Spring 4-24-2020

Rheumatoid Arthritis: A Literature Review and Comprehensive Treatment Analysis

Charlton Mechling
University of South Dakota

RHEUMATOID ARTHRITIS: A LITERATURE REVIEW AND COMPREHENSIVE TREATMENT ANALYSIS

by

Charlie Mechling

A Thesis Submitted in Partial Fulfillment
Of the Requirements for the
University Honors Program

Department of Health Sciences
The University of South Dakota
May 2020

The members of the Honors Thesis Committee appointed
to examine the thesis of Charlie Mechling
find it satisfactory and recommend that it be accepted.

_____

Mrs. Jonelle Hook
Instructor of Health Sciences
Director of the Committee

_____

Mrs. Jamie Turgeon-Drake
Instructor of Health Sciences

_____

Dr. Amy Nelson
Lecturer of Health Sciences

ABSTRACT

Rheumatoid Arthritis: A Literature Review and Comprehensive Treatment Analysis

Charlie Mechling

Director: Jonelle Hook, PTA MA

Rheumatoid arthritis (RA) is a systemic and debilitating autoimmune disease. The varying levels of severity of rheumatoid arthritis make it notably unique. 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. This literature review examines the pathophysiology of RA, its implications on the body, and current treatment options to ameliorate some of its symptoms and complications. A particular focus on the efficacy and potential value of diet, psychosocial interventions, physical activity, and therapeutic modalities is central to the current work. Evidence using a literature review of peer-reviewed articles discussing RA and its many facets is utilized. A survey of patients with RA reveals patient attitudes and discretions towards their arduous personal experiences with rheumatoid arthritis. Overall, the findings indicate that having a well-versed interprofessional team of physicians and health professionals supporting patients with rheumatoid arthritis using an integrated model of care, is critical to improved overall well-being and disease outcomes.
KEYWORDS: Rheumatoid Arthritis, Autoimmune, Treatment, Survey

TABLE OF CONTENTS

CHAPTER ONE

Introduction

Rheumatoid Arthritis (RA) is a common chronic inflammatory autoimmune disease affecting over 1.5 million people in the United States, the majority of which are females (Gibofsky, 2012). An immune response characterized by lymphocytes, neutrophils, mast cells, synovial tissue cells, and platelet microparticles play a fundamental role in the inflammatory process within the synovial fluid (Boilard et al., 2010) leading to synovitis, joint deformity, and structural bone damage. This inflammation can cause considerable levels of pain and swelling to the joints with ensuing severe joint dysfunction. One of the most noteworthy symptoms of RA is the presence of severe fatigue – which is far more intense and distinct than general fatigue experienced by those without an RA diagnosis. Factors associated with heightened fatigue levels among RA patients include medical-related issues, along with psychosocial and lifestyle factors. These determinants include reduced social participation, lack of sleep, decreased physical activity that is vital to overall well-being, and a sense of loss of control over the prognosis (Nikolaus et al., 2010).

In addition, the economic burden of RA is extensive. The total medical costs exceed $19 billion annually with many patients spending up to $30,000 a year on medications alone (Freeman, 2018). The cost in medication ranges between 8 to 24% and hospitalization constitutes anywhere between 17 and 88% of the total cost. Also, patients report a median duration of up to 39 missed workdays annually (Burton et al., 2005). Although research has helped formulate a better understanding of the condition, the

underlying pathophysiology is still not fully understood. It is suggested that epigenetic factors can ameliorate the interaction of genetic and environmental factors that contribute to the complexity and lifelong complications of this disease. The severe extra-articular manifestations and economic burden of this disease illustrate that it is imperative to use a holistic approach. Incorporating various aspects of lifestyle modifications can ensure better management of RA and its many manifestations.

CHAPTER TWO

Pathogenesis and Pathophysiology

The pathogenesis and pathophysiology of RA 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 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.

CHAPTER THREE

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, p.124), "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, p.126). These nodules are subcutaneous and occur in roughly 30% of RA patients (Prete et al., 2011, p.126). Because rheumatoid nodules can 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).

CHAPTER FOUR

Articular Manifestations

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.

CHAPTER FIVE

Extra-Articular Manifestations

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 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 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, p. 622). 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).

CHAPTER SIX

Genetic and Environmental Factors

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 inflammatory-based 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).

CHAPTER SEVEN

Pharmacological Therapy

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 (non-steroidal 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, p.162). 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 well-known 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 steroid-based 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 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 anti-inflammatory 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).

CHAPTER EIGHT

Non-pharmacological Therapy

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 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.

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, p. 19). 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.

Physical Activity

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 functioning (Cooney et al., 2011). Physically inactive patients increase their risk of developing cardiovascular disease and/or rheumatoid cachexia. Several research studies provide substantial evidence that 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)

Therapeutic Modalities

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.

Psychosocial Interventions and Significance

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 impacts of symptomatic flare-ups. A few patients in this study reported having "ear-shattering pain" even when no noticeable swelling occurred (Hewlett et al., 2011, p. 71). 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, p. 72). 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 depressive-episodes (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).

CHAPTER NINE

Rationale

The findings of the literature review reveal the broad scope of RA as an autoimmune disease and thus its complications for treatment. The systemic nature of RA makes it a particularly difficult disease to not only diagnose, but to manage over time. Despite advancements in the medical treatment of RA, patients still feel as though their lives are adversely impacted by the disease and have difficulty rationalizing the risks and side effects associated with strong pharmaceutical medications. While many non-pharmacological treatment options are becoming more widely utilized, their efficacy is still not fully understood. Moreover, just because new and emerging treatments are insufficiently supported by empirical-based research, it does not necessarily mean that they will fail in ameliorating patient symptoms or that they will not become standardized in the future. Therefore, a survey was developed to evaluate the experiences and opinions of RA patients who had obtained official RA diagnoses. The survey was designed to gain additional information regarding patient treatment plans and whether or not patients deemed these plans to be effective in managing their RA symptoms or in achieving remission. It also gave insight into how this disease has affected patients emotionally, and whether they feel their symptoms have been adequately managed.

The understanding that many patients will not be diagnosed with RA when they first notice symptoms was taken into consideration, along with knowledge of how genetic and environmental risk factors may exacerbate symptoms and extra-articular manifestations. It was expected that the majority of patients utilize pharmacological

treatments and that many may have changed their treatment plans depending on how long they have lived with the disease. The hope is for patients and professionals to gain an increased awareness of the extensive and systemic nature of this disease beyond inflammation of the distal joints. New research regarding treatment options that go beyond the restrictions of a medical doctor should continue to be acknowledged and researched. A holistic approach is essential to manage and treat such an impactful and life-altering disease.

CHAPTER TEN

Methods

Materials

The survey was created de novo by the author and approved by the Institutional Review Board (IRB) at the University of South Dakota. It was conducted online via Google Forms, an online survey collection tool. The IRB approval can be found in Appendix B. The survey consisted of 15 multiple choice and free response questions. A greater emphasis was placed on free response questions due to the variability in potential answers.

The survey began by asking generalized questions regarding the individual's gender, age, ethnicity, and age at which they were diagnosed with RA. This was designed to obtain an overall understanding of the demographics of the participant and was used to compare to the national demographic RA statistics.

The survey progressed to gain more specific insight into each participant's experience with RA by asking questions regarding the type of RA they were diagnosed with, how their diagnosis made them feel, and what their initial treatment plan entailed. The respondents were asked to answer a free response question regarding whether or not they had changed treatment plans throughout their disease and to provide an explanation as to why they had or had not.

The final questions were created to determine what the participants felt had been the most effective or least effective regarding their treatment plans. These free response questions allowed participants to expand on their answers and provide insight as to how

their diagnosis was affecting them currently. The final question asked the respondents to disclose whether they felt their symptoms were under control. This was used to gain an overall understanding of how participants viewed their disease at this exact point in time, regardless of when they were initially diagnosed or how their treatment plans had changed. The complete survey is included in Appendix D.

Procedure

The survey was distributed to the public via email and social media (i.e. Facebook). Included in the invitation was a short description of the survey's purpose, the target group, and a link to the survey on Google Forms. The survey was designed only for patients who had been diagnosed with rheumatoid arthritis; it is possible that the survey could have been completed by a family member with more advanced computer skills, or by an individual who had not received a proper RA diagnosis.

Individuals who opened the survey link were directed to Google Forms and presented with a complete description of the survey and an informed consent form. All participants were informed that their participation was voluntary and to be completed at their leisure. Acceptance of the informed consent was implied if the respondent clicked "yes" on the opening page to access the survey. No identifying data were collected from participants ensuring that all responses were anonymous.

