve years[51].According to the UK’s National Rheumatoid Arthritis Society, Young age at onset, long disease duration, the concurrent presence of other health problems(called-co-morbidity),and characteristics of severe RA-such as poor functional ability or overall health status, a lot of joint damage on x-rays, the need for hospitalization or involvement of organs other than the joints-have been shown to associate with higher mortality[63].A 2005 study by Mayo Clinic noted that RA sufferers suffer a double risk of heart disease[64].independent of other risk factors such as diabetes, alcoholabuse, and elevated cholesterol, blood pressure and body mass index(BMI).The mechanism by which RA causes this increased risk remain unknown, the presence of chronic inflammation has been proposed as a contributing factor[65].

8.2.Prevention:*There is no known prevention for the condition other than the reduction of risk factors [66].*The cause of RA has been a subject of intensive research. One theory is that infections may provoke the autoimmune response characteristic of rheumatoid arthritis. One example of this theory is that unique bacterial species associated with periodontitis may initiate an autoimmune response in genetically susceptible individuals by citrullinating self-proteins, thus leading to production of ACPAs[4].

Meta-analysis found an association between periodontal disease and RA but the mechanism of this association remain unclear[67]. Vitamin D deficiency is more common in people with rheumatoid arthritis than in the general population[68]. 1,25-dihydroxyvitamin D₃ (1,25D), an active metabolite of vitamin D, affects bone metabolism indirectly through control of calcium and phosphate homeostasis[69]. One meta-analysis found that vitamin D levels are low in people with rheumatoid arthritis and that vitamin D status correlates inversely with prevalence of rheumatoid arthritis, indicating that vitamin deficiency is associated susceptibility to rheumatoid arthritis[70].

XI. Conclusion

There is no known prevention for rheumatoid arthritis (RA) other than the reduction of contributory factors. Therapy goals are to reduce pain and inflammation and improve quality of life. Surgery to repair, replace or fuse joints may help in serious conditions.

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Murtaza Mustafa "Clinical advancement in Rheumatoid Arthritis. "IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), Volume 17, Issue 2 (2018), PP 55-61.