IJBPAS, July, 2023, 12(7): 2963-2976

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

TRACING THE LINKAGE BETWEEN RHEUMATOID ARTHRITIS, HAEMATOLOGICAL AND SEROLOGICAL PARAMETERS

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Received 10th July 2022; Revised 15th Sept 2022; Accepted 13th Oct. 2022; Available online 1st July 2023

https://doi.org/10.31032/IJBPAS/2023/12.7.7205

ABSTRACT

Rheumatoid arthritis (RA) is one of those autoimmune and inflammatory disease that affect the body's muscles and the joints. This all can result in the loss of capacity to complete daily work goals. Rheumatoid arthritis's symptoms are briefly explained here. The rationale for RA's distinction from all other varieties of comparable disorders, as well as how the body's immune cells such as T-cells, B-cells, and macrophages work as the primary driver of RA evolution in the body, are also highlighted. Numerous factors can be used to categorise or diagnose RA, including haematological factors including platelet count, mean platelet volume, haemoglobin concentration, and serological factors are also mentioned. To avoid the RA from becoming more severe, a comprehensive diet review is also advised here.

Keywords: Rheumatic diseases, Rheumatoid Arthritis, Immune Cells, T-cells, B-cells, Macrophages, Inflammation, Seropositive, Seronegative, Rheumatoid Factor, Anaemia, Diet

INTRODUCTION:

Rheumatic diseases seem to be autoimmune as well as inflammatory conditions in which our immune system affects our joints, muscles, bones, and organs negatively. Over 100 diseases and pathological states are covered by the term "arthritis," which commonly includes rheumatic disorders. This does not apply to osteoarthritis, the most prevalent form of arthritis, which results in the breakdown of bone and cartilage in joints rather than inflammation. Our major internal organs,

including the respiratory system, cardiovascular system, neurological system, kidneys, skin, and eyes, can all be negatively impacted by rheumatic disorders. Rheumatic illnesses can be so severe that patients are unable to carry out basic activities like bathing, dressing themselves, and walking without extreme discomfort and difficulty, if not impossibility. Rheumatic diseases are chronic and progressive diseases. They harm the locomotor system and render the patient disability. The patient's quality of life is drastically reduced by these illnesses. The social effects of rheumatic disease can be described using the terminology below:

- Physical and Biological- as limitations in carrying out routine life functions,
- Professional- referring to limitations in one's ability to work or total incapacity for work,
- Legal- acquisition of benefits defined in relevant legal acts, such as disability pensions and sickness benefits **[1]**.

The term "rheumatic diseases" refers to a group of painful, frequently disabling, and chronic diseases that are caused by various rheumatic conditions. The musculoskeletal system is where people with these illnesses most typically complain about their symptoms. Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Fibromyalgia Syndrome (FS), and psoriatic arthritis are the four rheumatic disorders with the highest prevalence, affecting 1% to 2% of the population as a whole. These illnesses place a heavy social and financial burden on society since they are frequently chronic and incapacitating. RA, ankylosing spondylitis, and psoriasis are well-known immune-related conditions **[2]**.

Research Methods:

Electronic search has been carried out using the databases viz. Google, Google Scholar, PubMed for the study. The search will be restricted for a period of 45 years ranging from 1976-2021.

Findings:

Rheumatoid arthritis: An Autoimmune Diseases

As one of the chronic, inflammatory autoimmune diseases, rheumatoid arthritis (RA) is characterised by the body's immune system mistakenly attacking healthier and better-functioning cells, leading to inflammation and painful swelling in the affected areas. Small joints are where it starts, then the skin, eyes, heart, kidneys, and lungs. Tendons and ligaments weaken, and joint bone and cartilage are frequently damaged. Rheumatoid arthritis usually affects the hand, wrist, and knee joints. The abnormalities and bone erosion caused by all of this joint deterioration are typically excruciatingly painful for the sufferer.

Morning Rheumatoid arthritis is characterised by a number of symptoms, including sore, swollen, and heated joints, weariness, fever, weight loss, and rheumatoid nodules under the skin. Between the ages of 35 and 60, this illness typically manifests, with phases of remission and exacerbation. Juvenile RA (JRA), a condition that can also afflict young children under the age of 16, is comparable to RA but does not have the rheumatoid factor **[3]**.