CHAPTER ELEVEN

Patient Survey Results (n = 28)

Figures 2-4: Participant Demographics
**Question 1 formatted as participant informed consent*

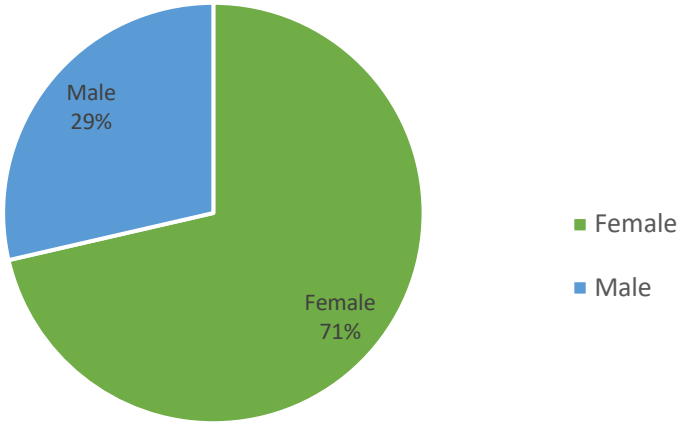

Figure 2. What is your gender?

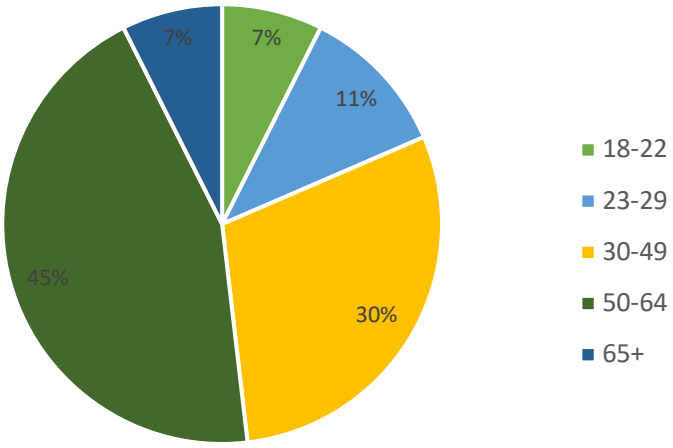

Figure 3. What is your age?

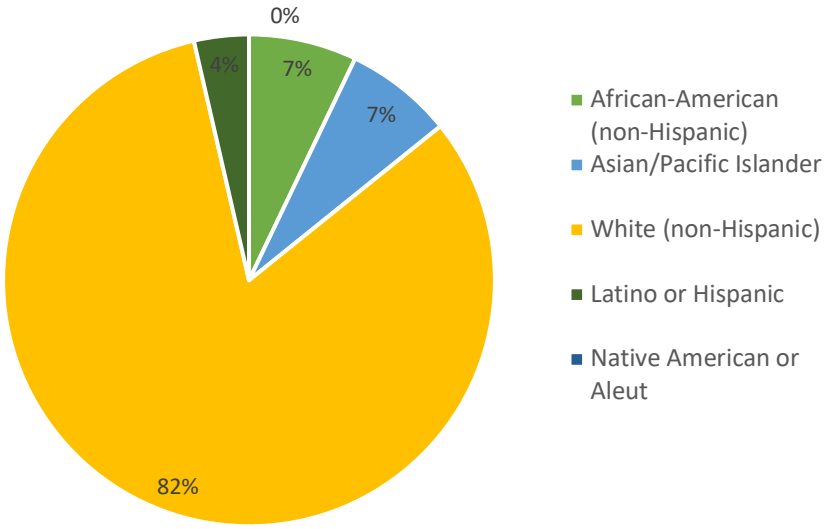

Figure 4. To which racial or ethnic group(s) do you most identify?

Figures and Questions 5-8: Patient Responses to Initial Diagnoses

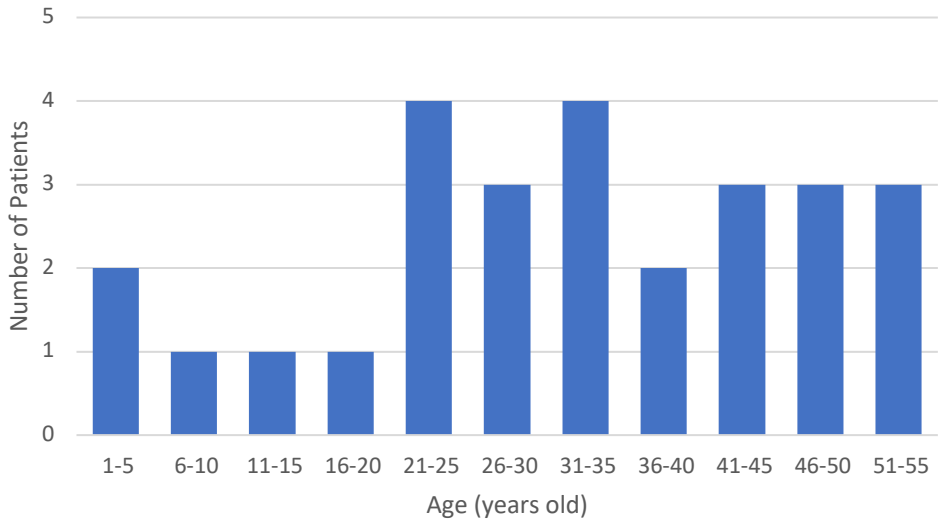

Figure 5. How old were you when you were first diagnosed with Rheumatoid Arthritis?

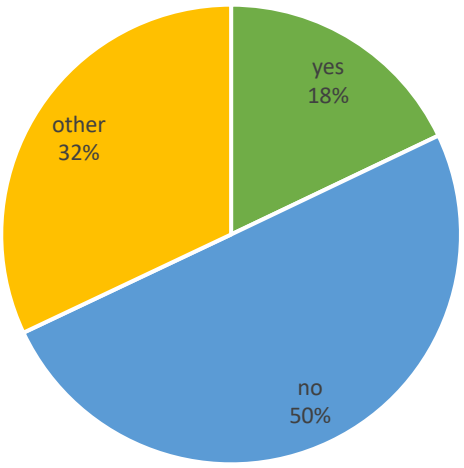

Figure 6. Were you diagnosed immediatley after your symotoms first appeared?

Figure 6. Responses to "other" option

"Other" Responses
I started noticing differences in my daily fatigue levels but thought I was just overworking myself. Once I stepped back from a few responsibilities and the fatigue continued I made an appointment with my doctor
I had been exceptionally sore for a long while
No, I was just diagnosed recently
Shortly after
yes, but took 6 months to get into a Rheumatologist
Soon after, my knees and lower joints really blew up
I wasn't sure what was wrong until the symptoms got really bad
I had been having symptoms for a while, but I didn't realize their severity
I was misdiagnosed

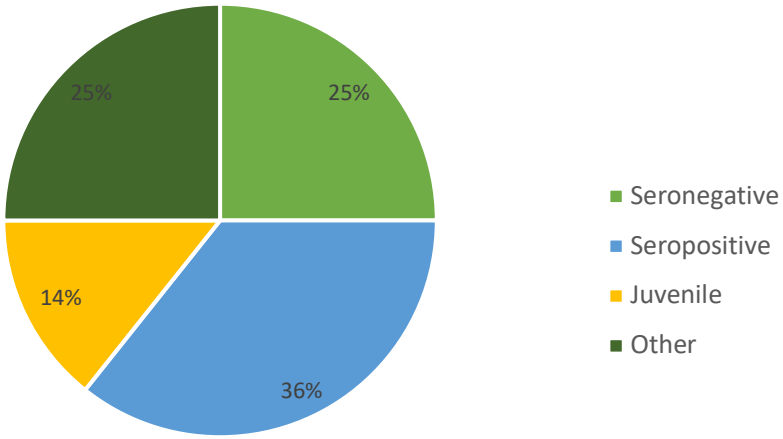

Figure 7. What type of Rheumatoid Arthritis were you diagnosed with?

Figure 7. Responses to "other" option

"Other" Responses
Unknown
I was diagnosed with Lupus
unsure
Tested positive for RF and ACPA
unknown
Dr. never specified
Ankylosing Spondylitis

Question 8 - How did this diagnosis make you feel?

