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Pathophysiological Approach of Rheumatoid Arthritis: A Review

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Abstract: A chronic autoimmune disease that mostly affects the peripheral joints, rheumatoid arthritis (RA) is characterized by synovitis, which causes pain, swelling, and stiffness in the joints. If left untreated, the condition, which primarily affects women in their 30s to 50s, can cause severe joint degeneration and disability. RA can impact the skin, blood vessels, lungs, eyes, and heart. Pathogenesis, which is aggravated by genetic variables such as HLA-DR alleles and environmental triggers including infections and smoking, involves the immune system attacking self-tissues. Clinical assessment, imaging, and blood testing are used to make the diagnosis. Anti-citrullinated protein antibodies (ACPA) must be identified early and this requires blood tests. Non-specific anti-inflammatories have been supplanted by targeted biologics and DMARDs (disease-modifying antirheumatic drugs) as the primary treatments to prevent immune dysregulation and maintain joint function. Monoclonal antibody treatments that target tumor necrosis factor (TNF) and other cytokines essential to the pathophysiology of RA are among the most recent developments. Notwithstanding advancements in treatment, problems with early diagnosis and disease management continue to exist, affecting patient outcomes and quality of life. Current research attempts to develop personalized medicine approaches employing genetic markers, immunological profiles, and environmental factors to increase prognosis accuracy and therapy success in RA.

Keywords: Autoimmune disease, Synovitis, Anti-citrullinated Protein Antibodies, Rheumatoid arthritis

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Introduction

Synovitis is the main symptom of rheumatoid arthritis, an autoimmune inflammatory illness (Komatsu and Takayanagi, 2022). Usually, it causes painful, swollen, and heated joints. After rest, pain and stiffness frequently get worse. Inflammatory arthritis of the peripheral joints,

typically with a symmetrical distribution, is the most notable presentation of Rheumatoid arthritis (Harsh, 2019). Other bodily organs that could be impacted by the illness include the skin, eyes, lungs, heart, nerves, and blood (Handout on Health, 2014). Women in their 30s to 50s are the most common age group affected; the incidence is 1 in 150 (Hayes and Dennerstein, 2005). The prevalence rate varied regionally and ranged from 0.5% to 1% of the population in 2002. The most desirable outcomes (i.e., reduced joint destruction, less radiologic progression, no functional disability, and DMARD-free remission) and cost-effectiveness are measured by the date of diagnosis, which is thought to be the key improvement index (Silman and Pearson, 2002). The 2500-year-old Greek word for "flowing current," which describes how the afflicted joints flow throughout the body, is where the word "rheumatism" originates. Humanity has suffered from this illness for a very long time, and there is a lengthy medical history behind its treatment (Van Der Linden *et al.*, 2010). A 2,500-year-old document claims that consuming a decoction made from the bark of European white willow trees reduces pain (Miles, 2021). It was discovered that salicin was a part of the bark. Acetylsalicylic acid was first synthesized by Gerhardt (1853) and showed better *in vivo* stability than salicin. Hoffmann in Bayer first marketed acetylsalicylic acid as a tablet for arthralgia in 1897, and it is currently used for other conditions all over the world. When cortisone was first administered to rheumatoid arthritis patients in 1949, according to Dr Hench's report, the patients' significant improvement was widely acknowledged. In 1950, he received the Nobel Prize in Physiology/ Medicine. In order to reduce pain and swelling, glucocorticoids and non-steroidal anti-inflammatory drugs were used to treat rheumatoid arthritis in the 20th century. Unfortunately, disease control was insufficient, and joint destruction could not be stopped from progressing (Hedner and Evert, 1998). The first monoclonal antibody treatment against tumour necrosis factor (TNF), a cytokine that is crucial to the pathophysiology of rheumatoid arthritis, was approved in 1998. Treatment approaches underwent a paradigm shift as a result of its groundbreaking therapeutic impact. Disease-modifying antirheumatic drugs (DMARDs) are the name given to immuno-suppressive medications used to treat rheumatoid arthritis. Currently, DMARDs are divided into two categories: biologic DMARDs, which are made from biological agents, and synthetic DMARDs, like methotrexate (Joshi and Dhaneshwar, 2014).

