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Periodontal Disease and Rheumatoid Arthritis; A pilot study using self-reported questionnaire

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PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS; A PILOT STUDY USING SELF-REPORTED QUESTIONNAIRE

By

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B.S., Dental Hygiene, University of New Mexico, 2013

THESIS

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Dedication

"What you get by achieving your goals is not as important as what you become by achieving your goals." –Zig Ziglar

The time and effort placed into this study as well as my graduate education has been one of the biggest accomplishments for me thus far. Pursuing higher education has always been attractive for me because it is in this realm where I can definitively see the challenge and step up to meet it. Within this realm is where I find comfort in the coming together of great minds, which like myself, thirst for knowledge and enjoy the journey one takes in searching for understanding. Simply the process of asking questions that allow my mind and spirit to enjoy the search for answers and truths awoke something inside of me. I've taken the time to explore just a small part of my field and have come to see its vastness and realize there is so much that is still unknown. I found that many answers are better than only one answer and not knowing anything definitive is more exciting than knowing something for certain. That's what keeps the quest for understanding alive. The shades of gray are better than black and white. Through this education I have experienced wonderful professional insight. The decision to step into greater professional development came at a time when I needed to also step into great personal development. Though this originally was primarily an academic pursuit it resulted in tremendous personal growth. It was a time in which I acknowledged the complexity of my own personal challenges and stepped up to meet them. By asking the questions I dare not ask myself and pushing my perceived boundaries, I learned to find comfort in my own thoughts and explored the unknown vastness of my strengths and

determination. In the pursuit of understanding, I found a bigger journey, one where I searched within myself to find a spirit that is my own, to find my voice worthy of being heard and a more defining sense of self. Through the days, months and years there were many tears and struggles. But though my labor I tapped into the richness of my fortitude, the abundance of my resilience, and an unmatched level of confidence not held before. I awoke something, I awoke someone, Me. I think for the first time I understand and accept that seeing myself in shades of gray is more beautiful than seeing myself only in the colors of black and white.

I dedicate this paper to those who always saw the potential in me before I knew it, those who believed in me before I did and those who saw me before I saw myself. I believe you now. This is just the beginning. Thank you.

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PERIODONTAL DISEASE AND RHEUMATOID ARTHRITIS; A PILOT STUDY USING SELF-REPORTED QUESTIONNAIRE

By

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ABSTRACT

Study Design: Retrospective cohort pilot-study of periodontal disease (PD) prevalence in rheumatoid arthritis (RA).

Objective: Evaluate prevalence of PD in cohort of RA subjects for DAS28 score, rheumatoid factor (RF), erythrocyte-sedimentation rate (ESR), C-Reactive Protein (CRP), and anti-cyclic-citrullinated-peptide antibody (CCP)

Methods: UNMH rheumatoid arthritis patients completing a 12-question survey with validated questions for PD.

Results: PD was present in 16/42 (RR=38%, CI95% (24, 54) compared to New Mexico NHANES data (53.7%, CI95, 52.3, 52.60). Other variables RF, CCP, ESR, CRP and the medications methotrexate and prednisone showed no statistical association with PD. (RF p=.24, CCP p=.24, ESR p=.74, CRP p=.28, Methotrexate (p=0.81) and Prednisone (p=0.75)).

Conclusions: The retrospective design of the study gathered a recent disease activity for RA and is measured against an unknown current disease activity for PD. Validated survey questions show PD prevalence to be between 38%-71% which is significant but prospective studies are needed to reveal PD association with RA.

