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PATHOGENESIS, PATHOPHYSIOLOGY AND MANAGEMENT OF RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis is characterised by inflammation leading to irreversible destruction of the joints, and it is connected with considerable morbidity, mortality and health related costs. Current research reveals the pervasive influence of environmental factors on the disease's severity and activity. The pain and joint deformity are often associated with disability, depressive symptoms, a negative impact on social relationships and poorer health related quality of life. Key to more successful outcomes in chronic disease are effective selfmanagement strategies, particularly as long-term conditions. The treatment of patients with rheumatoid arthritis aims to relieve pain and to control inflammation, and the final goal is to achieve remission or at least low disease activity for all patients. The interaction between what the body experiences externally and how it reacts internally increases the variance in predictors for disease activity and complicates the understanding of the pathogenesis of rheumatoid arthritis. As new research and information regarding the biological and environmental factors that impact the disease become available, a better understanding and appreciation for the chronic, and sometimes invisible, effects of rheumatoid arthritis are likely to emanate.

Keywords: Pain, Pathogenesis, Pathophysiology, Rheumatoid Arthritis.

1. Introduction

Rheumatoid arthritis (RA) is an incurable disease with an incidence of ~1% (Smolen, Aletaha & McInnes, 2016). It is characterised by inflammation leading to

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irreversible destruction of the joints. It is associated with considerable morbidity, mortality and health related costs (Cross, Smith & Hoy, 2014). RA typically affects small joints of the hands and feet in a symmetrical pattern (NICE, 2009), causing synovial inflammation and joint destruction, muscle atrophy and loss of function (Porth, 2005).

The pain and joint deformity are often associated with disability, depressive symptoms (Porth, 2005), a negative impact on social relationships and poorer health related quality of life (Katz, 1998; Hakkinen et al., 2005; Ruppi et al., 2006). Key to more successful outcomes in chronic disease are effective self-management strategies (Azevedo et al., 2015), particularly as long-term conditions such as RA have been associated with poor treatment adherence and less positive outcomes (Connelly, Woolf & Brooks, 2006).

It is a systemic and debilitating autoimmune disease. The varying levels of severity of rheumatoid arthritis make it notably unique (Ajiboye, Vanda-Ice, et al., 2026). Rheumatoid arthritis is not strictly an inflammatory disease of the joints; it is an extensive disease with many extra-articular manifestations that complicate its treatment and management. In addition to being a disease that is internally driven by the body's immune system, current research reveals the pervasive influence of environmental factors on the disease's severity and activity.

About 1% of the population is affected, and the disease onset generally occurs between 30 years and 50 years of age, with a higher incidence in women. The therapy is complex and includes different classes of drugs with different routes of application but also non-pharmacologic interventions. The most important are patient education followed by exercise and physical and occupational therapy. Because of an increased risk of coronary atherosclerosis, efforts should be made to reduce risk factors such as smoking, hyperlipidemia, hypertension, and obesity.

To relieve pain and swelling fast and to gain control of the inflammation, glucocorticoids (GC) are used widely in acute disease flares either orally or as intraarticular injections. Oral GC is for short-term use (up to 3-4 month) only and should be tapered to prevent side effects as soon as possible (Hoes et al., 2007). To control inflammation in the long run, Disease Modifying Anti-Rheumatic Drugs (DMARD) to spare GC are needed. Nowadays, there are a bunch of opportunities that can be challenges or chances. The treatment of patients with RA aims to relieve pain and to control inflammation, and the final goal is to achieve remission or at least low disease activity for all patients (Smolen et al., 2014). The study is aimed at exploring the pathogenesis, pathophysiology and management of rheumatoid arthritis.

2. Literature Review

Pathogenesis and pathophysiology of rheumatoid arthritis

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T The pathogenesis and pathophysiology of rheumatoid arthritis are not well-defined. A combination of biological markers and environmental factors complicate the understanding of RA and its systemic effect on the body. In adults, RA is typically classified into one of two types: seropositive rheumatoid arthritis or seronegative rheumatoid arthritis. Blood tests identifying the presence of rheumatoid factor (RF) and antibodies to citrullinated protein antigens (ACPAs) indicate seropositive RA (Nordberg et al., 2016).