Characteristics increasing the risk of Rheumatoid arthritis:

- **Age:** Although RA can start at any age, the chance rises with advancing years. Adults in their sixties had the highest incidence of RA onset.
- **Sex:** Women often have two to three times as many new instances of RA as men do.
- **Genetics or Inherited Traits:** RA is more prone to occur in those who were born with particular genes. These Human Leukocyte Antigen (HLA) class II genotypes are known to worsen arthritis. When persons with these genotypes are subjected to external variables like smoking or being fat, their risk of developing RA may be at its maximum.
- **Smoking:** Smoking raises a person's likelihood of getting RA and can make the condition worse.
- **Early Life Exposures**: Some early life experiences may make it more likely that an adult may acquire RA. For instance, the chance of having RA as an adult may be doubled in children whose mothers smoked. Adult RA development is more likely to occur in children of lower-income parents.
- **Obesity**: Obesity can raise one's risk of having RA. Studies studying the impact of obesity discovered that a person's risk of acquiring RA increased with increasing weight.

Rheumatoid arthritis showing the worst complications:

Rheumatoid arthritis (RA) can reduce quality of life and has numerous negative social and physical effects. It may result in suffering, impairment, and early demise.

- **Premature Heart Diseases:** People with RA are more likely to develop other chronic illnesses including diabetes and heart disease. Treatment for RA also involves lowering heart disease risk factors in order to protect persons with RA from getting heart disease. For instance, medical professionals may

suggest quitting smoking and losing weight to RA patients.

- **Obesity:** Obese individuals with RA are more likely to develop heart disease risk factors such high blood pressure and high cholesterol. Obesity also raises the risk of getting chronic diseases like diabetes and heart disease. Finally, compared to RA patients who are not obese, obese RA patients gain less from their medical treatment.
- **Employment:** RA might make it challenging to work. Adults with RA have a lower employment rate than those without the condition. Many RA patients discover they are unable to do as much as they once could when the disease worsens. Most RA sufferers who lose their employment are those with physically demanding jobs. People who have jobs with fewer physical demands or jobs where they may control the pace and activities of their workday experience less work loss.

1. **Seropositive Rheumatoid Arthritis:**

Seropositive RA is one of the most common forms of rheumatoid arthritis. Antibodies that aid in diagnosing the disease can be found in the blood of a person who has this disorder. These antibodies are referred to as rheumatoid factors or anti-cyclic citrullinated peptides (anti-CCPs) (RF). These can exist one at a time or both. The emergence of RA symptoms and joint inflammation are linked to their presence. Other variations between patients with seropositive and seronegative RA can be seen. A shared amino acid sequence, or shared epitope, is encoded in the HLA genetic locus in patients who test seropositive, or anti-CCP-positive. This human leukocyte antigen locus generates immune response-regulating proteins.

About 75–80% of individuals with RA have anti-CCPs, RF, or both. They may also be detected on blood testing anywhere between 5 and 10 years before we begin to experience any rheumatoid arthritis symptoms.

Most of the Seropositive RA affected patients are more likely to experience more serious symptoms than seronegative patients, Seropositive RA patients have an increased risk of developing:

- Rheumatoid Nodules
- Vasculitis
- Rheumatoid Lung issues
- Cardiovascular diseases

Seropositive RA patients are more likely to develop associated diseases, especially if their illness isn't properly controlled. Some of the ailments linked to seropositive RA include:

- Carpal Tunnel Syndrome
- Widespread Inflammation
- Eye Inflammation
- Cervical Myelopathy
- Joint Damage
- CVS and Pulmonary Diseases

2. **Seronegative Rheumatoid Arthritis:**

An individual who tests negative for both Cyclic Citrullinated peptides (CCP) and the Rheumatoid factor (RF) has rheumatoid arthritis. But to fully understand this response, some background information is needed. Swollen, aching joints are a symptom of rheumatoid arthritis (RA). The form of joint degeneration that develops with ageing, osteoarthritis, is distinct from this.

Rheumatoid Factor: The rheumatoid factor (RF) test is one of the blood exams that can help confirm RA. A natural antibody that can inflame tissue in our body is bound by RF, a protein (antibody) produced by our immune system. Infections like hepatitis C and parvovirus can occasionally coexist with autoimmune illnesses like RA and Sjogren's syndrome to cause elevated RF levels **[4]**.

Cyclic Citrullinated peptides (CCP) Antibody: RF testing, however, can't provide a conclusive diagnosis. High levels of RF may be present in the blood of healthy individuals without autoimmune diseases, especially as they get older. People with RA can exhibit typical levels of RF, further complicating the problem. A more recent antibody against cyclic citrullinated peptides that some persons will test positive for (CCP). Anti-CCP, also referred to as CCP antibody, is more sensitive and specific and can manifest before RF **[5]**.