Participant Responses
I didn't really know what to think or how it would affect my life. I had to stop playing many sports which really scared me
Depressed and anxious
sad but relieved
Anxious and worried
At first fearful, once I met my dr I felt better
very sad because I am very active
Relieved to have answers!
Glad to have a diagnosis for my symptoms. But also afraid of the medications to treat RA.
It didn't affect my feelings until I was about 13 years old because it made me quit all my sports.
Scared
Ambiguous
Worried an unsure of how to best deal with it
Very scared, nervous, somewhat relieved to know what was wrong
Anxious, upset, wanting more information
Unsure, worried
Relived I had been fatigued for a very long time prior
Concerned
I didn't think it was Lupus. I had to wait a long time to see a Rheumatologist before I got the proper diagnosis
I didn't know RA was an autoimmune disease. I thought I was getting old WAY too fast
Relieved
Like I was getting older
happy to know what it was, scared for what was to come
Confused
A little anxious, but my doctor helped me to feel better about it
Worried, but glad to know I wasn't going crazy
Concerned, but I knew where my fatigue was coming from
Annoyed as I have always been very active
Confused since my blood tests were not positive

Figures and Questions 9-12: Patient Responses to Initial Treatment Plans

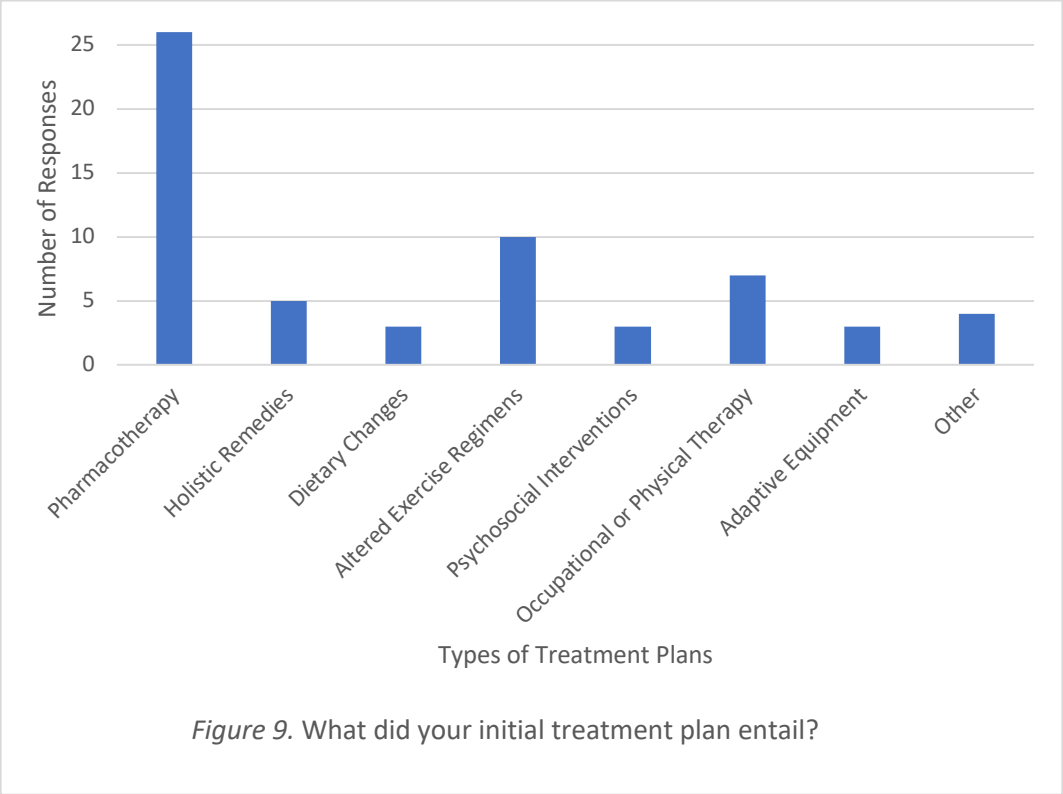

Figure 9. What did your initial treatment plan entail?

Figure 9. Responses to "other" option

"Other" Responses
Methotrexate
Cortisone injection under full sedation in both knees and ankles
18 Ecotrin aspirin a day

Question 10 - Have you changed the course of your treatment during the duration of your diagnosis? Why or why not?

"Other" Responses
Yes, I originally was only taking Aleve to relieve the pain in my joints. The pain got worse around middle school and I was briefly put on steroid medication (which I hated). I have now been taking Meloxicam for years and it seems to work great.
Somewhat. I added attending a support group several months after being and eventually I've added massage and acupuncture
Not really
Started with non-steroidal medicine but I am now taking Humeria one a week
We tried multiple medications till we found the biologic that worked. It took two years to gain control with biologics and medical cannabis
Yes, I have changed drugs several times
Yes. Many times. Sometimes due to something not working effectively and other timed due to allergies

Minimally. I take less methotrexate now since the disease is under control. I also take naproxen for pain control. I take less than the recommended dose.
Yes because I had knees the size of softballs which made me paralyzed for a short time
Yes! So many new meds out today! Thank goodness!
Added an additional drug
I have added in some dietary changes to try to reduce inflammation. I have added some natural ant inflammatory supplements to my routine
Yes, I have tried different drugs and exercise during flare ups. My OT has really focused on helping me with small daily tasks that I am embarrassed to ask for help with like buttons, cutting food etc
yes, as it started to make my joints deteriorate, I had shoulder replacement surgery, have changed my exercise habits and have changed medications
Yes,
Yes
No
Yes; different therapies, different medication
Yes, wasn't seeing any change from the medications
Yes, I began receiving cortisone injections and they have worked quite well
Yes, I've researched many different anti-inflammatory diets and have yet to find one I like
Yes, I've changed medications
I've stuck with the same med for the past few years and they've worked great. I still see my OT but not too often
yes, I began taking methotrexate in my 20s and it has worked quite well. A few side effects but nothing too harsh
Yes, I am deeply involved with the treatment of Rheumatoid Arthritis. I have changed medications many times and have developed my won remedies
Yes, I was taking methotrexate but found it to negatively affect my lungs
yes, I like to keep up-to-date on different DIY treatments along with non-steroidal medications

Question 11 – What have you found to be the most effective in regard to your treatment plan?

Participant Responses
Medication is best for immediate relief when I have a flareup. Finding support groups and others with my diagnosis and talking with therapists to help with depression. Working with professionals to improve my ability to do everyday things so that my boyfriend doesn't have to. Adding exercise to my life
rest
Fish oil supplements
remaining active even though some days you don't feel like it
My rheumatologist and I keep in touch. I just started on Humira and have found it to be beneficial thus far
Biologics
My medications
The addition of Humira actually put me in remission for two years a few years ago. Unfortunately the disease became active again and I am now back on Humira with methotrexate. Also staying physically active is very key to keeping the disease from being active
Methotrexate
Medical cannabis and swimming
Combination of all of the previous methods (meds, massage and acupuncture, exercise helps as well but I haven't been good at maintaining just because of time constraints, not arthritis)
Lifestyle Changes
Naproxen
surgery, medication changes, anti-inflammatory supplements and physical therapy after surgery was absolutely necessary
Taking my medication daily, but also exercise! When I skip a few days of exercise, I am noticeably more stiff and sore
Humeria or Enbrel
Celebrex
Therapy

My Rheumatologist has been incredible. He is well aware of the many other manifestations RA can take in the body
Drugs for pain, exercise for stiffness and better mental health and positivity
Heat!
THC oil
Rituxan was by far the best treatment and the easiest for me to tolerate
methotrexate, changing diet to eliminate high inflammatory foods
Humira
Medication, yoga, and fish oil supplements
Communication with my doctor
Exercise, change in diet
Cortisone injection under full sedation in both knees and ankles
18 Ecotrin aspirin a day

Question 12 – What have you found to be the least effective or most difficult to attain in regard to your treatment plan?