Antibodies to citrullinated proteins are pathogenic autoantibodies produced by B memory cells in the body's humoral adaptive immune system. The adaptive immune system is characterized by lymphocytes, T and B cells, and dendritic cells that target pathogens in the body. Antibodies to citrullinated proteins are highly specific for RA because they attack extracellular citrullinated protein antigens that are produced in response to inflammation in body tissues and organs (Derksen et al., 2017; Surmont & Diamond, 2015). Recent studies suggest that the presence of these autoantibodies may inadvertently amplify inflammation, directly enhancing arthritis in the body (Elkon & Casali, 2015).

Various sources indicate that these autoantibodies may be present years before the onset of RA-related symptoms occur, signifying the potential for systemic effects of RA that cannot be determined by clinical phenotypes (Brennan & Mcinnes, 2008; Suurmond & Diamond, 2015). In contrast to seropositive RA, seronegative RA patients are ACPA negative. In 2010, the American College of Rheumatology redefined the classification criteria for seronegative patients. The criteria deemed that seronegative patients must show inflammation in 10 or more joints to meet the criteria for an RA diagnosis. Joint inflammation occurs when the immune system attacks and thickens the synovium lining around the joints. If inflammation around the joints persists, the cartilage and bone within the joint can be permanently damaged.

Historically, seropositive RA has been considered to be more severe than seronegative RA, but recent findings propose otherwise. A 2016 report in the Annals of the Rheumatic Diseases found that in a study of 234 patients with either a seropositive or seronegative RA diagnosis, the seronegative patients reported higher disease activity in comparison to the seropositive patients (Nordberg et al., 2016). This insight could be of interest to diagnosing physicians and rheumatologists as swollen joints and the presence of ACPA may not be the most useful factors in identifying the severity of disease. Further research should be enacted to determine the varying severity levels of seropositive versus seronegative RA and their criteria for diagnosis.

The second component that adds to the complexity of the development and progression of RA is the interaction between the body's immune response to environmental factors. Smoking, infectious agents, periodontal disease, the gastrointestinal microbiome, and adverse life events are all related to the onset of rheumatoid arthritis (McInnes & Schett, 2011). Reports indicate that smoking, one of the strongest known risk factors for RA, may perpetuate the production of

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citrullinated proteins, resulting in the subsequent development of ACPAs (Demoruelle & Deane, 2011).

The interaction between what the body experiences externally and how it reacts internally increases the variance in predictors for disease activity and complicates the understanding of the pathogenesis of RA. As new research and information regarding the biological and environmental factors that impact the disease become available, a better understanding and appreciation for the chronic, and sometimes invisible, effects of RA are likely to result.

Rheumatoid arthritis as a systemic disease

Rheumatoid arthritis is predominantly classified by its manifestations and physical phenotypes in the major joints of the body. When people think of “arthritis,” they think of bone atrophy, aging, inflammation, and fatigue. While each of these factors play a role in the course of this chronic autoimmune disease, new research indicates that the underlying systemic involvement of RA is much greater than previously thought. According to Prete et al. (2011), “the natural history of the disease in most patients involves chronic low-grade inflammation, with periodic flares, that may progressively lead to joint destruction, deformity, disability and even premature death.”

Yet, the overall effects of the disease appear to be much more intense than the symptoms that result from low-grade flares of inflammation. Fatigue, for example, was at one time considered to be a primary symptom related to elevated levels of inflammation in the body. More recently, researchers believe fatigue to be associated with other RA-related symptoms, including depression, anxiety, and the inability to exercise (Moreland & Curtis, 2009). These psychosocial factors influencing disease activity suggest the personal burdens associated with an RA diagnosis are more far-reaching than presumed by early research. Other indicators such as the presence of rheumatoid nodules and constitutional symptoms including fevers, highlight the misunderstanding of RA as being regarded as a type of arthritis, rather than a systemic disease.

Kelly O’Neil Young, author of the book, Rheumatoid Arthritis Unmasked: 10 dangers of Rheumatoid Disease, provides a great amount of research regarding the symptoms of RA that go beyond joint inflammation. She highlights how the Mayo Clinic lists fever as one of the primary symptoms of rheumatoid arthritis (Rheumatoid arthritis, 2019), and yet most patients who visit their primary care physicians or rheumatologists rarely, if ever, have their temperatures taken upon arrival (Young, 2017). A low-grade fever may indicate RA activity and subsequent flare-ups, even if there are no signs of physical inflammation or swollen joints.

Similarly, rheumatoid nodules are a symptom of RA that “can form before joint involvement and may be associated with an increased risk of other extra-articular manifestations” (Prete et al., 2011). These nodules are subcutaneous and occur in roughly 30% of RA patients (Prete et al., 2011). Because rheumatoid nodules can

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develop before joint involvement, clinicians may not be aware of disease activity if a more thorough examination of the patient's symptoms is not completed.