The similar symptoms might be caused by other diseases, which can make seronegative RA harder to identify. These include certain forms of arthritis, such as:

- Osteoarthritis, which is the "wear and tear" type of arthritis
- Psoriatic arthritis, which also affects our skin
- Ankylosing spondylitis, which usually affects the spine

- Gout, which can cause sudden pain, usually in the big toe
- The people who smoke or are obese may be more likely to be seronegative.

3. **Juvenile Idiopathic Arthritis.**

In children, juvenile idiopathic arthritis is the most prevalent chronic rheumatic disease of uncertain cause and typically manifests as peripheral arthritis. According to demographic traits, clinical traits, treatment options, and disease prognosis, the disease is categorised into a number of subgroups. Recurrent fever and rash are the hallmarks of systemic juvenile idiopathic arthritis, one of the most common disease subgroups. Young female patients with oligoarticular juvenile idiopathic arthritis are frequently also diagnosed with anterior uveitis and anti-nuclear antibody positivity **[6]**.

There are many different clinical states on the illness spectrum. It has been demonstrated that both endogenous and external antigens with heightened inflammatory responses are crucial in the pathophysiology of the illness. The patient's daily activities and productivity are restricted by chronic inflammation. By definition, the diagnosis of JIA implies that the disease begins before the age of 16 and that the arthritis last for more than six weeks. JIA is a new, popular moniker for a number of ailments that were previously thought of individually. Additionally, the phrases juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis have both previously been used to refer to the same clinical entity **[7]**. According to reports, it affects populations in Europe and North America at rates of 2 to 20 and 16 to 150 per 100,000, respectively **[8]**.

Stastny first stated that there is a link between RA and HLA-DR4 **[9]**. Nine years later, on the basis of the finding that the RA-associated DRB1 alleles encode a similar sequence of amino acids corresponding to residues 67–74, Gregersen *et al*., **[10]** suggested the shared epitope (SE) hypothesis. Since then, it has been discovered that a number of SE-positive (SE+) DRB1 alleles, including the DR4 subtypes DRB1*0401, *0404, *0405, and *0408 as well as the DRB1*0101, *1402, and *1001 alleles, are linked to RA. The relative risk estimates for three of the most prevalent SE+ DRB1 alleles in the Caucasian population have been compiled

by Nepom for Caucasians [11]. The DRB1*0401 allele carries a relative risk of 6, compared to 5 for the DRB1*0404 allele and 1 for the DRB1*0101 allele. As a result, while the relative risk for people with the DRB1*0401 or *0404 alleles is roughly five times higher than it is for people who do not have these alleles, the DRB1*0101 allele does not by itself increase risk **[12]**.

Haematological Based Evaluation of the Rheumatoid Arthritis:

There is growing evidence that certain haematological markers are essential for assessing treatment response. To measure clinical disease activity, a number of composite indices have been developed, including the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), DAS 28 and DAS 28-3 score (Modified Disease Activity Score). The DAS 28-3 score system, which measures disease activity using three variables - tender joint count, swollen joint count, and ESR—is the most widely used parameter today because it is thoroughly validated and clinically comprehensible but largely depends on clinical findings **[13]**. In the current era of evidence-based clinical practise, adding laboratory-based investigations such as some haematological parameters like haemoglobin (Hb) level, platelet count, and mean platelet volume (MPV) which are found to be altered in this chronic inflammatory disease can further improve the assessment status of disease activity.

White blood cells and antibodies have been the subject of the majority of studies examining the involvement of the immune system in rheumatoid arthritis (RA), while platelets may also play a role. Many of the evidences have indicated that MPV plays a significant function as a measure of inflammation and disease activity. But very few studies have examined the relationship between these three haematological variables taken as a whole and indicators of RA disease activity based on dependable indices like the DAS 28-3 score, particularly in the Eastern part of India.

The pathogenesis of joint inflammation appears to involve platelets. Platelet indices (PIs), which include platelet count (PC), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) are indicators of platelet activity. PCT calculates total platelet mass as a proportion of blood volume occupied. PDW, which identifies platelet anisocytosis, defines the size distribution of the megakaryocyte's generated platelets.

The synthesis of platelets in the bone marrow is stimulated by systemic rheumatoid inflammation, which is mediated by many cytokines, growth factors, and autoantibodies. Despite being anucleate cells, platelets may generate

microparticles and synthesise proteins on their mRNA (MPs). Within RA synovium and synovial fluid, a significant number of MPs and a large number of platelets can be seen **[14]**.