Early diagnosis is still difficult, though, since it depends primarily on clinical data from the patient's physical examination and medical history, which is further supported by imaging analysis and blood testing. The causes of a delayed diagnosis differ significantly amongst nations with different health care systems (Raza *et al.*, 2011). Patient and physician factors seem to play a role in the reasons behind a delay in starting DMARD therapy in RA patients (Ometto *et al.*, 2011).As of 2015, 24.5 million people were affected by RA (Vos *et al.*, 2016). This translates to 5–50 per 100,000 newly diagnosed cases per year, or between 0.5 and 1% of adults in the developed world (Smolen, 2016). Women are affected 2.5 times more frequently than men, with middle age being the most common age of onset. 38,000 people died as a result in 2013, compared to 28,000 in 1990 (Naghavi *et al.*, 2015). Dr. Augustin Jacob Landré-Beauvais (1772–1840) of Paris provided the first acknowledged description of RA in 1800 (Landré-Beauvais, 2001).

Signs and symptoms of RA

Everybody is affected by rheumatoid arthritis differently. Some people experience joint pain over a period of years. For others, the symptoms of rheumatoid arthritis worsen quickly (Bingham *et al.*, 2009). There are periods when RA symptoms worsen, referred to as flares, and periods when they get better, referred to as remission (Ajeganova *et al.*, 2017). The majority of RA patients experience a gradual onset that frequently starts with fever or malaise, which is a generalized sense of discomfort, sickness, or unwellness, arthritis, or joint pain, weakness prior

to swelling and inflammation of the joints (Aletaha *et al.*, 2010).

Signs and symptoms of RA include:

• More than one joint experiencing pain or aching; more than one joint experiencing stiffness; more than one joint experiencing tenderness and swelling. The identical symptoms in the hands and knees on opposite sides of the body.

• Loss of weight

•Hand and foot symmetric polyarthritis (synovitis) with persistent deformity (defining characteristic)

• Deterioration of the articulations over time

• Interaction outside of the joint

• Having trouble carrying out daily living activities (ADLs)

• Signs of constitutional disease (Kung and Bykerk, 2014).

Risk factors of RA:

Risk Factors that be controlled:

• *Age*: Although RA can start at any age, the likelihood rises with age. The majority of adults in their sixties experience the onset of RA.

• *Sexual relations*: Women usually experience two to three times as many new cases of RA as men do.

• *Inborn characteristics/genetics*: Individuals with particular genes at birth are predisposed to RA. HLA (human leukocyte antigen) class II genotypes are genes that can exacerbate arthritis. Those who carry these genes may be more susceptible to RA if they smoke or are obese, among other environmental factors (Zhang *et al.*, 2014)

Environmental risk factor:

Environmental risk factors like toxins and infections may not always be preventable, but it is still important to be aware that they can cause RA, particularly in those who are genetically susceptible.

Contaminations: It has been proposed that the Epstein-Barr virus, *Escherichia coli* (*E. coli*), and Hepatitis C are potential causes of autoimmunity and RA. According to one theory, infections cause the immune system to overreact, which leads to chronic inflammation and eventually autoimmune arthritis. Additionally, some researchers believe that certain antibodies and healthy cells may react with one another. Antibodies typically target a single antigen, but some, like those produced against Epstein-Barr, may also target normal tissue (Balandraud and Roudier, 2018).

Poisons: Although not all of the links between various toxins, pollutants, and chemicals and RA have been established, many have. The ones with a definite correlation are pesticides, asbestos, silica dust, and second-hand smoke. Autoantibodies are known to develop as a result of chronic lung inflammation, and researchers theorize that these antibodies may spread from the lungs to other locations, such as the joints. There are probably a lot more toxins connected to RA, but more investigation is required to identify the worst culprits (Oliver and Silman,2006).

Trauma experienced as a child: There is growing evidence connecting childhood violence, abuse, and neglect to RA in adults. It is well recognized that emotional distress sets off an immune response that can result in autoimmune disease. It also influences other symptoms and pain associated with arthritis. Adults with RA who had experienced childhood trauma were found to be significantly more in pain in one study than comparable patients who had not experienced trauma (Brawer and Goel, 2016).

Life style risk factors:

It is possible to prevent RA regardless of your genetic risk by leading a healthy lifestyle. According to some rheumatologists, the new paradigm for treating RA is to treat it like heart disease—a preventable condition for which some common risk factors can be controlled. These include:

• *Smoking*: Cigarette smoking along with heart disease and a number of other chronic illnesses is known to increase the risk of developing RA. It

plays a role in the progression of RA from pre-clinical stage, in which autoantibodies are present but symptoms are absent, to clinical stage. In people who smoke at least a pack a day for 20 years or more, it may even cause RA in those who are not genetically susceptible. Smoking can worsen RA symptoms and reduce the effectiveness of treatment (Ishikawa and Terao, 2020).