Current research suggests that the extent of disease activity in RA patients may be much more difficult to determine than once thought. This is critical for clinicians and researchers to consider as they move forward in determining the future of RA treatment and the clinical evaluation of the disease. Patients may be suffering from the systemic symptoms of RA without showing any signs of inflammation in the joints. This likely means that numerous patients could be misdiagnosed or receive treatment for RA considerably later than what is recommended by physician-researchers. Like most other chronic diseases, the early treatment and diagnosis of RA is crucial in preventing significant progressions and retarding the long-term severity of disease (Heidari, 2011).

Articular manifestations of rheumatoid arthritis

Articular (pertaining to a joint or joints) inflammation and destruction due to RA is generally considered to be the primary symptom indicating disease activity. The destruction of the joints can lead to functional decline and increase the risk of comorbidity in various systems in the body (Brennan & Mcinnes, 2008). Clinicians look for symmetrical inflammation of the small joints in the hands and feet during an initial evaluation of patient symptoms (Weissman et al., 2018). Synovial inflammation can become so severe that the patient experiences a drastic decrease in muscle mass, referred to as rheumatoid cachexia. Studies suggest that rheumatoid cachexia is directly related to the presence of pro-inflammatory cytokines in the joints of patients with RA (Santo et al., 2018).

Cytokines are proteins released by cells that interact with other cells. Cytokines can be either anti inflammatory or pro-inflammatory, with evidence supporting that specific pro-inflammatory cytokines are directly involved with pathogenic pain (Zhang & An, 2007). The elevated presence of cytokines in inflamed joints serve as helpful biomarkers for therapies directed towards mitigating the progressive destruction of the joints and extreme muscle loss seen in patients with rheumatoid cachexia. Understanding the influence of cytokines on the primary articular manifestations of RA is paramount towards formulating therapies that both attack pro-inflammatory cytokines to prevent destruction, and also to limit pathogenic pain (Zhang & An, 2007). Reducing patient pain and fatigue is key to hindering the magnitude of co-morbidities and extra-articular manifestations that tend to develop throughout the disease.

Extra-Articular Manifestations of Rheumatoid Arthritis

Extra-articular manifestations are the associated symptoms and conditions of RA that are not related to the articular joints or musculoskeletal system of the body (Cojocaru et al., 2010). While these are considered secondary symptoms to the articular manifestations in the synovial linings, they are not to be confused with complications. Approximately 40% of RA patients present extra-articular symptoms, with the onset occurring at any stage in the disease and with the likelihood of

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occurrence equal amongst both men and women (Cojocaru et al., 2010; Weissman et al., 2018). The extra-articular manifestations in RA patients most commonly and severely impact the heart, lungs, larynx, and vascular systems. Involvement with extra-articular organs positively correlates with the severity of the disease, contributes to increased mortality, and is influenced by genetic and environmental factors (Cojocaru et al., 2010; Prete et al., 2011).

The extra-articular involvement within the major organs of the body make these secondary symptoms of RA dangerous and yet are often overlooked. A discussion regarding the severity of the complications associated with extra-articular manifestations will be reviewed, along with an explanation of how environmental and genetic risk factors complicate symptoms. Rheumatoid arthritis patients often present with phonatory (of speech and sound) and respiratory symptoms that can be subtle and misleading, resulting in seldomly made diagnoses and treatment plans. Inflammation of the cricoarytenoid joint in the larynx can produce symptoms such as loss of voice, hoarseness, pain in the throat, vocal cord dysfunction, immobility, and fixation (Young, 2017).

Recent studies show that laryngeal involvement is seen in up to 90% of RA cases, with up to 50% of patients reporting that laryngeal inflammation is the sole manifestation of their RA symptoms (Hamdan & Sarieddine, 2013). While most laryngeal symptoms are not life-threatening, they can impact and restrict one's quality of life. Aphonia, the loss of the ability to speak, results from inflammation in both vocal cords (Hamdan & Sarieddine, 2013). Rheumatoid arthritis patients who experience this type of disruption to their vocal cords must visit a clinician for treatment of the symptoms. In addition, patients who present with laryngeal symptoms and no articular symptoms may be in the early stages of RA, and the early detection of inflammation in the vocal cords could lead to a better disease prognosis (Young, 2017).