Participant Responses
any major dietary changes
Pain free days
I've heard about changes to diet but I jus haven't been able to force myself to make any concrete changes to my diet quite yet
None
Staying up to date on different at-home remedies. There are too many and they are always changing
nothing
Dietary changes are hard. Very busy professional. Eat out most nights
I am concerned about flareups returning and getting worse
Exercise
excursive regimens that don't hurt my back
Going to therapy - I never have time!
exercising regularly without running
At home remedies - I can't maintain
Consistent morning stretch routine
Getting in to see my doctor
Use of adaptive equipment. I've had several hand braces over the years and they are uncomfortable and a drag to take on and off
some of the drugs I took
At this point, nothing
Non-steroidal medicines
Getting off prednisone
An exercise plan
Changes in diet
Changing my diet has been very hard. I a young and it is hard to afford healthy foods and hard to find the time to prepare them. I am making small changes and adding new ones that I can manage with my boyfriend.
Meloxicam
Good diet
The side effects of the steriods and getting off them
Therapy
Dietary changes only because it is hard to change lifelong habits of eating certain foods

Figures and Questions 13-16: Patient Responses Regarding Current Symptoms and Attitudes

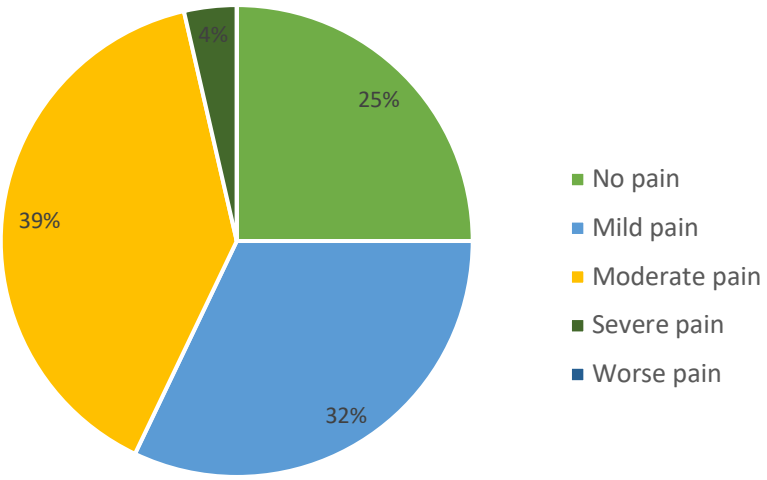

Figure 13. Compared to when you were initially diagnosed, how would you rate your pain today?

Question 14 – Are there any activities you can no longer pursue due to your Rheumatoid Arthritis symptoms?

Participant Responses
running
I can no longer run because it puts a lot pf pressure on my knees. The same thing goes for really any activities that require my body to sort of pound against the ground
Not really, except anything related to strength in my arms or putting weight on my wrists when they are bent at 90 degrees
not really, just tire out faster
I can do just about anything on a good day but I will be sore from it
I was an organist/pianist/accompanist for 25 years in churches. While I may still play the piano for enjoyment, the level I was at is now gone
No. I stay very physically active, and I think this really helps not only my mental status, but my physical status as well
Yes, all sports and bike riding
Running
None
Running or walking long distances, typing on a keyboard, holding items for any length time, lifting heavy things
Many. I also have to take several days off work whenever I have a flare up. The swelling and pain in my hands is the worst because it makes working at a computer almost impossible. My employer is not sympathetic and thinks I over state my diagnosis and pain. Anything using my hands has to stop during flareups. Very frustrating
No heavy pressure on my shoulders. No weight lifting, limited upper body movement with my arms and shoulders
Downhill hiking
No
Running. It takes a long time for my body to warm up to begin exercising
It takes me a while to get up and moving in the am

I do not lift as much weight as I use to
Sewing
My hands don't grasp my outdoor tools like they used to
I've been wary to do many activities. It's been a trial and error process of what causes pain and what does not
grasping pencils or moving quickly in the morning
I don't do too many overhead movements when I work out. My shoulders can't handle much
Just the typical "getting older" activities
I am not as active as I used to be. I no longer play basketball
Hike less

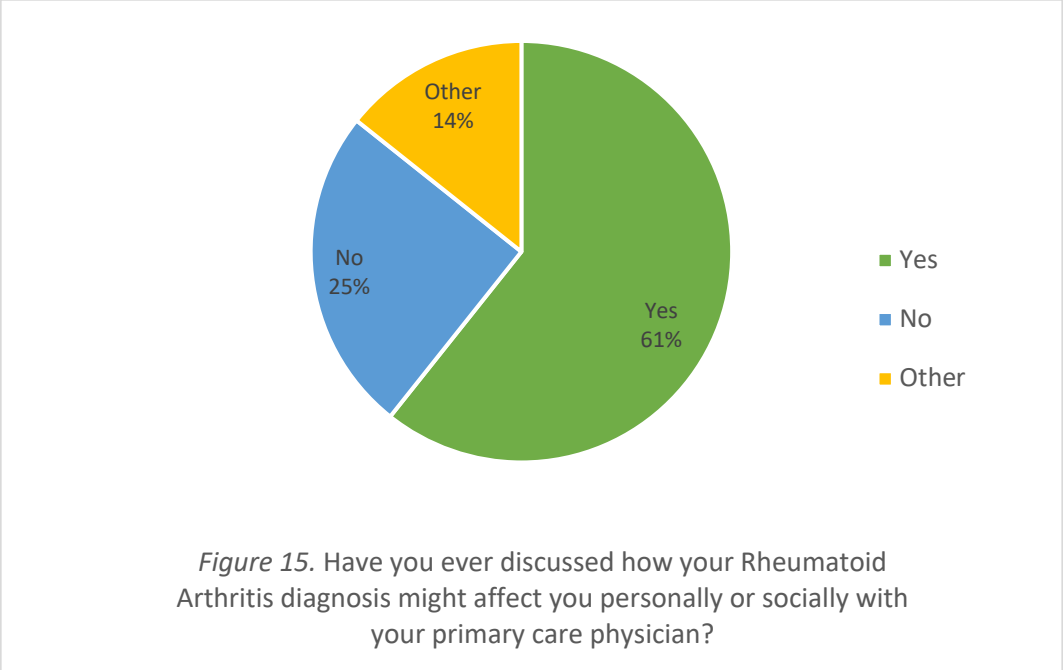

Figure 15. Have you ever discussed how your Rheumatoid Arthritis diagnosis might affect you personally or socially with your primary care physician?

Figure 15. Responses to "other" option

"Other" Responses
Yes, but there weren't many avenues to explore with other people
Briefly, after proper diagnosis by my Rheumatologist
Has little speech to discuss a determination of this possibility
My rheumatologist recommended I join the Arthritis Foundation fb page and I've been able to share my experiences with others and vice versa

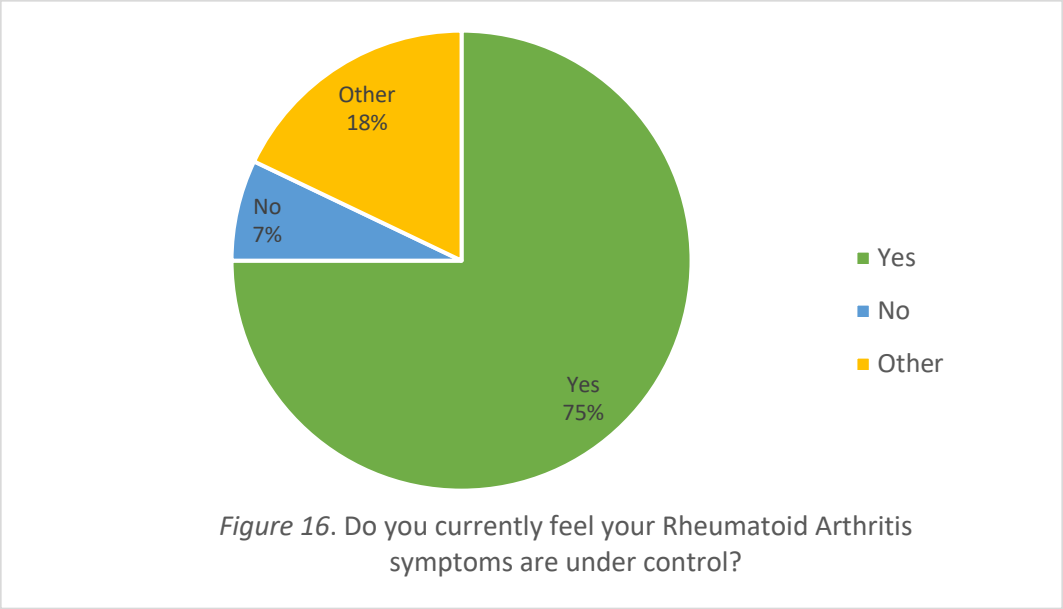

Figure 16. Do you currently feel your Rheumatoid Arthritis symptoms are under control?