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Chapter I

Introduction

Introduction

Diseases characteristics that exhibit chronic inflammation over extended periods of time have shown to have varying degrees of destruction on adjacent hard and soft tissues of the body. While the variability and extent of destruction is dependent on many factors, multiple inflammatory sources can increase potential negative outcomes. Periodontal Disease (PD) and Rheumatoid Arthritis (RA) are two diseases that may have a relationship in this manner. While PD pathogenesis is mainly reliant on localized bacterial agents, its destructiveness of the periodontium can be contributed to chronic inflammation. In contrast, RA is classified as an autoimmune disease but is similar to PD in that the joint destructiveness can be contributed to chronic inflammation. The diseases and their relation to the humoral response, which can both result in adjacent bone and tissue damage in the disease sites, makes this a relationship that warrants further evaluation. Therefore an evaluation of the presence of PD in a population of RA patients, given different RA disease activity levels and inflammatory markers may shed light on a relationship. Identifying prevalence of PD in populations increases awareness of incidence for providers and diagnosed individuals. Improved understanding of the importance of PD treatment in populations at greatest risk merits increased research in associations that could improve potential PD/RA positive outcomes.

Statement of the Problem

Though the exact relationship between periodontal disease and rheumatoid arthritis is not known it bears investigation. The question raised; given a population of patients with Rheumatoid Arthritis is there greater prevalence of periodontal disease and is there a relationship between presence of periodontal disease and RA disease activity?

Significance of the Problem

Periodontal Disease (PD) is a significant disease that affects almost half (47%) of the American adult population over age 30.[30] Similar to heart disease, PD is classified as a chronic inflammatory disease. The disease is characterized by gingival bleeding, oral malodor, gingival inflammation and tissue destruction.[44] Left untreated it results in destruction of the surrounding gingival tissues, underlying alveolar bone, periodontal ligament and can result in eventual tooth loss. This disease is often long term and includes periods of activity and inactivity where there may be health and/or rapid destruction. A significant contributing factor to this disease is the presence of hard and/or soft deposits that accumulate on the teeth as well as hereditary factors, the host inflammatory response and concurrent systemic diseases.

The mouth is estimated to have over 700 bacterial species.[31] However, the mere presence of bacteria within the mouth does not indicate disease status. Certain bacteria have been shown to induce a significant inflammatory response than others. In addition, the host response is unique within every individual and can often be overly exaggerated.[42] A relationship has been proposed between a virulent periodontal pathogen, *Porphyromonas gingivalis*, and its ability to create citrullinated proteins

whose antigen inducing properties may facilitate alveolar bone destruction and contribute to a total systemic increase in anti-citrullinated protein antibodies which are specific to RA .[40] Another theory is that the chronic inflammation produced by PD acts like a first wave of inflammation which then combines with a second wave of arthritogenic inflammation to induce rheumatoid arthritis leading to an over exaggerated immune response.[41] Thus, it is proposed that both conditions could influence each other in a bidirectional manner.

Inflammatory mediators are proteins that are released by the complement system of the body that initiate and control the flow of white blood cells to the site of infection. Inflammatory mediators have been shown to be both complementary and destructive, depending on their quantity and the susceptibility of the surrounding tissues. Varying degree of damage can occur in the periodontium or a RA joint as a result of this process. Within PD, proteins like this not only find their way to the site of infection within the tissue but also are produced in the saliva and crevicular fluids[32]

Rheumatoid Disease is a chronic inflammatory polyarthritis. Rheumatoid Arthritis (RA) is an autoimmune disease that mainly affects the joints in the hands, knees and other parts of the body.[43] RA frequently results in deformed and painful joints, stiffness and swelling which can lead to loss of function. In some cases RA can also affect organs like the eyes or lungs. An imbalance between pro-inflammatory and anti-inflammatory cytokines, which is thought to be responsible for tissue damage, is evident in both RA and PD. Both diseases are associated with bone destruction mediated by inflammatory cytokines such as interleukin 1, tumor necrosis factor-alpha (TNF-a) and prostaglandins.

Operational Definitions

Periodontal Disease (PD)-a group of diseases that affect the periodontal tissues (gingiva, alveolar bone, periodontal ligament)

Rheumatoid Arthritis (RA)-a chronic, systemic inflammatory/autoimmune disorder that primarily affects joints leading to stiffness and loss of function.