According to Habets *et al*., in the very early stages of RA, anti-citrullinated protein antibodies (ACPA) may be able to mediate platelet activation. They established a correlation between platelet activation and disease activity as well as the proportion of ACPA in total IgG by incubating platelets from healthy people with plasma from RA patients. P-selectin expression is greater and more soluble CD40 ligand is produced in platelets from RA patients (sCD40L). P-selectin expression and sCD40L release are both indicators of platelet activation. Interestingly, high ACPA titers were linked with P-selectin expression levels and sCD40L release. These findings actually suggest a novel paradigm in which platelets play a significant role in the pathogenesis of joint inflammation **[15]**.

Are Rheumatoid Arthritis and Anaemia Co-related?

Anaemia is a significant consequence of rheumatoid arthritis (RA), which is linked to death and physical impairment. It can be brought on by RA in a number of different ways. One possible factor is the treatments people take to treat RA, such as methotrexate and nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs and methotrexate both have the potential to lead to a folate shortage as well as GI ulcers and blood loss. Anaemia can result from either of these disorders. Some RA patients may use immunosuppressants like azathioprine or cyclophosphamide to reduce their symptoms. Reduced production of bone marrow, which is responsible for producing red blood cells, is a negative effect of this kind of drug. Red blood cells' lifespan may be shortened as a result of RA. If the body is unable to manufacture enough new red blood cells at a suitable rate, this could result in anaemia.

It is determined that anaemia, which has an 84 percent prevalence and is highly connected with increased disease activity in rheumatoid arthritis patients, is a prevalent extra-articular symptom. In patients with rheumatoid arthritis, anaemia of chronic disease is the most prevalent kind. Since serum ferritin is an acute phase reactant and can rise in some people with RA even when they have an iron deficiency state, it is challenging to distinguish between anaemia of chronic disease and iron deficiency anaemia from RA patients. Additionally, ACD and IDA may coexist in some cases. Furthermore, it has been found that higher haemoglobin levels are related to a lower level of disability and a higher quality of life. Therefore, managing individuals with rheumatoid arthritis requires screening for and treating anaemia **[16]**.

The cause of RA-related anaemia will determine the course of treatment. Taking medicine to treat RA symptoms can frequently also help with anaemia. Steroids like prednisone or disease-modifying antirheumatic medicines (DMARDs) are examples of these therapies.

DMARDs are categorised by doctors as either traditional or biologic. These medications have very specific and targeted effects on immune system performance. DMARDs can help RA sufferers with their inflammation. People with chronic disease-related anaemia may experience less symptoms if the inflammatory response is minimised **[17]**.

Immune Cells of Our Body as the Booster cause for Rheumatoid Arthritis:

Immune cells, primarily B-cells, T-cells, and macrophages, are crucial in the pathogenesis of RA because it is an autoimmune condition. These cells might circulate in the peripheral circulation or live in the synovium. In order to support RA, B-cells release physiologically significant proteins such rheumatoid factors (RFs), anti-citrullinated protein antibodies (ACPA), and pro-inflammatory cytokines. Through the production of costimulatory molecules, B-cells also play a role in T-cell activation. T-cell activation and fibroblast conversion into tissue-destructive cells is the primary role of T-cells in RA. A number of cytokines and chemokines are produced by activated macrophages to support joint inflammation, just like T- and B-cells do. This section explains in great depth how different immune cells affect the pathogenesis of RA.

B-cells are well known to play a significant role in human adaptive immunity, but in the case of RA, they also serve as one of the primary causes of RA onset. Autoreactive B-cells are B-cells that recognise host antigens and then go on to kill the corresponding cells or tissues **[18]**. Autoreactive B-cells are typically destroyed by mending mechanisms either when early immature B-cells develop into immature B-cells in the bone marrow or before the B-cells grow into naive B-cells. The central and peripheral B-cell tolerance checkpoints of the immune system play a major regulatory role in each of these processes **[19]** B-cell growth factors, which influence B-cell receptor (BCR) and toll-like receptor (TLR) signalling, are in charge of the central B-cell tolerance checkpoint **[20]**.

The basic cause of all autoimmune illnesses, the T-cell-mediated destruction of "own" cells, has also been targeted for suppression. In addition, scientists and pharmaceutical businesses are jointly looking into the use of T-cell and B-cell depletion therapy. The tissue of the synovium frequently contains macrophages. Under typical circumstances, most macrophages rest within the tissues.