However, a few clinical autopsies have found that rheumatoid cricoarytenoid arthritis is not always clinically detectable (Young, 2017). This can lead to a lack of awareness of laryngeal involvement and a subsequent delay in therapy. As with laryngeal involvement, pulmonary RA manifestations can generate a wide spectrum of symptoms and disorders. The most common pulmonary manifestations are interstitial lung disease, rheumatoid nodules, and pleural effusions (Gauhar et al., 2007), with 50% of patient cases reporting pleural involvement and only 10% being clinically detected (Cojocaru et al., 2010). Researchers are beginning to explore the role of inflammatory cytokines (the proteins found in the inflamed synovia of RA patients) to determine their involvement in pulmonary inflammation.

While the exact effect of cytokines in pulmonary inflammation is not well-understood, further investigations are suggested to explore the role of cytokines in pulmonary involvement to formulate target therapies (Moreland & Curtis, 2009). Likewise, in her book, Young describes how most studies have shown that there is no correlation between the degree of severity of articular destruction and the extent of pulmonary involvement (Young, 2017). Thus, pulmonary symptoms could be severe, while the clinical assessment of joint, cartilage, and bone damage could

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potentially be mild. Without considering pulmonary involvement as an indicator of rheumatoid activity, the clinical phenotypic observation of the joints would fail to provide an accurate assessment of disease activity and severity.

In like manner to the heightened risk of developing pulmonary symptoms, the risk of developing coronary artery disease and heart failure is twice as likely for patients with RA and can be evident before an official RA diagnosis (Crowson et al., 2013). Recent literature highlights the critical role of inflammation of the vasculature and its correlation with an increased risk of cardiovascular disease and mortality. Vascular leakage and atherosclerosis are examples of two vascular diseases that result from inflammation and a buildup of fatty material on the arterial walls. Both these diseases are associated with RA and contribute to high cardiovascular risk. The inflammatory proteins that cause synovitis, inflammation of the synovial linings of the joints, also attributes to vasodilation of the blood vessels and a decrease in overall blood pressure (Szekanecz & Koch, 2008).

Genetic and Environmental Factors of Rheumatoid Arthritis

While extra-articular manifestations can exist on their own or in conjunction with another, genetic predispositions and environmental risk factors can exacerbate the likelihood of developing RA, extra-articular manifestations, and increase mortality risk. Recent research coins a term ‘Preclinical RA,’ where circulating levels of RF and ACPAs are elevated in the bloodstream (Deane et al., 2017). This influx of autoimmunity defense mechanisms can be present in the body long before the clinically apparent synovitis in the joints. Because the propagation of autoimmunity may be present before an inflammatorybased RA diagnosis, the genetic and environmental risk factors associated with RA may also be influencing the body and its systems far in advance of the swelling of the distal joints.

Among seropositive patients, the familial genome may contribute to 50% of the risk of RA development (Deane et al., 2017). Within the overall genetic risk, new findings show that a specific group of alleles called the ‘shared epitope’ may contribute to 40% of the familial genome risk (Deane et al., 2017). The presence of these alleles is highly associated with ACPA seropositive patients and are considered to be high-risk alleles within the human genome. Additionally, environmental risk factors also influence the rate of disease and its severity. While researchers don’t know exactly when these environmental risk factors act in the natural history of RA, it is widely known that they do have an effect on the disease over time.

Most notably, exposure to smoking and specifically to tobacco may account for up to 30% of environmental risk in RA patients (Deane et al., 2017). The effect of smoking on the pulmonary system may attribute to high inflammation of the pleural cavity with patients who experience symptoms from extra-articular manifestations in the lungs. Further evidence also indicates that diet, the health of the microbiome, and exposure to silica dust, are primary environmental risk factors for the development and severity of RA (Badsha, 2018; Deane et al., 2017; Guahar et al., 2007).

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Because the coordination of clinician involvement may be difficult to obtain for RA patients who are suffering from symptoms of extra-articular manifestations, the management and treatment of RA is overwhelmingly complex. Like many other chronic diseases, rapid pharmaceutical intervention is most beneficial within the first 12 months of the diagnosis. It has been established that many RA patients suffer from extra-articular manifestations, which also require rapid and often long-term treatment. Over time, the medications required of an RA patient can be difficult on the body. The most common medications used to treat the underlying disease and symptoms of rheumatoid arthritis are DMARDS (disease-modifying anti-rheumatic drugs), corticosteroids, and NSAIDS (nonsteroidal anti-inflammatory drugs) (Mota et al., 2013).