Rheumatoid Factor (RF)- autoantibody is characteristic to autoimmune diseases

Erythrocyte Sedimentation Rate (ESR)- acute phase reactant significant in systemic infection

Cyclic-Citrullinated Peptide (CCP)- antibodies that develop in response to citrullinated proteins specific to RA

C-Reactive protein (CRP)-acute phase reactant significant in systemic infection

Porphyromonas Gingivalis (P. *gingivalis*) non-motile facultative Gram-negative bacterial species, found in severe periodontitis

Chapter II

Review of Literature

Introduction

This review of the literature is focused on the association between periodontal disease (PD) and Rheumatoid arthritis (RA). General information regarding PD and RA will be discussed. The systemic implications, known origins and impacts of both diseases will be examined. Aspects of PD indicators like periodontal pathogens especially *Porphyromonas gingivalis* and the host response aspects has been researched in some detail. Inflammatory markers for RA and PD have been researched as well. The PubMed/MeSh databases were used to research the medical and dental literature. Searches were performed using the keywords: "Periodontal disease," "rheumatoid arthritis", and "*Porphyromonas gingivalis*", "citrullination," and other related terms.

Review

Periodontal disease

PD is the most common disease affecting the oral cavity after dental caries. It is multifactorial in origin yet is considered a bacterially induced chronic inflammatory disease. PD occurs in 10-15% of the adult population, independently of ethnicity and geographic location.[1] Periodontal disease first starts with a microbial infection followed by a hyper-inflammatory host-mediated response that will often destroy the surrounding tissues.[2] Often asymptomatic, the clinical signs of PD include gingival inflammation, formation of deep pockets surrounding the dentition, attachment loss of the supporting tissues, root exposure and loss of alveolar bone. Ultimately this may lead to tooth loss and negatively impact the quality of life of the individual.

Host mediated response

The presence of bacteria and their byproducts do not necessarily cause destruction of the periodontal tissues; rather they play a part in the initiation of a host-mediated response. The inflammatory response is a critical factor in tissue destruction. Leukocytes produced in chronic inflammation have components such as IL-1 and TNF that increase levels of prostaglandins and lytic enzymes that aid in the production of other chemokines contributing to connective tissue breakdown.[3,4] In healthy individuals, excess TNF in the blood is blocked naturally but in those who have conditions like RA, higher levels of TNF in the blood lead to more inflammation, joint destruction and persistent symptoms. In addition, systemic diseases such as diabetes and cardiovascular disease can impact the periodontium and correlate to increase risk of PD. Similarly, genetic disorders that have underlying factors that cause changes in the immune, endocrine and connective tissues status can generate PD as a primary result or by aggravation of a pre-existing condition attributable to local factors.[5]

Rheumatoid Disease

Rheumatoid Disease is a chronic inflammatory polyarthritis with a prevalence of 0.5%-1.0% in industrialized countries. According to the National Health and Nutrition Examination Survey (NHANES) 1.5 million adults were afflicted with RA in 2007.[33] The disease is more common among women than men (3:1) and prevalence rises with age, with a peak in the fifth or sixth decade.[55,63] The cause is multifactorial and pathogenesis is not well understood but is considered an autoimmune disorder. The risk of developing RA is 50% attributable to genetic factors. The disease mainly affects the joints resulting in deformed and painful joints, which can lead to loss of function. RA is

an inflammatory response within the capsule around the joints resulting in swelling of synovial cells, excess synovial fluid and development of fibrous tissue in the synovium. Rheumatoid arthritis also affects the bone and can cause thinning and destruction of the cartilage. Synovitis can lead to tethering of tissue with loss of movement and erosion of the joint surface causing deformity and loss of function.[35] There is not a single test for diagnosing RA; however, a physical exam, lab tests and x-rays are used to make a diagnosis. Typically blood tests can show Anemia, elevated levels of Rheumatoid factor (RF), antibodies to cyclic citrullinated peptides (anti-CCP), erythrocyte sedimentation rate (ESR) and C-Reactive Protein (CRP). Higher levels of these factors are noted particularly if it has been less than six months since onset of symptoms. Those with RA also have composite diseases like Sjrogren's syndrome and if poorly maintained are at increased risk for cardiovascular disease such as atherosclerosis and stroke.[36] Life expectancy of those with RA may be reduced by as much as 5 to 15 years.[37] Cardiovascular disease is generally considered to be the leading cause of mortality in patients with RA, accounting for about half of all deaths.[38]