Figure 16. Responses to "other" option

"Other" Responses
Will require new shoulders again in ten years. Pain is manageable but the deterioration in the shoulder socket continues
Occasional flare ups from time to time
Yes, the do have flareups every to often but I know how to control them
Somewhat. I feel my symptoms could probably be better managed
Somewhat. I wish I had more pain free days

CHAPTER TWELVE

Discussion

The results and implications of this survey shed light on many of the challenges RA patients face throughout their treatment. From facing unknown or misdiagnoses to feeling overwhelming levels of anxiety, fear, and confusion, there is nothing "easy" about navigating the world of rheumatoid arthritis and its extra-articular manifestations. In total, 28 patients with RA participated in this survey. Many of the free response questions required participants to elaborate on particular survey questions, allowing for a detailed description of their personal experiences. The results of the survey depict the need for additional research and acknowledgment of the extensive effects of this disease. Rheumatoid arthritis' name alone is misleading and confusing to many of those who are diagnosed at young ages. The word "arthritis" generally implies aging and the subsequent deterioration of the bones and joints. While inflammation, fatigue, and destruction of the joints are all major effects of RA, its systemic impact on the body is what makes it notably unique and is what differentiates it from other forms of arthritis. The results of this survey demonstrate the complexity of this disease and its profound impact on each patient as it takes on a chronic state within the body.

The respondent demographics aligned with national RA statistics. The majority of participants were female and 82% identified as White. However, no participants of this study identified as Native American or Aleut (see Figure 2), despite recent research suggesting an increase in RA prevalence amongst Native tribes (Ferucci et al., 2005). The 28 respondents ranged in ages from 18 to over 65 years old, and while varying ages of

initial diagnoses of RA were reported, the age ranges of 21-25 and 31-35 were the most common (see Figure 5). A possible explanation for this is the fact that 45% of participants fell between ages 60-64 and had likely been diagnosed in early to middle-adulthood (see Figure 3).

In regard to the diagnoses of RA, the results of the literature review examined how obtaining a formal diagnosis by a rheumatologist or primary physician can be a long and frustrating process. For instance, for those patients who do not produce blood samples with positive ACPA and RF factors, the diagnosing procedure is based solely upon the clinical phenotypic observance of the distal joints. The literature review also revealed that many other organ involvements, including that of the heart, lungs, and larynx, may be indicative of the presence of RA without any swelling of the distal joints. This information suggests that patients may be suffering from the onset of RA symptoms without visible inflammation of the joints. Participants in this survey were asked to reveal if they had been diagnosed immediately after first noticing their symptoms and the type of RA they were diagnosed with. Alarmingly, 50% of participants answered “no” to being immediately diagnosed, while 32% answered “other” (see Figure 6). Responses within the “other” option included answers ranging from patients being misdiagnosed, not realizing the extent of their symptoms, or not being able to make an appointment with a rheumatologist for 6 months. Likewise, when asked the type of RA they were diagnosed with, 36% of participants reported being diagnosed with seropositive RA, 25% seronegative RA, 14% juvenile RA, and 25% reported “other” (see Figure 7). Similar to the previous “other” responses, participants who elaborated in this section reported answers ranging from not knowing their diagnosis, being misdiagnosed with Lupus, to

their doctor never even specifying to them the type of RA their diagnosis entailed (see Figure 7). This information is distressing considering that similar to many other chronic diseases, treatment intervention of RA is most effective when the disease is detected accurately and early in its progression (Heidari, 2011; Mota et al., 2013). In addition, the fact that at least three participants did not know what type of RA they were diagnosed with is incredibly unsettling. For treatment to be effective, the patient must understand the full context of their diagnosis.

Similarly, the survey results disclosed pertinent information concerning the emotional and psychological toll of RA. When asked how their diagnosis made the participants feel, 23 participants reported feelings of worry, concern, anxiety, and confusion (see Question 8). While few expressed relief in knowing where their pain, fatigue, and symptoms were coming from, the overwhelming majority responded otherwise. From the results of the literature review, it was expected for some of the participants to not understand their diagnosis. When a young and seemingly healthy 30-year-old is told they have "arthritis," it would be surprising if they were not confused. This is precisely why professionals should integrate the education of RA and its differentiation from other forms of arthritis into their practice.

Along with this idea, Figure 15 depicts participant responses to whether or not they had ever discussed how their RA diagnosis might affect them personally or socially with a physician. 61% of participants responded "yes," 25% "no," and 14% responded "other." Among the "other" responses, one participant stated, 'Yes, but there weren't many avenues to explore with other people' (see Figure 15). These results signify that while it is apt that 61% of patients had discussed with their doctors how their diagnosis

might affect them personally or socially, the extent to what actions were taken after this discussion is unknown. Because the prevalence of major depressive disorder is so high amongst RA patients, this conversation between patient and doctor should be routine. This and the availability of more information regarding a patient's diagnosis should be available to mitigate feelings of confusion and worry after the initial diagnosis is made.

Figure 9 and Questions 10-12 demonstrate information related to patient perspectives regarding their treatment plans and how these plans have changed throughout their disease. The results shown in Figure 9 depict that over 25 patients reported pharmacotherapy as being included in their initial treatment plans. This survey question allowed participants to answer more than one treatment plan; participants may likely have chosen a multitude of answers to this particular question. Every treatment option available for this question was utilized; however, dietary changes, psychosocial interventions, and the use of adaptive equipment were each only reported as being included by 3 participants. Four participants answered "other" and each elaborative response within the "other" option included the pharmacotherapy use of methotrexate, cortisone injection, and aspirin (see Figure 9). While these results confirm medicine to be the 'go-to' option for initial RA treatment plans amongst the participants, the widespread utilization of non-pharmacological options gives insight towards where the future of RA treatment may be headed. Even if drug treatment is effective in slowing the progression of disease or in alleviating patient symptoms, a patient's quality of life may still be adversely affected. An overwhelming amount of research highlighted in the literature review revealed the positive effects of a comprehensive and holistic approach to the treatment of RA (Cunningham & Kashikar-Zuck, 2013; Goodacre, 2004; Vlieland, 2007).

Furthermore, when asked how many of the participants had changed the course of their treatment plans since their initial diagnoses, 24 reported that they had changed medications, while others stated that they had experimented with various self-treatments or home remedies (see Question 10). Markedly, participant responses to what they felt had been the most effective element of their treatment plans varied immensely. Among the vast amount of answers claiming medication to be the most efficacious, methotrexate, cortisone injections, and Humira were among the most popular (see Question 11). Humira, while not included in the literature review, is a type of medication called a biologic. Biologics are special forms of DMARDS that are often prescribed when a conventional DMARD is not effective (Biologics, n.d.). Along with this, many responses attested to the benefits of being active and consistent with daily lifestyle routines. Namely, it is noteworthy to consider the vast number of patients who reported a combination of treatments as being the most effective. While not overly popular among participant responses, 2 patients reported the use of medical cannabis and THC oil as being the most effective treatment modality (see Question 11). Because the benefits of medical cannabis and THC oil are not empirically researched to the extent of other medications and treatments, it is not well known how their use will impact RA patients over time. Nevertheless, the first-ever cannabis-based medical trial for the treatment of pain in RA was conducted in 2005; its results are worthy of further research. In a study of 75 patients, the researchers concluded that cannabis-based medicine produced "a significant analgesic effect and disease activity was significantly suppressed" (Blake et al., 2005, p. 51). While information and support concerning the use of cannabis in its

many forms are new and forthcoming, its efficacy in reducing pain amongst RA patients is favorable for larger research.

Among participant responses considering what they felt to be least effective in treating their symptoms, maintaining exercise regimens, dietary changes, and attending therapy were three of the most popular responses. A few respondents reported the use of non-steroidal medications to be ineffective, while one respondent stated the side effects of steroids as being a hindrance to their treatment plan (see Question 12). Because most non-pharmacological approaches entail major changes to the lifestyle, it is understandable why so many of the participants feel these are the least effective or most difficult to attain. Changing one's diet or maintaining an exercise regimen can be incredibly difficult for healthy adults, let alone for those who are suffering from extreme pain, fatigue, and inflammation. While the efficacy of these regimens is well known and supported, their implementation may be easier on paper than in one's actual lifestyle. While this may be the case, the effort put in by the participants of this study to try different treatment approaches should not be overlooked.

To conclude the survey, respondents were asked to compare their pain at the time of the survey compared to when they were first diagnosed. The final survey questions were designed to ask the participants to reflect on their journey's with RA and to reveal any activities they could no longer pursue due to their symptoms. While three respondents revealed that they could still pursue all their activities, the majority of responses revealed that the participants could either no longer do certain activities at all, or at least not to the extent that they were once able to. Activities like running or hiking were popular amongst the responses, likely due to the severe impact of these exercises on

the lower joints. Other activities, such as sewing, which require fine motor movements, were also common responses (see Question14). Interestingly, compared to when the participants were first diagnosed, 25% of participants stated they had "no pain," 32% had "mild pain," 39% had "moderate pain," 4% had "severe pain" and 0% reported "worse pain" (see Figure 13). Because the majority of patients reported to not be experiencing levels of 'severe pain,' it can be inferred that their treatment plans are contributing to the improvement of their symptoms. Similarly, 75% of patients reported "yes" to their RA symptoms currently being under control, while only 7% reported "no" and 18% reported "other" (see Figure 16). Among the "other" responses, a few patients felt that their symptoms were only "somewhat" controlled, while others seemed to be able to manage their pain but were concerned about symptomatic flare-ups.