Disease-modifying anti-rheumatic drugs are immunosuppressive and immunoregulatory drugs that are designed to slow the underlying progression of RA, not just treat the symptoms ("DMARDS," n.d.). Methotrexate is the most commonly prescribed DMARD and is generally considered to be the first line of defense in treating RA due to its well-established efficacy (Mota et al., 2013). While concerns surrounding the use of methotrexate are focused on its long-term gastrointestinal effects, numerous studies have found that methotrexate may also reduce cardiovascular activity in RA patients (Crowson et al., 2013; Salliot & Heijde, 2008), adding to its benefits as a disease-modifying agent. In 2013, the Brazilian Society of Rheumatology released a report outlining the guidelines for the drug treatment of RA, with a specific focus on the use and safety of DMARDS.

In their report, the authors state, "Early administration of DMARD treatment (less than nine months from symptom onset) produced a 33% relative reduction in the radiographic disease progression during the following three years" (Mota et al., 2013). Due to their disease-modifying abilities combined with their relatively safe effects on the body's systems, DMARDS are the current standard for drug treatment against RA. When combined with other symptom-suppressing medication, DMARDS prove to be overtly suitable for treating RA. Corticosteroids are a class of steroid-based drugs that target inflammation and pain. Their role in the body is focused on improving RA symptoms, rather than treating the underlying mechanisms of disease.

While DMARDS can eventually treat symptoms if they are able to slow disease progression, symptom relief is not immediate. Corticosteroids target symptoms directly, resulting in fast relief. Prednisone is a wellknown corticosteroid that is commonly prescribed for RA patients. While effective at treating symptoms, prednisone has many side effects that contradict long-term usage ("Prednisone," n.d.). Patients who are prescribed high doses of prednisone are at twice the risk of developing cardiovascular disease than those who are not prescribed a steroidbased anti inflammatory (Crowson et al., 2013, p. 624). Unless the progression of RA is static and under control, prednisone and other corticosteroids are not typically prescribed alone. Medical research suggests that the pharmacological treatment of RA is most successful when low doses of prednisone

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are used in combination with DMARDS or other disease-modifying medications to combat both the disease itself and its symptoms (Mota et al., 2013).

Non-steroidal anti-inflammatory drugs are anti-inflammatory medications that like corticosteroids, decrease inflammation and pain. Non-steroidal anti-inflammatory drugs, however, are unique because they do not contain steroids. While they are considered to be safer for long-term use, they are not as effective at managing symptoms. Common NSAIDS that are used to treat RA symptoms are Aspirin, Ibuprofen, and Meloxicam (Freeman, 2018). Even though the strength of NSAIDS is far less comparable to that of corticosteroids, physicians consider renal, hepatic, and cardiovascular adverse long-term effects when prescribing NSAIDS to patients. Depending on the severity and progression of disease, some RA patients may respond well to only taking an NSAID, though prescribed NSAIDS are of much greater strength than over-the-counter antiinflammatory drugs. If the patient responds well to NSAIDS and does not have worsening symptoms, research suggests that in combination with DMARDS, the use of NSAIDS is a favorable pharmaceutical treatment plan (Mota et al., 2013).

Non-pharmacological Therapy of Rheumatoid Arthritis

Despite recent advances in the pharmacology realm of rheumatoid arthritis treatment, a comprehensive approach including non-pharmacological treatment plans and an interprofessional team of physicians should be the accepted protocol towards treating RA and its extra-articular manifestations. Even when medicine-based treatment plans are effective at abating disease progression or decreasing pain, a patient's quality of life may still be severely impacted. Lifestyle changes, exercise, therapeutic modifications, psychosocial interventions, patient education, and alternative medicines are just a few examples of non-pharmacological treatment options that are becoming increasingly popular in treating RA.

Empirically-supported research strongly suggests exercise, psychosocial treatment, and patient education/self-management systems to be distinctly significant in improving patient outcomes and enhancing quality of life (Cunningham & Kashikar-Zuck, 2013; Vlieland, 2007). Patients tend to recognize the importance of taking strong medications to fight the progression and symptoms of RA. At the same time, however, patients also often wish that they could mitigate their usage of these harsh pharmacology treatments to abate their strong side effects. In 2004, a group of investigators published a study with 29 patients who had either begun taking a DMARD for the first time or switched to an alternative DMARD.