Rheumatoid Arthritis and Periodontal Disease

PD has a positive association with RA and both disease share many characteristics. Both diseases are chronic destructive inflammatory disorders characterized by dysregulation of the host inflammatory response. The etiology of both diseases is multifactorial and susceptibility to the diseases is influenced by shared genetic and lifestyle factors. Both diseases are cumulative, i.e. severity, loss of function and quality of life decrease with longer disease duration. There are common pathological mechanisms; both conditions are influenced by an exaggerated

inflammatory response and increases localized and systemically circulating pro-inflammatory mediators. This results in soft and hard tissue destruction of the periodontium and synovium respectively.[6] RA and PD share certain known pathogenetic processes as well. These include similarities in markers of inflammation; cytokine profiles, interleukin 1*B* (IL-1B) tumor necrosis factor-*a* polymorphisms, C-reactive protein (CRP), and presence of citrullinated proteins, just to name a few. This suggests that subjects susceptible to RA may also have higher rates of periodontal disease.[7] The prevalence of RA in patients with periodontitis has been found to be nearly four times the rate of the general population without periodontitis (3.95% vs 1%, respectively).[27] Evidence of *Porphyromonas gingivalis, Tannerella forsythensis* and *Prevotella intermedia* has been identified in the synovial fluid of RA, suggesting that periodontal pathogens play a role in disease initiation or propagation.[28] For this study it is important to note that autoimmunity to citrullinated proteins is highly specific for RA and may be of pathogenic significance.[8]

Periodontal pathogens

Although more than 700 bacterial species can colonize the oral cavity only a handful of those are highly implicated in PD.[9] Socransky et al. divided the pathogens into two main clusters of microorganisms and deemed them the “red” and “orange” complexes. Furthermore, defined in less pathogenic order as “green”, “yellow”, and “purple” which are bacterial complexes that form on the tooth surface prior to the colonization of the “orange” and “red” complexes.[10] (See Figure 1)