• *Obesity*: Because fat cells release inflammatory proteins called cytokines, which are essential in the breakdown of joint tissue, being overweight can lead to systemic inflammation. The body produces more cytokines the more fat cells it has. It is also less likely that the person will respond well to arthritis medications or experience a remission of the condition if overweight or obese (Smores *et al.*, 2022).

• *Gum disease*: Gum disease is now known to play a role in the development of RA, heart disease, lung disease, and Alzheimer's. There are over 700 different types of bacteria in mouth. The majority of microbes are helpful and aid in the control of harmful bacteria. Gingivitis and oral cancer can occur when dangerous bacteria overcome these defences. Additionally, bacteria can be inhaled and cause severe inflammation in the lungs. The joints may then become inflamed, among other areas of the body (Kaur *et al.*, 2013).

• *Food*: There is not a specific diet for arthritis, but diet has an impact on all areas of the health. Eating less red meat, dairy products, sugar, and high-fructose syrup and more fish, vegetables, and olive oil can help reduce the risk of developing arthritis and manage its symptoms (Cassotta *et al.*, 2021).

• *Modifications to the microbiome*: The large communities of helpful microorganisms that reside on and in the body, known as the microbiome, have gained recognition as a crucial factor in determining health and disease during the past 20 years. This is particularly relevant for autoimmune illnesses such as RA, as the immune system both regulates and is regulated by the microbiome. The microbiomes in mouth and gut are the most numerous and have the biggest influence on the health, despite the fact that every crevice in the body contains microbiomes (Hort-Bass *et al.*, 2017). Antibiotics are the most common cause of disruptions to the microbiome's equilibrium. However, a few foods, particularly processed and red meat, sugar, and dairy products; as well as stress, inactivity, trauma, and alcohol consumption also play a part.

Pathogenesis:

A chronic symmetric polyarticular joint disease, rheumatoid arthritis (RA) mainly affects the tiny joints of the hands and feet. Infiltration of inflammatory cells into the joints, which results in synoviocyte growth and the decomposition of bone and cartilage, is a characteristic of the inflammatory process (Tak and Kalden, 2011). Based on the existence or lack of anti-citrullinated protein antibodies (ACPAs), there are two main subgroups of RA (Klarenbeek *et al.*, 2010). The calcium-dependent enzyme peptidyl-arginine-deiminase (PAD) catalyses the post-translational change known as citrullination, which converts positively charged arginine into a polar but neutral citrulline. About 67% of RA patients have detectable ACPAs (Nishimura *et al.*, 2007).

Triggering stage:

An aberrant antibody response to several citrullinated proteins, such as histones, fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1 (EBNA-1), α-enolase, type II collagen, and fibrin, which are found all over the body, causes ACPA. There is evidence linking genetic and environmental variables to the generation of ACPA (Bizzaro *et al.*, 2013). ACPA-positive RA and its role in the development of ACPA-positive RA in an ACPA-positive RA is most strongly related with genes encoding HLA-DR, particularly HLA-DR1 and HLA-DR4, which are referred to as "shared epitopes" (SEs) (Rayachaudhuri *et al.*, 2012). It is believed that SE is a major risk factor for ACPA production because it affects RA outcome through ACPA production (Okada *et al.*, 2014). The lymphoid-specific protein tyrosine phosphatase known as protein tyrosine phosphatase non-

receptor type 22 (PTPN22) has also garnered a lot of attention due to polymorphisms linked to variety of ethnic groups(Mori *et al.*, 2005; Goh *et al.*, 2017)

In RA, the environment serves as a trigger for the production of ACPA, and genes and the environment are combined through epigenetic regulation. The reactivity of autoantibodies to citrullinated antigens in RA is influenced by gene-environment interaction. In RA, the environment serves as a trigger for the production of ACPA, and genes and the environment are combined through epigenetic regulation. The reactivity of auto-antibodies to citrullinated antigens in RA is influenced by gene-environment interaction (Van Der Woude *et al.*, 2010).