These patients were asked to voice their opinions and beliefs regarding their medication and what implications it had on their quality of lives. The investigators concluded that while DMARDS were believed to be central to many of the patients' treatment plans, patients voiced concerns regarding the long-term effects and potential 'toxicity' of their medications (Goodacre, 2004). These complex beliefs regarding the feasibility and longevity of pharmacology treatment may be of interest to researchers, physicians, rheumatologists, and scholars who are looking to evolve the medical approach to RA treatment. At this point, obtaining a multifaceted

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proposal to RA treatment is beginning to gain ground amongst professionals. A more in-depth discussion of possible non-pharmacological treatment options is described below.

1. Diet

Many patients with RA explore diets and other integrative modalities as a way to control the disease process. Although the connection between RA and diet is still poorly understood, it is estimated that about half of RA patients will try dietary modifications at some point following their diagnosis (Badsha, 2018). This is a logical next step as scientific findings have shown a compelling link between the gut microbiome and its influence on the immune system. Specifically, the filamentous bacteria in the gut tend to drive the inflammatory process through its effect on helper T cells which then activate B antibodies, resulting in the synovial inflammatory response (Badsha, 2018).

Dietary changes can either exacerbate or improve disease activity via their impact on the human intestinal microbiome. For example, Lectin, a legume protein, has proven to influence the pro-inflammatory response; while Genistein, a hormonal compound also present in legumes, has been shown to inhibit pro-inflammatory cytokines (Badsha, 2018). Current research most notably reports the positive influence of polyphenols, n-3 polyunsaturated fatty acids (n-3 PUFAs), and monounsaturated fatty acids in RA activity suppression. A 2018 study by Skoczyńska & Świerkot found that RA patients consuming foods such as fatty fish, which contain high amounts of n-3 PUFAs, saw a significant decrease in disease activity.

Therapeutic fasting, another modality, could help improve the pain and stiffness commonly seen in RA by improving gastrointestinal tract permeability and modulating the inflammatory process (Hafström et al., 1988; Nair, & Khawale, 2016; Sköldstam et al., 1979). While additional research should be conducted to better understand the role of diet in RA disease activity, the results of current findings are promising indicators of successful outcomes from dietary modification.

2. Physical Activity of Rheumatoid Arthritis

The importance of maintaining a regular physical activity regimen for patients with RA is critical towards sustaining overall well-being and cardiovascular health (Cooney et al., 2011; Metsios et al., 2007). A 2015 study by Salmon and colleagues examined the views of seven physiotherapists and two occupational therapists regarding physical activity and its effect on RA disease progression. Researchers agree that physical activity not only has a positive effect on mitigating fatigue in RA patients, but it also helps improve patients' psychosocial and overall well-being (Salmon et al., 2015).

However, it is noted that patients tend to exhibit limited physical activity due to several factors. Some of these factors include negative patient perceptions regarding the effect of exercise, lack of strength, persistent fatigue, and limited

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functioning (Cooney et al., 2011). Physically inactive patients increase their risk of developing cardiovascular disease and/or rheumatoid cachexia. Several research studies provide substantial evidencethat a combination of aerobic and strength training can drastically reduce disease activity as well as provide additional benefits to the patient by improving functional ability and reducing complications.

Improvement in cardiovascular, musculoskeletal, and joint health - as well as a reduction in pain and morning stiffness has been noted (Cooney et al., 2011). Engaging in high-intensity resistance training is a safe and effective way for patients to reverse muscular atrophy and restore strength. Additionally, aerobic exercise such as walking, cycling, and swimming can improve cardiovascular fitness and address symptoms of pain and fatigue (Cooney et al., 2011).

3. Therapeutic Modalities of Rheumatoid Arthritis

Therapeutic approaches, such as occupational therapy and physiotherapy, are essential parts of any RA treatment plan. The lack of autonomy associated with a reduced ability to execute activities of daily living can have a profound impact on a patient's emotional and psychological state. To address this issue, a 2015 report emphasized four critical areas for occupational therapists (OTs) to focus on during their evaluations of patient priorities: patient guidance and education, joint protection and energy conservation, modifying activity and work environments, and implementing the use of assistive technologies (De Almeida et al., 2015). Occupational therapists play an integral role within the multidisciplinary team to aid patients as they integrate daily approaches that minimize difficulties in performing daily tasks. Additionally, physiotherapy modalities, including hot/cold treatments, electrical stimulation, and hydrotherapy, are commonly used in RA treatment. While research does not suggest physiotherapy to have a direct effect on the clinical diagnosis, the objectives of this modality include disability prevention, increasing functional capability, pain relief, and patient education (Kavuncu & Evcik, 2004). Each of these objectives plays a critical role in improving patient outcomes. While there is limited research on the overall effects of physiotherapy for RA patients, its ability to improve patient well-being should be fully considered for future research.

