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The Correlation between Rheumatoid Arthritis and Periodontal Disease

Cayla Skinner

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By: Cayla A. Skinner

Abstract

Individuals with chronic conditions face challenges that can negatively impact their health in a variety of ways. One such example is the correlation between rheumatoid arthritis and the development of periodontal disease. Studies have suggested several possible biological mechanisms by which autoimmune conditions like arthritis and immune-inflammatory conditions like periodontal disease can interact. In this study we plan to look at possible linkage between a clinical condition, rheumatoid arthritis, and its possible subsequent relationship in creating the conditions for the development of periodontal disease due to its hindering the ability of an affected person to perform daily healthcare routines. Our methodology is to present a survey to individuals with or without rheumatoid arthritis and periodontal disease to ascertain the level of hindrance that their conditions have on their ability to perform day-to-day tasks. In doing so, I hope to identify the socio-economic factors that affect patients with rheumatoid arthritis and the development of periodontal disease.

Introduction

When we think about taking care of our bodies and managing our health, we typically think about diet and exercise but we often forget about our oral health. In fact, our oral health can be the underlying reason for some major health issues in a patient if it is left untreated. There are a number of health risks and diseases related to oral health that can cause a wide variety of other conditions, i.e., heart disease, cancer, or diabetes [4,7]. This proposed study aims to bring awareness to the importance of oral health and how other health conditions can play a role in adversely affecting one's oral health.

There are numerous health conditions that may directly affect the oral cavity, with periodontal disease being the most common in a large number of patients. Periodontal disease, also known as gum disease, is an inflammatory disease, which attacks the tissue surrounding the tooth that holds the tooth in place. If left untreated, this can damage not only the gums and jaw, but can also lead to tooth decay and subsequent tooth loss while leading to an increased risk of other severe diseases. Individuals that live with a chronic condition or illness often face challenges that can hinder everyday activities such as maintaining their health. This can lead to a lack of independence and a negative effect on an individual's quality of life. Individuals with a permanent disability may find it difficult to take care of their overall health such as oral hygiene. Rheumatoid arthritis is a common example of a chronic autoimmune disease that can have secondary lasting effects and of recently, periodontal disease has been linked to Rheumatoid Arthritis [19].

Rheumatoid Arthritis (RA) is an inflammatory disease that causes swelling and pain of the joints in a patient [7]. Individuals who suffer from rheumatoid arthritis are primarily unable to practice proper oral hygiene due to the stiffness found associated with the condition within the jaw and hand joints. Rheumatoid Arthritis affects the size of the jaw joint known as the Temporomandibular joint (TMJ). TMJs are found in front of each ear that connects the jawbone and skull [21]. Symptoms consist of: aching, difficulty eating and chewing, clicking, and dislocation [20]. This can make it extremely difficult to open and close the mouth as well as manipulate the hand joints in such a way to facilitate proper oral care [21]. If oral care is untreated, periodontal disease will most assuredly occur thereby increasing the risk of infections such as endocarditis, which occurs when bacteria, fungi, and germs from the mouth spread throughout the bloodstream to the heart.

Interactions between rheumatoid arthritis and inflammatory diseases have been seen previously in patients diagnosed with Sjögren's syndrome [2]. Evidence suggests that the process of citrullination and the bacterial species, *Porphynomonas gingivalis* share similar inflammatory pathways and environmental mechanisms such as smoking, which is a risk factor for periodontal disease and an environmental risk factor for the development of rheumatoid arthritis. The linkage between rheumatoid arthritis and periodontal disease is proposed to be common. The putative correlation has been discussed as early as the 1900s. In 2017, Dr. Felipe Andrade M.D., Ph.D from the Johns Hopkins University Division of Rheumatology provided new evidence demonstrating that a bacterium could be the potential mediator [9,19]. This bacterium *(Porphynomonas gingivalis)* induces chronic inflammatory conditions such as periodontitis and thereby trigger an inflammatory autoimmune response located within the joints of patients with rheumatoid arthritis.

With this information, this study will investigate the relationship between rheumatoid arthritis and the development of periodontal disease, and socio-economic factors that contribute to this relationship. This study will obtain current data from rheumatoid arthritis patients via an anonymous survey in addition to obtaining historical data through dental records in compliance with IRB standards and the use of human subjects.

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is an autoimmune and inflammatory disease that attacks the body's tissue within the joints [7]. This causes the body's immune system to mistake its tissues as foreign invaders causing stiffness, swelling, and pain to the lining of the joints. Not only does rheumatoid arthritis target the joints, it can affect other organs and tissues such as the eyes, lungs, skin, blood vessels, nerve tissue, bone marrow, heart, ligaments, the muscles, and cartilage [4,7].