Maturation stage:

Anti-cyclic citrullinated peptide antibody (ACCP) levels at the outset seem to be crucial in determining the amount of time until the disease manifests (Moeez *et al.*, 2013). The breakdown of immunological tolerance is reflected in the generation of ACPA. Numerous citrullination neoantigens would therefore stimulate T cells that are dependent on MHC class II, which would then assist B cells in producing more ACPA. In RA, ACPA can cause pain, inflammation, and bone loss (Krishnamurthy *et al.*, 2016; Wingerblad *et al.*, 2016). Angiogenesis and the infiltration of mononuclear cells (such as T cells, B cells, plasma cells, dendritic cells, macrophages, mast cells, and T cells) or their local activation, or both, are the causes of synovitis (Smolen and Steiner, 2003). Citrullination may have a special function in osteoclast differentiation and ACPA-induced osteoclast activation, which could account for some of the key aspects of RA's slow progression, such as the reason joints are targeted. Additional plausible factors encompass the biologic characteristics of the targeted autoantigen, local microvascular, neurologic, and biomechanical elements, and mechanisms associated with microtrauma may also play a role (McInnes and Schett, 2011).

Targeting stage:

When RA affects joints, the symptoms are typically recognizable, with symmetrical small joints experiencing synovitis (Burmester *et al.*, 1983). Multiple inflammatory cells infiltrating the joint fluid and pannus, followed by tissue destruction. In addition to other inflammatory mediators, chemokines are important in the pathophysiology of RA (Fang *et al.*, 2020).

In the context of inflammatory RA, the imbalances between pro-inflammatory M1 macrophage and anti-inflammatory M2 macro-phage also need to be taken into account. It has also been discovered that synovial membranes are heavily infiltrated by monocytes and macrophages (Tadito *et al.*, 2019). In fact, a recent study found that osteoclastogenesis in RA patients, particularly in ACPA-positive RA, is influenced by an imbalance in M1/M2 monocytes (Fukui *et al.*, 2018). Furthermore, according to one study (Hueber *et al.*, 2010), mast cells are the primary location of the pro-inflammatory cytokine interleukin (IL)-17A in RA joint samples. Additionally, mast cells can be activated by ACPA and TLR ligand (Suurmond *et al.*, 2015). There exist reports of DC accumulation in the articular cavity (Zvaifler *et al.*, 1985). It has been demonstrated that myeloid DCs or dendritic cells are APCs (antigen-presenting cells) that can induce T cell differentiation (Yang *et al.*, 2016). Patients with rheumatoid arthritis may have an accumulation of autoreactive T and B cells in their synovial tissues. Autoantigens do not affect T cells immunologically because they are immune-tolerant; however, when self-tolerance is compromised, autoreactive T cells become activated and stimulate B cells to produce autoantibodies. Autoantibodies combine with antigens to form immune complexes that are deposited in tissues and trigger complement activation, leading to histological damage (type III allergy) (Tran *et al.*, 2005). Lymphocyte accumulation, synoviocyte proliferation, and vasodilation are the hallmarks of synovitis-affected tissues. The buildup of memory T and B cells in tissues exhibiting diffuse inflammation can