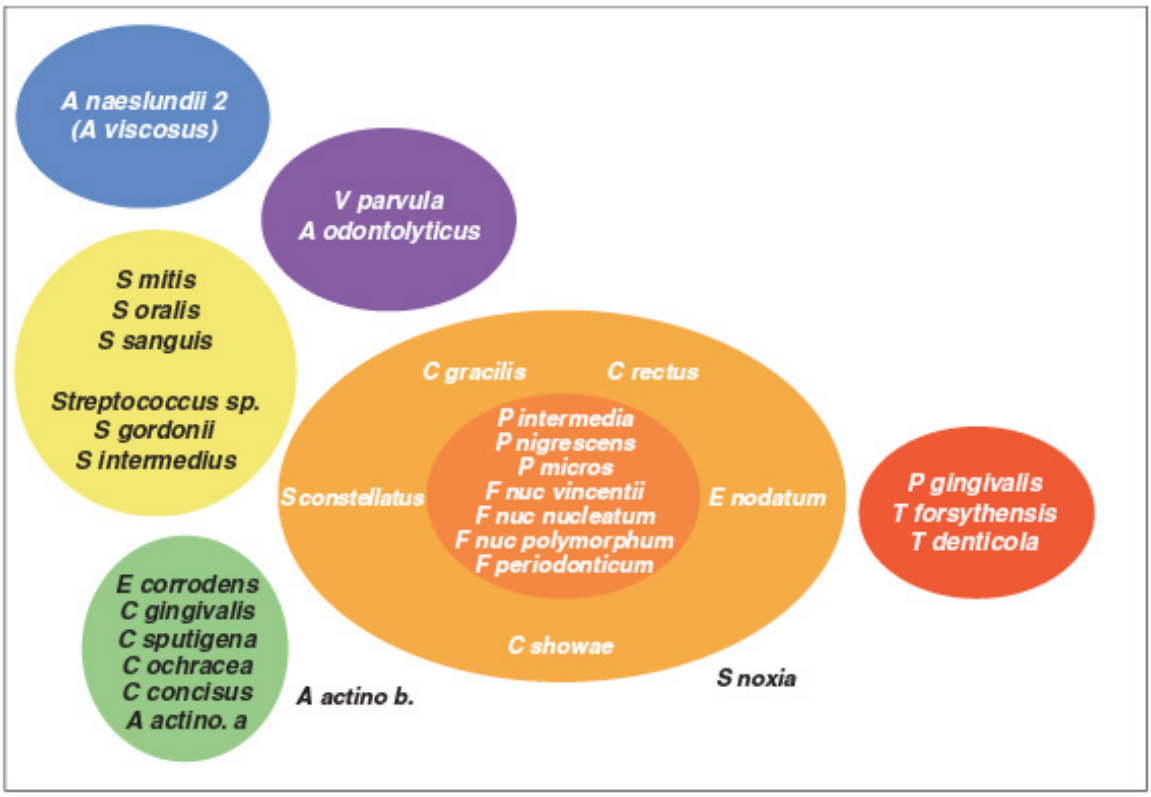

Figure 1: Microbial complexes in subgingival biofilm. Modified Image from CE world. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr., Microbial complexes in subgingival plaque. J Clin Periodontol. 1998;25:134–44.

The red complex bacteria; *Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola* are associated with severe forms of periodontal disease. [11] The "orange" complex" included F. nucleatum/periodonticum subspecies, P. i*ntermedia*, P. *nigrescens*, *Peptostreptococcus micros*, C. *rectus*, C. *gracilis*, C. *showae*, *Eubacterium nodatum*, and *Streptococcus constellatus*. The "yellow" complex comprised six *Streptococcus* species: *Streptococcus sp.*, *S. sanguis*, *S. oralis*, *S. intermedius*, *S. gordonii*, and *S. mitis*. The "green" complex was made up of *Capnocytophaga ochracea, Capnocytophaga gingivalis, Capnocytophaga sputigena, E. corrodens*, and *A. actinomycetemcomitans*. The fifth and final complex, the "purple" complex, consisted of

Veillonella parvula, *Actinomyces odontolyticus*, A. *actinomycetemcomitans* serotype b, *Selenomonas noxia*, and *Actinomyces naeslundii* genospecies (*Actinomyces viscosus*), but these did not make up any specific organizational group.[12]

Porphyromonas gingivalis

P. gingivalis is a black pigmented, non-motile facultative Gram-negative species that requires anaerobic conditions for growth, as well as the presence of heme and vitamin k in its nutrient milieu. It gains metabolic energy by fermenting amino acids.[13] This species is most highly associated with the chronic form of periodontitis and is detectable in up to 85% of diseased sites and is rarely detected in healthy sites. This may mean that the presence of P. *gingivalis* is a very strong predictor of disease progression.[14] Part of its strategy for survival within the host is the ability of P. *gingivalis* to invade cells, especially gingival epithelial cells, thus avoiding the host immune response, it maintains viability and ability to replicate. Virulence factors of P. *gingivalis* such as gingipains, fimbrillin peptides, capsule polysaccharides, lipopolysaccharides, haemagglutinating and haemolysing activities, toxic products of metabolism, outer membrane vesicles, and other enzymes have important roles in eliciting host responses in various ways. These factors significantly affect epithelial/endothelial cells and a major effect is observed on the seeming resistance to the neutrophil response.[15] Wherein, neutrophils are the predominant cells responsible for host defense against bacterial infections, they appear first in periodontal inflammatory lesions forming a wall of cells against the junctional epithelium creating a standoff between the bacterial infiltrations. However, some research states that bacterial evasion of the neutrophil may transform the neutrophil from defender to

perpetrator.[16] P. *gingivalis* has the ability to stimulate interleukin (IL-8) production but can also inhibit production as well, which hinders neutrophil chemotaxis. Thus P. gingivalis can incapacitate the first line of defense in periodontal tissues.[17]