4. Psychosocial Interventions and Significance of Rheumatoid Arthritis

Depression associated directly with RA is not well recognized, nor is it routinely treated. Studies show that anywhere from 13-42% of RA patients suffer from major depressive disorder (Margaretten et al., 2011). The combination of socioeconomic, genetic, and RA disease factors influence the prevalence of depressive disorders amongst the RA patient population. Specifically, long-term disability, limited function, and systemic inflammation are all associated with the development of depression (Margaretten et al., 2011).

Moreover, 'uncontrolled flares' tend to exacerbate persistent RA symptoms and can result in complete cognitive shutdowns and total social withdrawals. A study in 2011 explored the attitudes of 67 RA patients concerning their perspectives on the psychological and psychosocial imzpacts of symptomatic flare-ups. A few patients in

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this study reported having “ear-shattering pain” even when no noticeable swelling occurred (Hewlett et al., 2011). Others described their limited function to be unbearable, with one patient stating, “I can’t function like this. I’m hurting, I want to kill myself” (Hewlett et al., 2011).

These statements reveal the intense and devastating experiences of RA patients who are forced to endure the effects of ‘uncontrolled flares.’ These impacts on patient lifestyles, social participation, and overall well-being are difficult to comprehend. Psychosocial and psychological interventions should be integral components to the treatment of rheumatoid arthritis. The far-reaching systemic effects of this disease require professional involvement. While the emotional and mental impacts of RA are often not adequately addressed, they cannot go without being recognized. Cognitive approaches for patient therapy have shown to be successful, but more research is required to fully undertake and mitigate the depressive effects of RA.

The efficacy of cognitive-behavioral therapy (CBT) has been studied in various settings and trials with patients who have RA. The behavioral component to CBT for RA patients involves strategies to help patients find a balance between rest and exercise. Cognitive approaches help patients to cope with the stress related to chronic illnesses and to develop attitudes of optimism and realism regarding their diagnosis (Koulil et al., 2018; Sharpe, 2016). Studies show that CBT is considered as one of the most effective psychological approaches to managing RA-related pain, while additional strategies such as mindfulness-based interventions can benefit RA patients with a history of depressiveepisodes (Sharpe, 2016).

In addition to therapies designed to address the psychological symptoms associated with RA, a 2010 meta-analysis of randomized controlled trials examined self-regulation theory (SRT) and its effect on psychological variables, along with its potential ability to increase physical activity in RA patients. Utilizing this active, goal-directed approach to managing RA reduced depressive and anxiety symptoms far more than in subjects who did not partake in the SRT trials (Knittle et al., 2010). It is noteworthy to add that to optimize the efficacy of psychological approaches and to ensure successful results, these methods should be utilized early on in the disease process (Knittle et al., 2010).

Management of Rheumatoid Arthritis

Current management of RA involves the early institution of disease modifying anti-rheumatic drugs (DMARDs), initially with conventional synthetic agents (csDMARDs), followed by biological DMARDs/targeted synthetic DMARDs (bDMARDs/tsDMARDs) if required. The number of b/tsDMARDs available for RA has rapidly increased over the past few years, as have the total healthcare costs associated with them. Despite there being an improvement in outcomes for RA patients, medication adherence rates, especially with csDMARDs, have been poor with some studies showing full adherence in as few as 30% of patients (Salt & Frazier, 2010; Blum, Koo & Doshi, 2011). Evidence is emerging that some patients are progressing to b/tsDMARDs without using csDMARDs as prior or cotherapy, in

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contrast to guidelines and typical regulatory rules (Pharmaceutical Benefits Scheme, 2016).

Patient concordance with medications is associated with improved outcomes in RA (DiMatteo, Giordani & Lepper, 2002); (Wabe, Lee & Wechalekar, 2017). One of the biggest factors affecting concordance is the patient's personal belief about the disease and medications (Gagnon, Waltermaurer & Martin, 2017). Studies have shown that in order to improve adherence with DMARDs, clinicians should focus less on provision of medical information and be more aware of patients' beliefs (Wong, 2016) Understanding patient beliefs however is difficult and often relies on qualitative studies which are excellent at providing an in-depth thematic analysis of a specific issue, but are traditionally conducted on a small scale.