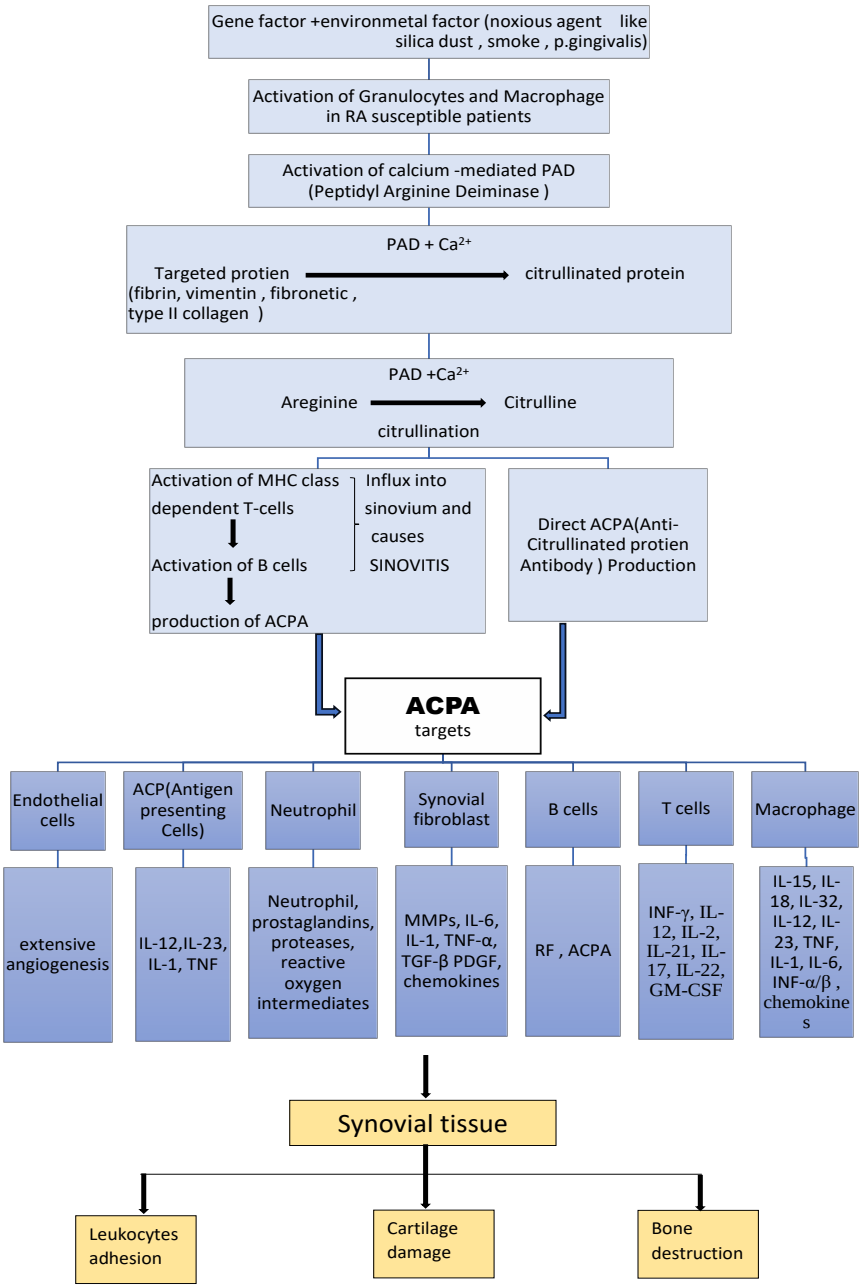

Fig. 1: Pathogenesis of Rheumatoid Arthritis.

lead to the development of structures resembling lymphoid follicles and germinal canters. In these structures, pro-inflammatory cytokines and co-stimulators are highly expressed, and close cellular interactions are seen (Smolen *et al.*, 2018).

Fluminant stage:

Hyperplastic synovium:

A combination of specialized FLSs (fibroblast-like synoviocytes) and macrophages derived from bone marrow characterize the synovium (Edwards, 1994). Hyaluronic acid and lubricin, which are secreted by synovial cells for joint lubrication and function, as well as waste product processing, help to maintain the steady state of the joint. Hyperplastic synovium in RA is caused by FLS dysfunction (Filer *et al.*, 2006). Large amounts of inflammatory cytokines, including TNF,

interleukin (IL)-1, and IL-6, are produced by these synoviocytes and lead to synovitis (Fujita, 2019).

Cartilage damage:

Synovial joints rely heavily on cartilage, which is made up of chondrocytes and a dense, well-organized extracellular matrix (ECM) that these chondrocytes synthesize and that contains type II collagen and glycosaminoglycans (GAGs). In RA, the hyperplastic synovium directs adhesion and invasion, which seriously damages the cartilage. On the other hand, FLS activity may be further stimulated by inflammatory signals, including those that are released from the ECM (Sabeh and Weiss, 2010). Moreover, synoviocytes stimulated by cytokines release matrix metalloproteinases (MMP) into the synovial fluid. These enzymes break down and absorb cartilage (Rengel *et al.*, 2007).

Bone erosion:

One of the pathological characteristics of RA is bone loss, which can be systemic, periarticular, or localized. The induction of osteoclasts and the suppression of osteoblasts lead to bone loss (Okamoto *et al.*, 2017). In order to trigger the maturation and activation of osteoclasts, synoviocytes and lymphocytes express receptor activator of nuclear factor-kappa B ligand, or Receptor activator of nuclear factor Kappa-B ligand (RANKL). Proliferative and stratified synoviocytes found in inflammatory granulation tissues proliferate until they come into contact with the bones (Reynolds, 2010).

Pathogenesis of Rheumatoid Arthritis: Figure 1 illustrates the detailed pathogenesis of rheumatoid arthritis.

Conclusion

As per several discoveries and vast studies on rheumatoid arthritis it is found that it is an autoimmune disease characterized by synovitis. The main pathophysiology for RA involves the interaction of gene factor and environmental factor that leads to citrullination of target protein to citrullinated protein. This citrullinated protein act as foreign body which further leads to activation of T cells, B cells that produces ACPA (anti citrullinated protein antibodies). These ACPA aggregates at synovial and produces inflammatory cytokines which leads to synovitis and it also causes bone erosion, bone destruction and damage to cartilage etc.