However, in an inflamed joint, they control the release of harmful enzymes and pro-inflammatory cytokines that are connected to inflammatory reactions and ultimately cause joint degeneration. RA-related biological processes such as lymphocyte recruitment, cartilage degradation, joint erosion, angiogenesis, and fibroblast proliferation are all mediated by macrophages in addition to generating cytokines and enzymes **[21]**. Leukocyte adhesion molecules and HLA-DR are extensively expressed on macrophages, which function as an APC and enable them to engage in T-cell activation alongside B-cells **[22]**. Effector T-cells are produced as a result of the macrophages-mediated T-cell activation, and pro-inflammatory mediators such IL-1, IL-1, and MMPs are expressed as a result, supporting the pathogenesis of RA **[23]**.

A Better Diet Plan Can Secure from Rheumatoid Arthritis and Serve a Good Health:

Rheumatoid arthritis (RA), a crippling autoimmune illness, is one condition that can benefit from self-help nutritional therapy. Due to factors like affordability, accessibility, and the availability of scientific evidence demonstrating significant benefits in reducing disease symptoms like pain, joint stiffness, swelling, and tenderness as well as the disability that is associated with disease progression, dietary interventions are required to have a broad appeal for both patients and clinicians. It should be ideal for rheumatologists to provide a supplemental "diet therapy" to RA patients given the mounting evidence that altered microbiome in the gut of RA patients is crucial for pathogenesis along with disease progression **[24]**.

In patients who were allowed to consume a small amount of vitamin and mineral supplements, carbohydrates, and energy in the form of vegetable juice, Fraser *et al*. found that subtotal fasting reduced CD4+ cell activation and numbers. It has been demonstrated that the progression of RA is caused by CD4+ T cell activation and subsequent differentiation into the Th1 and Th17 lineages. As a result, the 7–10 day fasting-induced decrease in T cell activation raises the possibility of a brief immunosuppression that would control RA **[25]**.

The duration of morning stiffness, ESR, articular index, concentrations of acute-phase reactants including orosomucoid, C3, and haptoglobin, and haemoglobin levels all decreased during fasting, according to Hafstrom *et al*. Furthermore, RA patients had less lysozyme released by their neutrophils, which is known to damage joints and promote inflammation. The pro-inflammatory mediator leukotriene B4 (LTB4) has a role in the activation of

neutrophils, eosinophils, and monocytes as well as the generation of pro-inflammatory cytokines, which further contribute to tissue inflammation and neutrophil-mediated tissue damage. At the end of the fasting week, it was revealed that neutrophils released much less LTB4 **[26]**.

So regardless of changes in intestinal microbiota, fasting combined with a vegan diet or a vegan di*et al*one may be able to lessen symptoms and disease activity in RA patients. The reduction in exposure to possible antigens caused by RA patients' omnivorous diets can be credited with the observed improvements.

Osteoclastogenesis, or the process by which osteoclast cells destroy bone tissue, has been recognised as a clinical occurrence in RA patients. Consuming dried plums, which are a high source of polyphenols, can reduce osteoclastogenesis by preventing the activity of TNF- and nitric oxide (NO) synthase and nuclear factor for activated T cells (NFATc1) **[27]**.

An ideal meal may consist of raw or gently cooked vegetables (plenty of greens and legumes), along with spices like turmeric and ginger, seasonal fruits, and probiotic yoghurt; all of these are excellent sources of natural antioxidants and have anti-inflammatory properties. Avoiding processed foods, foods high in salt, oils, butter, sugar, and animal products is advised for the patient. RA can also be managed with the aid of dietary supplements including vitamin D, cod liver oil, and multivitamins. With little cost strain, this nutrition therapy and low-impact aerobic workouts can be employed to improve RA self-management. To effectively treat and control RA, however, a higher level of patient compliance is always required **[28]**.

CONCLUSION:

One of the prevalent and often occurring autoimmune disorders is rheumatoid arthritis. which, when it happens, results in a lack of ability to work and in achieving daily objectives. In this kind of condition, the body's immune system began to harm the muscle tissue and the different joints, as well as to cause inflammation in numerous places. Almost all age groups are thought to be affected by these disorders. The severity of RA is primarily influenced by environmental factors, the daily food, and ideally, how well the body's numerous immune cells are working. There are various stages of RA based on when it first appears and how severe it is. Given that the symptoms of RA can also be found in other types of arthritis, it is difficult to prognose and diagnose the condition. In the modern era, RA can also be diagnosed through serological tests and classification, as well as by interpreting haematological parameters, which facilitates disease diagnosis and prognosis. The treatment for

such type of Arthritis involves the arresting the excess and improper regulation of the immune cells. The rehabilitation from RA might be aided by a diet plan that includes the right amount of the selected food type. Additionally, it has been observed that at least two weeks of moderate hunger serve as a booster dose for those recovering from rheumatoid arthritis. A healthy diet and appropriate medical care can aid in reducing the severity of arthritis.

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