With the vast number of patients reporting that their RA symptoms are under control, there is something to be said about the efficacy of their treatment plans. Yet, at the same time, this survey highlights the struggles faced by many RA patients when it comes to finalizing a treatment plan, maintaining new regimens, and dealing with the emotional toll that an RA diagnosis can bring. The need for comprehensive and personalized interprofessional teams is integral for the treatment of this complex disease.

Limitations

This survey does present a few key limitations. A sample size of only 28 respondents is not sufficient for this data to be considered significant nor can these findings be generalized to the general population. Survey and response bias may be present considering the primary researcher and conductor of this survey is also a patient

with an RA diagnosis. The survey also failed to depict a correlation between participant responses to allow for a more in-depth analysis of the efficacy of each respondent's treatment plans. Along with this, the wording of Question 6 is unclear and does not define "immediately" in terms of how long it took for the participants to receive an initial diagnosis after first noticing their symptoms (see Figure 6). The variability of answers to this question could be misleading. It should also be noted that a few of the research findings in the literature review are new and forthcoming, thus their reliability is limited. Finally, the validity and reliability of this survey have not been established.

CHAPTER THIRTEEN

Conclusion

The treatment for rheumatoid arthritis is variable and especially complex due to the underlying mechanisms of disease and its manifestations in the non-articular systems of the body. While it was once considered to strictly be a disease affecting the synovial linings of the distal joints, the overtly systemic impact of RA on all major systems of the body is becoming more realized by professionals due to the insights of recent research. While the pathogenesis and pathophysiology of the disease are still not well-understood, the implications for how genetic and environmental risk factors may exacerbate the mechanisms of the disease is central to the current work.

Because RA can show symptoms in the body without the clinical phenotypic observation of swelling in the distal joints, the results of the literature review reveal the urgent need for physicians and rheumatologists to explore non-articular patient symptoms with the insight that these symptoms could indicate the early presence of rheumatoid arthritis. Observance of the early indicators of disease activity present in the larynx, lungs, heart, and vascular systems could be transformative in the detection of RA. With knowledge of how the early detection of this disease can impact a patient's long-term prognosis (Hiedari, 2011; Mota et al., 2013), it is inherent for professionals to recognize the importance of patient symptoms that go beyond pain, fatigue, and joint inflammation.

The optimism demonstrated by the participants of this survey towards the exploration of non-pharmacological treatment options for RA indicates the need for further research regarding the efficacy of these treatment options. While the medical

treatment of RA will surely continue to improve with time, it is in the best interest of all RA patients to understand the full range of available treatment options. Likewise, the results of the literature review and patient survey affirm the struggles many RA patients experience in treating, managing, understanding, and accepting their disease.

The overall findings of this literature review and patient study point towards adopting a holistic, multifaceted, and interprofessional approach towards the treatment and chronic evaluation of rheumatoid arthritis. As an autoimmune disease with many manifestations, RA's elaborate impact within the body can be life-altering and devastating. By increasing awareness of the fundamental and unparalleled components of this disease, there is hope that future research will be directed towards expanding treatment options and improving the experiences and wellbeing of those who are affected and impacted by rheumatoid arthritis.

Appendices

Appendix A
Original IRB Approval

UNIVERSITY OF SOUTH DAKOTA

May 7, 2019

The University of South Dakota
414 E. Clark Street
Vermillion, SD 57069

PI: Jonelle Hook, Jamie Turgeon-Drake , Amy Nelson **Student PI:** Charlie Mechling
Project: 2019.045 - Rheumatoid Arthritis: A Literature Review and Comprehensive Treatment Analysis
Review Level: Exempt 2 **Risk:** No More than Minimal Risk
USD IRB Initial Approval: 5/7/2019
Approved items associated with your project:
Survey (2)
Consent Statement (attached) (2)
Advertisement (2)

The proposal referenced above has received an Exempt review and approval via the procedures of the University of South Dakota Institutional Review Board.

Annual Continuing Review is not required for the above Exempt study. However, when this study is completed you must submit a Closure Form to the IRB. You may close your study when you no longer have contact with the subjects and you are finished collecting data. You may continue to analyze the existing data on your closed project.

Prior to initiation, promptly report to the IRB, any proposed changes or additions (e.g., protocol amendments/revised informed consents/ site changes, etc.) in previously approved human subject research activities.

The forms to assist you in filing your: project closure, continuation, adverse/unanticipated event, project updates /amendments, etc. can be accessed at http://www.usd.edu/research/irb-application-forms

If you have any questions, please contact: humansubjects@usd.edu or (605) 677-6184.

Sincerely,

Ann Waterbury

Ann Waterbury, M.B.A.
Director, Office of Human Subjects
University of South Dakota
(605) 677-6067

Appendix B
Final IRB Amendment

UNIVERSITY OF SOUTH DAKOTA

May 16, 2019

The University of South Dakota
414 E. Clark Street
Vermillion, SD 57069

PI: Jonelle Hook, Jamie Turgeon-Drake , Amy Nelson **Student PI:** Charlie Mechling
Project: 2019.045 - Rheumatoid Arthritis: A Literature Review and Comprehensive Treatment Analysis
Review Level: Exempt 2 **Risk:** No More than Minimal Risk
USD IRB
Amendment Approved: 5/15/2019
Amendment: Survey (2)
Consent Statement (2)

The University of South Dakota Institutional Review Board (IRB) has received and reviewed your amendment. The University of South Dakota IRB has approved the amendment and the information has been added to the file. Thank you for keeping the IRB informed of project changes.

Prior to initiation, promptly report to the IRB, any proposed project updates / amendments (e.g., protocol amendments/revised informed consents) in previously approved human subject research activities.

Any research-related injuries (physical or psychological), adverse side effects or other unexpected problems encountered during the conduct of this research study needs to be reported to the IRB within 5 days of notification of the occurrence.

The forms to assist you in filing your: project closure, continuation, adverse/unanticipated event, project updates /amendments, etc. can be accessed at http://www.usd.edu/research/research-and-sponsored-programs/irb-application-forms-and-templates.cfm.

If you have any questions, please contact: humansubjects@usd.edu or (605) 677-6184.

Sincerely,

Ann Waterbury

Ann Waterbury, M.B.A.
Director, Office of Human Subjects
University of South Dakota
(605) 677-6067

Appendix C
Student Survey Informed Consent Statement

IRB Approval effective from: 5/15/2019
USD IRB

UNIVERSITY OF SOUTH DAKOTA
Institutional Review Board

Informed Consent Statement

Title of Project:	Rheumatoid Arthritis: A Literature Review and Comprehensive Treatment Analysis
Principle Investigators:	Jonelle Hook, 313 Beacom Hall, Vermillion, SD 57069 (605) 658-5953 Jonelle.Hook@usd.edu Jamie Turgeon-Drake, 321 Beacom Hall, Vermillion, SD 57069 (605) 658-5955 Jamie.Turgeon-Drake@usd.edu
Other Investigators:	Charlie Mechling, 120 Old Main, Vermillion, SD 57069

Purpose of the Study:
This research will highlight treatment options and the effectiveness of these options in treating Rheumatoid Arthritis. The survey portion of the study will evaluate the treatment experiences of patients who have been diagnosed with Rheumatoid Arthritis and the impact of these treatments on their personal medical journeys.

Procedures to be followed:
You will be asked to answer 15 questions on a survey. The questions are in two formats: multiple choice and free response, with a greater emphasis on free response questions. Multiple choice questions will provide a number of choices and you will need to select the best answer, a combination of answers, or indicate an option that was not included. Finally, the free response questions will consist of a prompt with space to record your answer.

Risks:
Some of the questions are personal and might cause discomfort. If you would like to talk to someone about your feelings regarding this study, you are encouraged to contact a national counseling hotline, or the University of South Dakota's Student Counseling Center at (605) 677-5777, which provides counseling services to USD students at no charge.

Benefits:
You may not benefit personally from participating in this research project, however:
- You may learn more about yourself by participating in this study.
- You may realize that others have had similar experiences as you.
- The information collected may help to inform others about the future of Rheumatoid Arthritis treatment.

Duration:
It will take approximately 15-30 minutes to complete the questions.