Rheumatoid arthritis commonly affects women than men and signs and symptoms begin with fever, feeling discomfort, pain in joints, inflammation and swelling at infected site. In severe case it is symptomize to pain, stiffness to more than one joints, tenderness and swelling etc. However, there is no cure for rheumatoid arthritis, early diagnosis and comprehensive management approach, including medication, lifestyle modify-cation, and sometime surgery, can significantly improve the quality of life for individuals with RA. The advancement in treatment options, including disease modifying antirheumatic drugs (DMARDs), NSAIDs, corticosteroids and biologics aims to manage the symptoms.

Research on treatment of rheumatoid arthritis is ongoing, with a focus on developing more targeted and effective therapies. Some area of current research include biologic therapies, precision medicine, stem cell therapy, combination therapy and lifestyle intervention.

Ethical Statement

This is a review article hence no Ethical Approval needed.

Author Contributions

Mohamed Shabi Mohamed Abdul Kader, *Suvabrata Chanda*, *Syeda Siddiqha*, *Raunak Kumari*: Conceptualization, Literature review and manuscript preparation; *Mohamed Shabi Mohamed Abdul Kader*, *Syeda Siddiqha*, *Jagruthi Mahesh*, *Keerthi Nanjegowda*: Review and editing; *Suvabrata Chanda*, *Syeda Siddiqha*, *Raunak Kumari*, *Avijit Paul*, *Tabasum*: Picture/Flowchart designed; *Mohamed Shabi Mohamed Abdul Kader*: Supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

References

Ajeganova S and Huizinga T. (2017) Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations. Ther Adv Musculoskelet Dis. 9(10): 249-262.

Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham III CO and Hawker G. (2010) Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatism 62: 2569-2581.

Balandraud N and Roudier J. (2018) Epstein-Barr virus and rheumatoid arthritis. Joint Bone Spine 85: 165-170.

Bingham C, Pohl C, Alten R, Christensen R, Choy E, Hewlett S and Furst D. (2009) Flare and disease worsening in rheumatoid arthritis: time for a definition. Int J Adv Rheumatology 7: 85-91.

Bizzaro N, Bartoloni E, Morozzi G, Manganelli S, Riccieri V, Sabatini P and Forum Interdisciplinare per la Ricercanelle Malattie Autoimmuni (FIRMA Group) null@ null. com. (2013) Anti-cyclic citrullinated peptide antibody titer predicts time to rheumatoid arthritis onset in patients with undifferentiated arthritis: results from a 2-year prospective study. Arthritis Res Therapy 15: 1-9.

Brawer AE and Goel N. (2016) The onset of rheumatoid arthritis following trauma. Open Access Rheumatol. 8: 77-80.

Burmester GR, Dimitriu-Bona A, Waters SJ and Winchester RJ. (1983) Identification of three major synovial lining cell populations by monoclonal antibodies directed to Ia antigens and antigens associated with monocytes/macrophages and fibroblasts. Scandinavian J Immunol. 17: 69-82.

Cassotta M, Forbes-Hernandez TY, Cianciosi D, Elexpuru Zabaleta M, Sumalla Cano S, Dominguez I and Battino M. (2021) Nutrition and rheumatoid arthritis in the 'omics' era. Nutrients 13: 763.

Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M and Cooper LT. (2015) Global regional and national age-sex specific all-cause and cause-specific mortality for 240 causes of death 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 385: 117-171.

Edwards JC. (1994) The nature and origins of synovium: experimental approaches to the study of synoviocyte differentiation. J Anat. 184: 493-501.

Fang Q, Zhou C and Nandakumar KS. (2020) Molecular and cellular pathways contributing to joint damage in rheumatoid arthritis. Mediators Inflamm. 2020: 3830212.

Filer A, Parsonage G, Smith E, Osborne C, Thomas AM, Curnow SJ and Buckley C D. (2006) Differential survival of leukocyte subsets mediated by synovial, bone marrow and skin fibroblasts: site-specific versus activation-dependent survival of T cells and neutrophils. Arthritis Rheumatism 54: 2096-2108.

Fujita Y. (2019) 2-Nitrofuran arylamide compounds as innate immune modulators. Ph. D. Thesis, University of California, San Diego.

Fukui S, Iwamoto N, Takatani A, Igawa T, Shimizu T, Umeda, M and Kawakami A. (2018) M1 and M2 monocytes in rheumatoid arthritis: a contribution of imbalance of M1/M2 monocytes to osteoclastogenesis. Front Immunol. 8: 1-10.