Citrullinated proteins

Citrullination or deimination is a post-translational modification of the amino acid Arginine from proteins into the nonessential amino acid Cirulline by enzymes called peptidylarginine deiminase (PAD). This modification is a normal physiologic response that occurs in many dying cells.[51] Citrullination is an inflammation associated phenomenon, occurring in a wide range of tissues. It is predominantly observed in proteins of the cellular cytoskeleton.[6] The immune system often attacks citrullinated proteins, leading to autoimmune diseases such as rheumatoid arthritis.[62] Some have proposed that P. *gingivalis* infection of the periodontal sulcus may be a source of citrullinated peptides that could serve as antigens that trigger RA. P. *gingivalis* possesses a unique microbial enzyme, peptidyl arginine deiminase (PAD), which has the capability of deiminating arginine in fibrin in the periodontal lesion, a characteristic shared with human PAD, an established susceptibility factor for RA.[18] So far there are 5 PAD enzymes that have been described in humans. Recently PAD2 and PAD4 have been detected in the periodontium.[19, 39] The antibodies that develop in response to citrullinated proteins, called anti-citrullinated protein antibodies (ACPA) are specific to RA and is likely the result of an abnormal humoral response to these proteins and depends on the genetic make up on the individual. Blood analysis revealing elevated levels of anti-cyclic citrullinated peptide antibody (CCP) can be useful in the diagnosis

of individuals with RA but is not definitive as people with RA can also have normal levels of CCP.

Inflammatory markers

The diagnosis and activity of RA involves blood analysis to evaluate the markers for inflammation. C-Reactive Protein (CRP) is produced as a response to inflammation by cells within the liver. Erythrocyte sedimentation rate (ESR) is defined as the distance that erythrocytes settle in anti-coagulated whole blood, under gravity in one hour and is also instrumental in identifying amounts of inflammation in the body. Both of these acute phase reactants are used for diagnostic purposes but do not specify the source of infection.[49] Variable levels of CRP can determine risk for cardiovascular disease; ≥1mg/L indicate low risk, 1 ≤ ≥ 2.9mg/L means intermediate risk and in amounts 3≥mg/L can mean high risk.[49] Also of importance is that elevated levels of CRP can be found in the presence of periodontal disease.[48] Distinguishing ESR time can indicate presence of infection: normal ≤20/30mm/hr.[50] Another consideration within blood analysis is the presence of the autoantibody Rheumatoid Factor (RF). This autoantibody is characteristic to autoimmune diseases but is not specific of RA. About 20% of those with RA can have normal RF result while 5% of people who do not have RA will have an abnormal RF test.[52] Abnormal levels do not guarantee the diagnosis and normal levels do not exclude the diagnosis. Normal range for RF is 0-15u/ml.

Anti-rheumatic therapy

There is currently no cure for RA, therefore, the goal of anti-rheumatic therapy is to decrease symptoms and to sustain and prolong joint function. There is no single treatment however, a composite of medications are frequently used and may need to be

changed during the course of the disease. Non-steroidal anti-inflammatory drugs (NSAIDS) when used in higher does than that used for headaches are effective anti-inflammatory medications and corticosteroids, like prednisone, are used early in treatment to reduce acute inflammation, reduce pain and to slow joint damage. A class of antineoplastic and immunosuppressant drugs, considered disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (Rheumatrex), leflunomide (Arava) hydroxychloroquine (Plaquenil), sulfasalazine (Azulfidine), and minocycline are frequently administered to slow the progression of erosive damage over time. However, some of those can also significantly increase risk of liver damage, bone marrow suppression, and severe lung infections. Biologic therapies targeting cytokines also have been successfully used in controlling RA as they block or control the actions of TNF-a.[29] Some anti-TNF-α drugs are Infliximab (Remicade), Etanercept (Enbrel), Adalimumab (Humira), Certolizumab (Cimzia), Golimumab (simponi). These are all delivered by intravenous infusion or subcutaneous injection. Long-term use of these drugs can increase risk of cancers and rare neurological disorders.