Statement of Confidentiality:
The statement does not ask for any information that would identify who responses belong to. Therefore, your responses are recorded anonymously. If this research is published, no information that would identify you will be included since your name is in no way linked to your responses.

All survey responses received will be treated confidentially and stored on a secure server. However, given that the surveys can be completed from any computer (e.g. personal, work, school), we are unable to guarantee the security of the computer on which you choose to enter your responses. As a participant in our study, we want you to be aware that certain "key logging" software programs exist that can be used to track or capture data that you enter and/or websites that you visit.

Right to Ask Questions:
The researchers conducting this study are Jonelle Hook, Jamie Turgeon-Drake, and Charlie Mechling. You may ask any questions you have now. If you later have questions, concerns, or complaints about the research please contact Jonelle Hook at (605) 658-5953 during the day.

If you have questions regarding your rights as a research subject, you may contact The University of South Dakota-Office of Human Subjects Protection at (605) 677-6184. You may also call this number with problems, complaints, or concerns about the research. Please call this number if you cannot reach research staff, or you wish to talk with someone who is an informed individual who is independent of the research team.

Compensation:
You will not receive compensation for your participation.

Voluntary Participation:
You do not have to participate in this research. You can stop your participation at any time. You may refuse to participate or choose to discontinue participation at any time without losing any benefits to which you are otherwise entitled.

You do not have to answer any questions you do not want to answer.

For this study, you must be 18 years of age or older to consent to participate in this research study.

Completion and return of the survey implies that you have read the information in this form and consent to participate in the research.

Please keep this form for your records or future reference.

Appendix D
Patient Survey

Rheumatoid Arthritis Journey – A Patient Survey

Introduction: This research will highlight treatment options and the effectiveness of these options in treating Rheumatoid Arthritis. The survey will evaluate the treatment experiences of patients who have been diagnosed with Rheumatoid Arthritis and the impact of these treatments on their personal medical journeys. To maintain anonymity, please refrain from using names or any other identifying information in the free response questions.

1. I have read and understand the previous information regarding my rights as a research participant.
    a. Yes
    b. No

Patient Demographics

2. What is your gender?
    a. Male
    b. Female
    c. Other
3. What is your age?
    a. 18-22 years old
    b. 23-29 years old
    c. 30-49 years old
    d. 50-64 years old
    e. 65 years and older
4. To which racial or ethnic group(s) do you most identify?
    a. African-American (non-Hispanic)
    b. Asian/Pacific Islander
    c. White (non-Hispanic)
    d. Latino or Hispanic
    e. Native American or Aleut
    f. Other (please specify)

Patient Responses to Initial Diagnoses

5. How old were you when you were first diagnosed with Rheumatoid Arthritis?
    a. Entry
6. Were you diagnosed immediately after your symptoms first appeared?
    a. Yes
    b. No
    c. Other (please explain)
7. What type of Rheumatoid Arthritis were you diagnosed with?
    a. Seropositive
    b. Seronegative
    c. Juvenile
    d. Other (please explain)

8. How did this diagnosis make you feel?
    a. Entry

Patient Responses to Initial Treatment Plans

9. What did your initial treatment plan entail? Check all that apply
    a. Pharmacotherapy
    b. Holistic remedies
    c. Dietary changes
    d. Altered exercise regimes
    e. Psychosocial interventions
    f. Occupational or physical therapy
    g. Adaptive equipment
    h. Other (please explain)
10. Have you changed the course of your treatment during the duration of your diagnosis? Why or why not?
    a. Entry
11. What have you found to be the most effective in regard to your treatment plan?
    a. Entry
12. What have you found to be the least effective or most difficult to attain in regard to your treatment plan?
    a. Entry

Patient Responses Regarding Current Symptoms and Attitudes

13. What have you found to be the least effective or most difficult to attain in regard to your treatment plan?
    a. No pain
    b. Mild pain
    c. Moderate pain
    d. Severe pain
    e. Worse pain
14. Are there any activities you can no longer pursue due to you Rheumatoid Arthritis symptoms?
    a. Entry
15. Have you ever discussed how your Rheumatoid Arthritis diagnosis might affect you personally or socially with your primary care physician?
    a. Yes
    b. No
    c. Other (please explain)
16. Do you currently feel your Rheumatoid Arthritis symptoms are under control?
    a. Yes
    b. No
    c. Other (please explain)

References

Badsha, H. (2018). Role of diet in influencing rheumatoid arthritis disease activity. *The Open Rheumatology Journal,12*(1), 19-28. doi: 10.2174/1874312901812010019

Biologics (n.d). Arthritis Foundation. https://www.arthritis.org/drug-guide/biologics/biologics

Blake, D. R., Robson, P., Ho, M., Jubb, R. W., & Mccabe, C. S. (2005). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*, *45*(1), 50–52. doi: 10.1093/rheumatology/kei183

Boilard, E., Nigrovic, P. A., Larabee, K., Watts, G. F., Coblyn, J. S., Weinblatt, M. E., ... & Lee, D. M. (2010). Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. *Science*, *327*(5965), 580-583.

Brennan, F. M., & Mcinnes, I. B. (2008). Evidence that cytokines play a role in rheumatoid arthritis. *Journal of Clinical Investigation*, *118*(11), 3537–3545. doi: 10.1172/jci36389

Burton, W., Morrison, A., Maclean, R., & Ruderman, E. (2005). Systematic review of studies of productivity loss due to rheumatoid arthritis. *Occupational Medicine*, *56*(1), 18–27. doi: 10.1093/occmed/kqi171

Cojocaru, M., Cojocaru, I. M., Silosi, I., Vrabie, C. D., & Tanasescu, R. (2010). Extra-articular manifestations in rheumatoid arthritis. *Maedica*, *5*(4), 286–291.

Cooney, J. K., Law, R., Matschke, V., Lemmey, A. B., Moore, J. P., Ahmad, Y., . . . Thom, J. M. (2011). Benefits of exercise in rheumatoid arthritis. *Journal of Aging Research,* 1-14. doi: 10.4061/2011/681640

Crowson, C. S., Liao, K. P., Davis, J. M., 3rd, Solomon, D. H., Matteson, E. L., Knutson, K. L., Hlatky, M. A., & Gabriel, S. E. (2013). Rheumatoid arthritis and cardiovascular disease. *American HeartJjournal, 166*(4), 622–628. doi: 10.1016/j.ahj.2013.07.010

Cunningham, N. R., & Kashikar-Zuck, S. (2013). Nonpharmacological treatment of pain in rheumatic diseases and other musculoskeletal pain conditions. *Current rheumatology reports*, *15*(2), 306. https://doi.org/10.1007/s11926-012-0306-y

De Almeida, P. H., Pontes, T. B., Matheus, J. P., Muniz, L. F., & Da Mota, L. M. (2015). Occupational therapy in rheumatoid arthritis: What rheumatologists need to know? *Revista Brasileira De Reumatologia, 55*(3), 272-280. doi: 10.1016/j.rbr.2014.07.008

Deane, K. D., Demoruelle, M. K., Kelmenson, L. B., Kuhn, K. A., Norris, J. M., & Holers, V. M. (2017). Genetic and environmental risk factors for rheumatoid arthritis. *Best Practice & Research. Clinical Rheumatology, 31*(1), 3–18. doi: 10.1016/j.berh.2017.08.003

Demoruelle, M. K., & Deane, K. (2011). Antibodies to citrullinated protein antigens (ACPAs): Clinical and pathophysiologic significance. *Current Rheumatology Reports*, *13*(5), 421–430. doi: 10.1007/s11926-011-0193-7

Derksen, V. F. A. M., Huizinga, T. W. J., & van der Woude, D. (2017). The role of autoantibodies in the pathophysiology of rheumatoid arthritis. *Semin Immunopathol*, *39*(4), 437–446. doi:10.1007/s00281-017-0627-z

DMARDS. (n.d.). Arthritis Foundation. https://arthritis.org/drug-guide/dmards/dmards

Elkon, K., & Casali, P. (2008). Nature and functions of autoantibodies. *Nature Clinical Practice Rheumatology*, *4*(9), 491–498. doi: 10.1038/ncprheum0895

Ferucci, E. D., Templin, D. W., & Lanier, A. P. (2005). Rheumatoid arthritis in American Indians and Alaska natives: A review of the literature. *Seminars in Arthritis and Rheumatism, 34*(4), 662–667. doi: 10.1016/j.semarthrit.2004.08.003

Freeman, J. (2018, October 27). *RA medications: Which NSAID and analgesic is best for RA?* Rheumatoid Arthritis Support Network https://www.rheumatoidarthritis.org/treatment/medications/nsaids/

Freeman, J. (2018, October 27). *RA treatment costs: What are the costs of RA medications and surgery?* Rheumatoid Arthritis Support Network https://www.rheumatoidarthritis.org/treatment/costs/

Gauhar, U. A., Gaffo, A. L., & Alarcón, G. S. (2007). Pulmonary manifestations of rheumatoid arthritis. *Seminars in Respiratory and Critical Care Medicine*, *28*(4), 430–440. doi: 10.1055/s-2007-985664

Gibofsky, A. (2012). Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *The American journal of managed care*, *18*(13 Suppl), S295-302.