Goh LL, Yong MY, See WQ, Chee EY W, Lim P Q, Koh ET and Leong KP. (2017) NLRP1, PTPN22 and PADI4 gene polymorphisms and rheumatoid arthritis in ACPA-positive Singaporean Chinese. Rheumatol Int. 37: 1295-1302.

Harsh Mohan (2019) Textbook of pathology. 8th edn., Jaypee Brothers Medical Publishers (P)Ltd.

Handout on Health (2014) Rheumatoid Arthritis. National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Hayes R and Dennerstein L. (2005) The impact of aging on sexual function and sexual dysfunction in women: A review of population-based studies. J Sexual Med. 2: 317-330.

Hedner T and Everts B. (1998) The early clinical history of salicylates in rheumatology and pain. Clin Rheumatol. 17: 17-25.

Horta-Baas G, Romero-Figueroa MDS, Montiel-Jarquín AJ, Pizano-Zárate ML, García-Mena J and Ramírez-Durán N. (2017) Intestinal dysbiosis and rheumatoid arthritis: a link between gut microbiota and the pathogenesis of rheumatoid arthritis. J Immunol Res. 2017: 4835189.

Hueber AJ, Asquith DL, Miller AM, Reilly J, Kerr S, Leipe J, Melendez AJ and McInnes IB. (2010) Mast cells express IL-17A in rheumatoid arthritis synovium. J Immunol. 184(7): 3336-3340.

Ishikawa Y and Terao C. (2020) The impact of cigarette smoking on risk of rheumatoid arthritis: a narrative review. Cells 9: 1-24.

Joshi P and Dhaneshwar S. (2014) An update on disease modifying antirheumatic drugs. Inflammation Allergy-Drug Targets 13: 249-261.

Kaur S, White S and Bartold PM. (2013) Periodontal disease and rheumatoid arthritis: a systematic review. J Dental Res. 92: 399-408.

Klarenbeek NB, Güler-Yüksel M, Van Der Heijde DMFM, Hulsmans HMJ, Kerstens PJSM, de Sonnaville PBJ and Allaart CF. (2010) Clinical synovitis in a particular joint is associated with progression of erosions and joint space narrowing in that same joint, but not in patients initially treated with infliximab. Annals Rheumatic Diseases 69: 2107-2113.

Komatsu N and Takayanagi H. (2022) Mechanisms of joint destruction in rheumatoid arthritis—immune cell–fibroblast–bone interactions. Nature Rev Rheumatol. 18: 415-429.

Krishnamurthy A, Joshua V, Hensvold AH, Jin T, Sun M, Vivar N and Catrina AI. (2016) Identification of a novel chemokine-dependent molecular mechanism underlying rheumatoid arthritis-associated auto-antibody-mediated bone loss. Annals Rheumatic Diseases 75: 721-729.

Kung TN and Bykerk VP. (2014) Detecting the earliest signs of rheumatoid arthritis: symptoms and examination. Rheumatic Disease Clinics 40: 669-683.

Landré-Beauvais AJ. (2001) The first description of rheumatoid arthritis. Unabridged text of the doctoral dissertation presented in 1800. Joint Bone Spine 68: 130-143.

McInnes IB and Schett G. (2011) The pathogenesis of rheumatoid arthritis. New England J Med. 365: 2205-2219.

Miles A. (2021) The Trees that Made Britain: Revised Edition. BBC Books; Penguin Random House Ireland Limited, pp. 256.I

Moeez S, John P and Bhatti A. (2013) Anti-citrullinated protein antibodies: role in pathogenesis of RA and potential as a diagnostic tool. Rheumatol Int. 33: 1669-1673.

Mori M, Yamada R, Kobayashi K, Kawaida R and Yamamoto K. (2005) Ethnic differences in allele frequency of autoimmune-disease-associated SNPs. J Human Genetics 50: 264-266.

Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S and Kumagai S. (2007) Meta-analysis: diagnostic accuracy of anti–cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Annals Internal Med. 146: 797-808.

Okada Y, Kim K, Han B, Pillai, NE, Ong RTH, Saw WY and Raychaudhuri S. (2014) Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations. Human Molec Genetics 23: 6916-6926.

Okamoto K, Nakashima T, Shinohara M, Negishi-Koga T, Komatsu N, Terashima A and Takayanagi H. (2017) Osteoimmunology: the conceptual framework unifying the immune and skeletal systems. Physiol Rev. 97: 1295-1349.

Oliver JE and Silman AJ. (2006) Risk factors for the development of rheumatoid arthritis. Scandinavian J Rheumatol. 35: 169-174.