Usage of Social Medial on Chronic Disease

Social media is widely used by patients to discuss medical issues(Benetoli, Chen & Aslani, 2018); in 2012, 26% of internet users were using social media for health issues, making it a rich source of information about patient beliefs (Hamm, Chisholm & Shulhan, 2013). A common technique for analysing social media content is sentiment Analysis (SA), which involves analysing the sentiment expressed in textual content (Pang & Lee, 2008). Such analysis has already been shown to have utility in industries such as entertainment and stock market (Yu, Duan & Cao, 2013; Rui, Liu & Whinston, 2013).

Social media encompasses services including blogs, wikis, virtual worlds and social networking sites that utilise platforms to integrate participation, communication, user-centerdness, collaboration and openness (Berenbaum, 2014). Social media usage continues to grow worldwide with a projection of 2.77 billion users by 2019, up from 2.46 billion in 2017 (Statistica, 2021). In the UK, almost three quarters of adults use mobile devices for internet access, more than double the number reported in 2011 (Office for Nation Statistics, 2017). Social media is now part of daily life for many, routinely used for entertainment, education, financial management, and increasingly for health information and support (Sarasohn-Kahn, 2008).

Those with chronic disease are more likely to use social media to access health literature and aid self-management (Fox, 2011). Users create and link networks of people with shared interests/ experiences in a user-centric and collaborative manner, which could play an important role in patient-centred care (Statistica, 2021; Sarasohn-Kahn, 2008; Kamel & Wheeler, 2007). Virtual worlds and online discussions have facilitated the creation of a collective forum of knowledge about chronic medical conditions that was seldom previously accessed (Fox, 2011).

Using social media to access information can empower and support those with RA and provide an alternative resource that will reduce the burden of treatment and ease social pressures (Fox, 2011). In chronic disease management where lifestyle behaviours can have an impact upon people's wellbeing, this approach is valuable (Sarasohn-Kahn, 2008; Ficarra, 2011). Social media may not only ease the burden

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of self-management in chronic disease, but also offer opportunities to meet patients' needs that are not met in traditional face-to-face clinical encounters (Meroli, Gray & Martin-Sanchez, 2013). Potentially, health professionals could share accurate, real-time health information while maintaining professional boundaries and patients' privacy rights (Sarasohn-Kahn, 2008; Ficarra, 2011; Meroli, Gray & Martin-Sanchez, 2013; Privacy Act, 2000), the latter being a particular concern for patients and professionals alike (Colineau & Paris, 2010).

Software applications (apps) are computer programmes designed to run on mobile devices (smartphones, tablets or smartwatches). The use of apps on mobile phones has increased considerably, and varies with the user's context, location and the time of day (Antheunis, Tates & Neiboer, 2013; Ludwig, 2012). In healthcare, many apps can assist practitioners with day-to-day tasks (time management, e-records, consultations, information gathering, patient monitoring, and so on) (Ludwig, 2012), and in some chronic diseases, such as diabetes, apps currently exist to aid self-management (Antheunis, Tates & Neiboer, 2013; Ludwig, 2012). A recent systematic review concluded that mobile devices with enabled apps could perform important roles in patient education, self-management, and remote monitoring (Böhmer, et al., 2011). In RA, disease activity calculators (Böhmer, et al., 2011) and forums for symptom reporting (Ventola, 2014) do exist, but there is limited evidence of social media usage, or of professionals recognising the potential role of apps in the self-management of inflammatory arthritis.

3. Conclusion

Rheumatoid arthritis is predominantly classified by its manifestations and physical phenotypes in the major joints of the body. The pathogenesis and pathophysiology of rheumatoid arthritis are not well-defined. A combination of biological markers and environmental factors complicate the understanding of RA and its systemic effect on the body. In adults, rheumatoid arthritis is typically classified into one of two types: seropositive rheumatoid arthritis or seronegative rheumatoid arthritis.

Studies have identified rheumatoid arthritis disease activity calculators and forums for symptom reporting do exist, but there is limited evidence of social media usage, or of professionals recognising the potential role of apps in the self-management of inflammatory arthritis.

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Conflicts of Interest

The authors declare no conflict of interest.

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Author Responsibility Statement

AOA: Conceptualization, Writing - original draft, Introduction, Literature, Conclusion. IVO: Writing - original draft, Literature, Editing. DOA: Literature, Editing. AOA: Editing. The authors read and approved the final manuscript.