Goodacre, L. J. (2004). Factors influencing the beliefs of patients with rheumatoid arthritis regarding disease modifying medication: Reply. *Rheumatology*, *43*(12), 583–586. doi: 10.1093/rheumatology/keh396

Hafström, I., Ringertz, B., Gyllenhammar, H., Palmblad, J., & Harms-Ringdahl, M. (1988). Effects of fasting on disease activity, neutrophil function, fatty acid composition, and leukotriene biosynthesis in patients with rheumatoid arthritis. *Arthritis & Rheumatism: Official Journal of the American College of Rheumatology*, *31*(5), 585-592.

Hamdan, A. L., & Sarieddine, D. (2013). Laryngeal manifestations of rheumatoid arthritis. *Autoimmune Diseases*, *2013*, 1–6. doi: 10.1155/2013/103081

Heidari, B. (2011). Rheumatoid arthritis: early diagnosis and treatment outcomes. *Caspian Journal of Internal Medicine*, *2*(1), 161–170.

Hewlett, S., Sanderson, T., May, J., Alten, R., Bingham, C. O., Cross, M., … Bartlett, S. J. (2011). I'm hurting, I want to kill myself: rheumatoid arthritis flare is more than a high joint count--an international patient perspective on flare where medical help is sought. *Rheumatology*, *51*(1), 69–76. doi: 10.1093/rheumatology/keq455

Kavuncu, V., & Evcik, D. (2004). Physiotherapy in rheumatoid arthritis. *MedGenMed: Medscape General Medicine, 6*(2), 3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1395797/.

Knittle, K., Maes, S., & Gucht, V. D. (2010). Psychological interventions for rheumatoid arthritis: Examining the role of self-regulation with a systematic review and meta-analysis of randomized controlled trials. *Arthritis Care & Research, 62*(10), 1460-1472. doi: 10.1002/acr.20251

Koulil, S. S. V., Ferwerda, M., Van Beugen, S., Van Middendorp, H., Van de Kerkhof, P., Van Riel, P. L., & Evers, A. W. (2018). Tailored therapist-guided internet-based cognitive-behavioral treatment for psoriasis and rheumatoid arthritis: Two case reports. *Acta dermato-venereologica*, *98*(1-2), 225-233.

Margaretten, M., Julian, L., Katz, P., & Yelin, E. (2011). Depression in patients with rheumatoid arthritis: description, causes and mechanisms. *International Journal of Clinical Rheumatology*, *6*(6), 617–623. doi: 10.2217/ijr.11.62

McInnes, I. B., & Schett, G. B. (2011). The pathogenesis of rheumatoid arthritis. *The New England Journal of Medicine*, *365*(23), 2205–2219. doi: 10.1056/NEJMra1004965

Metsios, G. S., Stavropoulos-Kalinoglou, A., Veldhuijzen van Zanten, J. J. C. S., Treharne, G. J., Panoulas, V. F., Douglas, K. M., ... & Kitas, G. D. (2007). Rheumatoid arthritis, cardiovascular disease and physical exercise: a systematic review. *Rheumatology*, *47*(3), 239-24

Moreland, L. W., & Curtis, J. R. (2009). Systemic nonarticular manifestations of rheumatoid arthritis: focus on inflammatory mechanisms. *Seminars in Arthritis and Rheumatism*, *39*(2), 132–143. doi: 10.1016/j.semarthrit.2008.08.003

Mota, L. M. H. da, Cruz, B. A., Brenol, C. V., Pereira, I. A., Rezende-Fronza, L. S., Bertolo, M. B., … Pinheiro, G. da R. C. (2013). Guidelines for the drug treatment of rheumatoid arthritis. *Revista Brasileira De Reumatologia*, *53*(2), 158–183. doi: 10.1590/s0482-50042013000200003

Nair, P. M., & Khawale, P. G. (2016). Role of therapeutic fasting in women's health: An overview. *Journal of mid-life health*, *7*(2), 61

Nikolaus, S., Bode, C., Taal, E., & M. A. F. J. Van De Laar. (2010). New insights into the experience of fatigue among patients with rheumatoid arthritis: a qualitative study. *Annals of the Rheumatic Diseases, 69*(5), 895–897. doi: 10.1136/ard.2009.118067

Nordberg, L. B., Lillegraven, S., Lie, E., Aga, A.-B., Olsen, I. C., Hammer, H. B., … Haavardsholm, E. A. (2016). Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria. *Annals of the Rheumatic Diseases*, *76*(2), 341–345. doi: 10.1136/annrheumdis-2015-208873

Prednisone. (n.d). Arthritis Society. https://arthritis.ca/treatment/medication/medication-reference-guide/medications/prednisone

Prete, M., Racanelli, V., Digiglio, L., Vacca, A., Dammacco, F., & Perosa, F. (2011). Extra-articular manifestations of rheumatoid arthritis: An update. *Autoimmunity Reviews*, *11*(2), 123–131. doi: 10.1016/j.autrev.2011.09.001

Rheumatoid arthritis. (2019, March 1). Mayo Clinic. Retrieved February 29, 2020, from https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes/syc-20353648

Salliot, C., & Heijde, D. V. D. (2008). Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: systematic literature research. *Annals of the Rheumatic Diseases*, *68*(7), 1100–1104. doi: 10.1136/ard.2008.093690

Salmon, V. E., Hewlett, S., Walsh, N., Kirwan, J. R., Urban, M., Morris, M., & Cramp, F. (2015). 152. Development of a physical activity intervention for rheumatoid arthritis fatigue: Allied health professionals' views. *Rheumatology, 54*(1), I109. https://doi-org.ezproxy.usd.edu/10.1093/rheumatology/kev089.039.

Santo, R. C., Fernandes, K. Z., Lora, P. S., Filippin, L. I., & Xavier, R. M. (2018). Prevalence of rheumatoid cachexia in rheumatoid arthritis: A systematic review and meta-analysis. *Journal of Cachexia, Sarcopenia and Muscle*, *9*(5), 816–825. doi: 10.1002/jcsm.12320

Sharpe, L. (2016). Psychosocial management of chronic pain in patients with rheumatoid arthritis: Challenges and solutions. *Journal of Pain Research, 9*, 137-146. doi: 10.2147/jpr.s83653

Skoczyńska, M., & Świerkot, J. (2018). The role of diet in rheumatoid arthritis. *Reumatologia, 56*(4), 259-267. doi:10.5114/reum.2018.77979

Sköldstam, L., Larsson, L., & Lindström, F. D. (1979). Effects of fasting and lactovegetarian diet on rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, *8*(4), 249-255.

Suurmond, J., & Diamond, B. (2015). Autoantibodies in systemic autoimmune diseases: specificity and pathogenicity. *Journal of Clinical Investigation*, *125*(6), 2194–2202. doi: 10.1172/jci78084

Szekanecz, Z., & Koch, A. E. (2008). Vascular involvement in rheumatic diseases: vascular rheumatology. *Arthritis Research & Therapy*, *10*(5), 224. doi: 10.1186/ar2515

Vlieland, T. P. M. V. (2007). Non-drug care for RA is the era of evidence-based practice approaching? *Rheumatology*, *46*(9), 1397–1404. doi: 10.1093/rheumatology/kem149

Weissman, S., Alsheikh, M., Kamar, K., Breslin, J., Khabut, A., & Maruf, M. G. (2018). Non-insidious large joint manifestation of severe cachectic rheumatoid arthritis. *Cureus*, *10*(9). doi: 10.7759/cureus.3266

Withall, J., Haase, A. M., Walsh, N. E., Young, A., & Cramp, F. (2016). Physical activity engagement in early rheumatoid arthritis: A qualitative study to inform intervention development. *Physiotherapy*, *102*(3), 264-271

Young, K. O. N. (2017). *Rheumatoid arthritis unmasked: 10 dangers of rheumatoid disease*. RA Patient Insights, LLC.

Zhang, J.-M., & An, J. (2007). Cytokines, inflammation, and pain. *International Anesthesiology Clinics*, *45*(2), 27–37. doi: 10.1097/aia.0b013e318034194e