Ometto F, Botsios C, Raffeiner B, Sfriso P, Bernardi L, Todesco S and Punzi, L. (2010) Methods used to assess remission and low disease activity in rheumatoid arthritis. Autoimmunity Rev. 9: 161-164.

Raychaudhuri S, Sandor C, Stahl EA, Freudenberg J, Lee HS, Jia X and De Bakker PI. (2012) Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nature Genetics 44: 291-296.

Raza K, Stack R, Kumar K, Filer A, Detert J, Bastian H and Buckley CD. (2011) Delays in assessment of patients with rheumatoid arthritis: variations across Europe. Annals Rheumatic Diseases 70: 1822-1825.

Rengel Y, Ospelt C and Gay S. (2007) Proteinases in the joint: clinical relevance of proteinases in joint destruction. Arthritis Res Ther. 9: 1-10.

Reynolds SL. (2010) Vascular dysfunction in rheumatoid arthritis. https://core.ac.uk/reader/40001770

Sabeh F, Fox D and Weiss SJ. (2010) Membrane-type I matrix metalloproteinase-dependent regulation of rheumatoid arthritis synoviocyte function. J Immunol. 184: 6396-6406.

Silman AJ and Pearson JE. (2002) Epidemiology and genetics of rheumatoid arthritis. Arthritis Res Ther. 4: 1-8.

Smolen JS. Aletaha D and McInnes IB. (2016) Rheumatoid arthritis. Lancet 388: 2023-38.

Smolen JS and Steiner G. (2003) Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov. 2(6): 473-488.

Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein, GS, Kavanaugh A, McInnes IB, Solomon DH, Strand V and Yamamoto K. (2018) Rheumatoid arthritis. Nature Rev Disease Primers 4: 18001.

Somers TJ, Blumenthal JA, Dorfman CS, Huffman KM, Edmond SN, Miller SN and Keefe FJ. (2022) Effects of a weight and pain management program in patients with rheumatoid arthritis with obesity: a randomized controlled pilot investigation. J Clin Rheumatol. 28: 7-13.

Suurmond J, Rivellese F, Dorjée AL, Bakker AM, Rombouts YJ, Rispens T and Toes RE. (2015) Toll-like receptor triggering augments activation of human mast cells by anti-citrullinated protein

antibodies. Annals Rheumatic Diseases 74: 1915-1923.

Tak PP and Kalden JR. (2011) Advances in rheumatology: new targeted therapeutics. Arthritis ResTher. 13: 1-14.

Tardito S, Martinelli G, Soldano S, Paolino S, Pacini G, Patane M and Cutolo M. (2019) Macrophage M1/M2 polarization and rheumatoid arthritis: a systematic review. Autoimmunity Rev. 18: 102397.

Tran CN, Lundy, SK and Fox DA. (2005) Synovial biology and T cells in rheumatoid arthritis. Pathophysiol. 12: 183-189.

van der Linden MP, Le Cessie S, Raza K, Van Der Woude D, Knevel R, Huizinga TW and van der Helm-van Mil AH. (2010) Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheumatism 62: 3537-3546.

van der Woude D, Alemayehu WG, Verduijn W, de Vries RR, Houwing-Duistermaat, JJ, Huizinga TW and Toes RE. (2010) Gene-environment interaction influences the reactivity of autoantibodies to citrullinated antigens in rheumatoid arthritis. Nature Genetics 42: 814-816.

Vos T, Allen C, Arora M, Barber, RM, Bhutta ZA, Brown A and Boufous S. (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388: 1545-1602.

Wigerblad G, Bas DB, Fernades-Cerqueira C, Krishnamurthy A, Nandakumar KS, Rogoz K and Svensson CI. (2016) Autoantibodies to citrullinated proteins may induce joint pain independent of inflammation. Annals Rheumatic Diseases 75: 730-738.

Yang Z, Shen Y, Oishi H, Matteson EL, Tian L, Goronzy JJ and Weyand CM. (2016) Restoring oxidant signalling suppresses proarthritogenic T cell effector functions in rheumatoid arthritis. Sci Translational Med. 8: 38-33.

Zhang Y, Zhang H, Huang Y, Sun R, Liu R and Wei J. (2014) Human leukocyte antigen (HLA)-C polymorphisms are associated with a decreased risk of rheumatoid arthritis. Molec Biol Rep. 41: 4103-4108.

Zvaifler NJ, Steinman RM, Kaplan G, Lau LL and Rivelis M. (1985) Identification of immunostimulatory dendritic cells in the synovial effusions of patients with rheumatoid arthritis. J Clin Invest. 76: 789-800.