With or without treatment, rheumatoid arthritis can be a severe condition causing physical disabilities. It affects more than 1.3 million Americans [4,22].

About 75% of RA patients are women. In fact, 1-3% of women may get rheumatoid arthritis in their lifetime [4]. The lifetime risk of developing rheumatoid arthritis is 3.6% for women and 1.7% for men [10]. Rheumatoid Arthritis can affect patients at any age. Usually, men and women are diagnosed between the ages of 30 and 60 [23].

The signs and symptoms that can occur include: a loss of energy and appetite, fevers, dry eyes and mouth (Sjogren's Syndrome), warm tender and swollen joints, weakness, stiffness in the mornings or activity overtime, the joints can deform and shift out of place if left untreated [7]. The characteristics of rheumatoid arthritis can consist of hyperplasia of the synovial membrane lining due to a large number of inflammatory cells, i.e., T and B lymphocytes, macrophages, neutrophils, and dendritic cells [11,13]. These cells are carried into the synovium and joint cavity resulting in a production of cytokines and proteases. Inflammatory cytokines such as TNF-α, IL-1β, IL-6, IL-17, the granulocyte macrophage colony stimulating factor (GM-CSF), and RANKL is central to the pathogenesis of rheumatoid arthritis [11,13].

Tumor Necrosis Factor Alpha (TNF-α) is a major pro-inflammatory cytokine involved in early inflammatory [11,13,17]. Whereas, Interleukin (IL-1β) is a proinflammatory cytokine that responds to infection and injury [11,13,14]. Interleukin-6 (IL-6) is a pleiotropic cytokine that responds to tissue damage and infections [11,13,15]. Interleukin-17 (IL-17) mediates protective immunity to pathogens of inflammatory diseases, such as psoriasis and rheumatoid arthritis [13,16]. The cytokines cause joint destruction by restoring synovial fibroblasts and chondrocytes to release degrading enzymes like matrix metalloproteinases and MMP as well as activating the distinction of osteoclast leading to the cartilage and bone destruction [13].

Medical professionals and researchers believe that there are high risk factors that can increase the degree of mobility at the joints. These factors consist of sex and age, heredity, smoking, environment exposures, and obesity [12]. Rheumatoid Arthritis is diagnosed by a rheumatologist, in which a blood test and an X-ray or MRI/ ultrasound image are needed in order to examine the patient. A rheumatologist uses a blood test to check for antibodies, abnormal blood, high levels of inflammation in the blood.

X-rays help detect rheumatoid arthritis and an MRI and ultrasound scanning can help confirm and conclude the severity of the diagnosis. There is no cure for rheumatoid arthritis but treatments such as medications, surgery, and therapy is recommended for rheumatoid arthritis patients. Depending on the severity of the symptoms, RA patients are provided 1.) (NSAID) Nonsteroidal anti-inflammatory drugs, which can relieve pain and decrease inflammation steroids, which reduces inflammation and pain as well as slowing joint damage. 2.) (DMARDS) Disease-modifying antirheumatic drugs, which can slow the progression of rheumatoid arthritis and save joints as well as tissues. 3.) Biologic agents (Biologic DMARDS), which helps improve the immune systems that are having trouble responding to the DMARDS [13,21].

Patients who are diagnosed will find it difficult to work, which can lead to unemployment and worse socio-economic conditions [22]. A patient may pay an estimated $30,000.00 annually for treatments [24] and between $15,000.00 - $20,000.00 for medications [10,24]. Home remedies such as a change in diet, light exercise (aerobics) and rest can help improve joint pressure and overall health.

Periodontal Disease

Periodontal disease, also known as Periodontitis or gum disease, is a common and preventable condition that can arise due to poor oral health [8]. Periodontal disease is an

immuno-inflammatory disease that consists of a serious infection and inflammation of the gums that causes destruction to the surrounding tissue that holds the tooth in place. If left untreated, it can destroy the bone, which can lead to tooth loss and other chronic diseases. Periodontal disease is a common and preventable condition by proper oral hygiene. Gingivitis is the first stage of periodontal disease. During the early stage of gingivitis, plaque starts to form and build up causing red, swollen, and bleeding gums [1,25].

There is prevalent irritation but no sign of tissue or bone damage. If untreated, gingivitis can lead to periodontal disease. During this stage of the periodontal disease, the inner layer of the gum and bone pulls away from the teeth creating pockets, which will gather waste causing an infection. As the body's immune system attacks the bacteria, the plaque grows and spreads under the gum line. Toxins are released from the plaque, which triggers a chronic inflammatory response [1].

The body reacts to the response and begins to attack the gum tissue by breaking down and destroying the bone and surrounding tissue that hold the teeth in place. The gums began to separate from the teeth as the pockets deepen due to infection and more gum tissue is completely destroyed. The teeth lose their support and start to loosen resulting in tooth loss [1]. Dentists may suggest removal of the tooth but most times the tooth will begin to fall out on its own. There are different types of periodontist. Patients can experience aggressive periodontitis, chronic periodontists, periodontitis as a manifestation of systemic diseases or necrotizing periodontal disease.

Periodontal disease can go unnoticed but it is helpful to pay attention to the signs and symptoms, which consist of swollen or puffy gums, pain when brushing or flossing, gums that bleed easily, bad breath, pus between the teeth and gums, loose or separating teeth, new spaces

between teeth, a change in the way your teeth fit together when you bite, receding gums, and shifting teeth [1]. Bacteria and inflammation can be responsible for linking periodontal disease to other diseases. Periodontal disease is linked to other systemic diseases such as osteoporosis, respiratory disease, and cancer [1]. Researchers found that men with gum disease were 49% more likely to develop kidney cancer, 54% more likely to develop pancreatic cancer and 30% more likely to develop blood cancers [1]. Women can develop periodontal disease through puberty, menstruation, pregnancy, and menopause or post menopause. Men are 56.4% more likely to develop periodontal disease than women 38.4% [1]. Men develop periodontal disease due to prostate health, heart disease, impotence, cancer and less visits to the dentist [1,25].

It is important for men to acknowledge oral health because it can impact health factors in a negative way. Periodontal disease can affect adolescents as well. Poor dental hygiene habits, junk food, and puberty can cause periodontal disease in adolescents but parents can help install good hygiene habits in adolescents at an earlier age, which will help prevent periodontal disease in the future. Patients with signs and symptoms of periodontal disease must visit a general dentist in order to be diagnosed. The dentist will review medical records, examine the mouth, measure the depth of the pocket, and take dental x-rays.

Once the patient is diagnosed, the dentist will refer a periodontist to perform the treatment. The treatment consists of cleaning the pockets around the teeth, saving the surrounding bone and reducing risk of infection and disease progression [1]. Sometimes treatment isn't necessary if the condition is mild but if it is severe the patient may require dental surgery such as flap surgery, soft tissue grafts, bone grafting, guided tissue regeneration, and tissue stimulating proteins [1]. To prevent periodontal disease, patients must practice good oral hygiene, change unhealthy lifestyles, and schedule regular dental visits.

The Linkage

Determining a linkage between rheumatoid arthritis and periodontal disease have been discussed for years [5]. There are studies and new evidence pinpointing the combining factors behind the relationship between oral and inflammatory conditions dating back to the belief that pulling teeth could cure arthritis in the early 1900's. Studies have found that a similar process in the joints of rheumatoid arthritis patients can be found in patients with periodontal disease. This mediator is called hypercitrullination. Citrullination is a process that occurs when the body produces a number of enzymes called peptidylarginine deiminases (PADS) [2,5,13].

The enzymes will change the amino acid, arginine (Ag) within a peptide into a peptidyl citrulline[2,5] Its importance consists of regulating the functions of proteins but if it becomes overactive, this can cause hyper citrullination and abnormal modified proteins. For example, Rheumatoid Arthritis synovial fluid was examined for protein citrullination. Healthy joints contained average to low amounts of citrullinated proteins in response to inflammation whereas unhealthy joints had a larger and wider amount of citrullinated proteins [2,9].

20 stimuli that promote inflammatory pathways in the joints were examined. It showed that two of the stimuli caused the hyper citrullination in rheumatoid arthritis patients [9]. There are two pathways that can lead to hyper citrullination are: the performing pathway, and the membrane attack complex (MAC) pathway [9]. Citrullination isn't the only factor involved.

Studies have shown that a bacterial species, P*orphynomonas gingivalis* found in periodontal disease is a part of the linkage between rheumatoid arthritis and periodontal disease [2,11,13,27]. It is a black-pigmented species that depends on anaerobic conditions to grow and the presence of hemin and vitamin K as its nutrition [28]. It gains energy through amino acids and survives in the deep pockets of the teeth where sugar lies. [13,27]. *P. gingivals* invade

gingival epithelial cells and tissue as well as invade human chondrocytes that are isolated from knee joints as well as induce cellular effects [27]. *P. gingivalis* has a number of characteristics that allow it to initially elude host defense mechanisms, promoting tissue ingress, with a resultant upregulation of a number of local inflammatory responses, further propagating tissue damage [2, 13].

P. gingivalis carries the enzyme (PAD) useful to citrullination, which triggers antibodies that cause inflammation to respond to the citrullinated proteins causing the body to attack its own tissues [18]. This response is signaled throughout the body making the bacterium a risk factor for rheumatoid arthritis development. *P. gingivalis* and citrullination are responsible for triggering the autoimmunity in patients with rheumatoid arthritis creating permanent tissue and joint damage [5,11]. Treating rheumatoid arthritis with antibiotics against bacterial anaerobic infections proves that there is an involvement of bacteria in the development of RA. Evidence support the idea that oral infections is the mediator between rheumatoid arthritis and periodontal disease by detecting bacterial DNA of anaerobes and high antibodies against the bacteria in both the serum and the synovial fluid of rheumatoid arthritis patients in early and later stages of the diagnosis [11]. Studies show that patients with rheumatoid arthritis have a high number of antibodies and the DNA of these bacteria in the blood and synovial liquid [11].

Other Findings

Recently, new studies have focused on the role of citrullination and production of autoantibodies in the pathogenesis of rheumatoid arthritis. The level of anti-citrullinated protein antibodies (ACPA) has been shown in the serum of 70% of rheumatoid arthritis patients up to a decade prior [2,11,13]. ACPA can be detected through a diagnostic test due to the reactivity against the synthetic cyclic citrullinated peptide (anti-CCP). The ACPA positive rheumatoid

arthritis results represent a more severe disease compared to the ACPA negative results in disease patients [18]. Another diagnostic standard for rheumatoid arthritis is the rheumatoid factor (RF) [13,18].

It is a polyclonal antibody that reacts to the Fc portion of immunoglobulin G (IgG) [13]. RF has limited specificity for early detection of the disease and can be detected in other diseases. RF can't contribute to the rheumatoid arthritis disease development alone. Studies have shown that a microbiome in the pathogenesis of inflammatory arthritis has been a possible modifier agent due to environmental factors in disease development. Mucosal surfaces such as the lung, intestine and periodontal tissues are areas of the immune surveillance and tolerance might contribute to the development of arthritis. Autoimmune responses cause mucosal surfaces to transition to extramucosal sites like the synovial joints due to the signs and symptoms of rheumatoid arthritis.

Rheumatoid arthritis patients had a higher bacterial level, an increase of pathogenic species, and a greater diversity of oral microbiota associated with periodontal disease compared to the patients with rheumatoid arthritis and without periodontal disease, resulting in bad periodontal conditions in those patients. Furthermore, changes in the oral microbiome such as an increase in pathogenic species like Prevotella, *Aggregatibacter actinomycetemcomitans* and *Parvimonas micra* were associated with poor rheumatoid arthritis conditions in patients with Rheumatoid arthritis and periodontal disease [6].

Tissue Destruction

The effects of cytokines consist of excessive production, poor control or inadequate inhibition of their biological activity. Inflammatory cytokines activate the molecular and cellular events associated with bone resorption. Patients with periodontal disease have similar cytokine events

like patients with rheumatoid arthritis. In both conditions, tissue destruction and disease progression involve high levels of cytokines that induce inflammation such as: interleukin 1β and tumor necrosis factor-α, and low levels of cytokines that inhibit inflammation [12]. However, high levels of enzymes that tend to degrade the tissues and low levels of inhibitors of the enzymes determines the active stages of rheumatoid arthritis and periodontal disease.

Methods

This study will investigate the relationship between rheumatoid arthritis and periodontal disease and the potential role of socio-economic factors. To answer this question, we will obtain current data from patients who have rheumatoid arthritis or have experienced periodontal disease through anonymous surveys in addition to obtaining historical data through dental records in compliance with IRB standards and the use of human subjects. This process will consist of reaching out to public health officials to help create the survey. The survey will consist of ten standard questions, which will include (income, age, sex, gender, race, dental history, i.e,). A rheumatologist and dentist from the local Columbus area or counties around Columbus will be contacted and given the surveys, which will be handed to the patients.

Discussion

During this research, I have found that there is a linkage between rheumatoid arthritis and periodontal disease, which is triggered by citrullination and the bacterial species, *Porphynomonas gingivalis*. I have learned that *P. gingivalis* influences the citrullination process encouraging the body to hypercitrullinate causing abnormal proteins. *P. gingivalis* carries the enzyme (PADs), during the citrullination process, triggering antibodies that cause inflammation. The body responds by attacking its own tissues. This response is signaled throughout the whole body making *P. gingivalis* and citrullination responsible for triggering the autoimmunity in

patients with rheumatoid arthritis creating long term tissue and joint damage. With this known information, I will further this study by collecting data from patients with or without rheumatoid arthritis to determine whether socio-economic factors contribute to the strengthened or weakened relationship between the rheumatoid arthritis and periodontal disease. By doing so, I look forward to seeing if an individual's social status plays a role in these known effects. My goal is to share this information with dentists and other health professionals, in order to bring awareness to patients diagnosed with RA and/or PD to help them understand the importance of oral health. I hope to use my research as a way of proposing a new idea and change in health care and in dentistry.

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