Review and Meta-analysis

One systematic review and a meta-analysis was published that evaluated five studies assessing the effects of intervention in subjects with RA and/or periodontitis. [23] The meta-analysis concluded that non-surgical periodontal therapy in individuals with PD and RA could lead to improvements in the markers of disease activity in RA. Another study by Ortiz et al. evaluated the effect of non-surgical periodontal treatment on the signs and symptoms of RA in patients treated with or without anti-tumor necrosis factor-alpha medications. The effect of anti-TNF-*a* therapy on periodontitis also was

assessed. Forty patients diagnosed with moderate/severe RA and severe periodontitis were randomly assigned to receive initial non-surgical periodontal therapy (NSPT) and oral hygiene instructions or no periodontal therapy. The outcome showed NSPT had a beneficial effect on the signs and symptoms of RA, regardless of medications used to treat the condition.[24] In a second study by Al-Katma et al. the objective was to determine if eliminating periodontal infection and gingival inflammation affects the severity of the active RA in patients with chronic inflammatory PD. Among the 29 subjects with confirmed RA and mild to moderate periodontal disease, 17 subjects received periodontal therapy /NSPT with oral hygiene instructions and 12 subjects received no treatment. The outcome of the study was that control of the periodontal infection and gingival inflammation by scaling and root planning and plaque control in subjects with PD may reduce the severity of RA.[25] Okada et al studied the effect of serum antibodies to P. gingivalis and citrulline levels in relation to disease activity of RA . Fifty-five patients with RA were randomly assigned to receive either oral hygiene instruction and supragingival scaling or no periodontal treatment. Periodontal and rheumatologic parameters and serum levels of cytokine and inflammatory markers citrulline and immunoglobulin (Ig)G to P. gingivalis were examined at baseline and 8 weeks later. These results suggest that supragingival scaling decreases DAS28-CRP and serum levels of IgG to P. gingivalis HBP35 and citrulline in patients with RA.[26] Since most of these studies have a small sample size and did not consider microbiology, there is a need for better designed experimental studies on the effect of periodontal treatment on RA disease activity.

Summary

The host mediated inflammatory response produced by PD and RA is well researched. The target treatment modality for both diseases is primarily for maintenance since there is no cure for either. There are many similarities in disease transition and progression due to shared inflammatory mediators and it is likely that PD affects RA as well as a potential bi-directional affect.

Chapter III

Methods and Materials

Introduction

This study evaluated the presence of periodontal disease (PD) in a group of patients with rheumatoid arthritis (RA). Some studies have shown a correlation between periodontal diseases and rheumatoid arthritis as reported in the previous chapter. A self reported survey with validated questions attempted to gather information regarding the presence or absences of periodontal disease among a group of patients with RA of varying degrees of disease activity. This information was analyzed for relationship and relative risk between RA disease activity levels and prevalence of PD and compared with the Feb 2016 NHANES report of periodontal disease prevalence in New Mexico.

Research Design

The study design was a retrospective cohort. The cohort were those diagnosed with rheumatoid arthritis recruited from the University of New Mexico Hospital, Department of Internal Medicine, Rheumatoid Arthritis Clinic. The group of interest was those within the cohort who had periodontal disease. The sample was drawn from the 100-150 patients being treated by the standard of care doctor who was also a co-investigator. The first layer of recruitment was performed by the standard of care physician through a chart screening of patients of record for eligibility. The criteria for eligibility were: must be a patient of record at the RA clinic, have a clinical diagnosis for RA with a DAS28 score, older than 30years of age, non-smoker (if known) and females not pregnant. Once gathered, that sample consisted of participants with varying

degrees of rheumatoid arthritis severity, male and female participants of various ages living in the Albuquerque, New Mexico metropolitan or surrounding areas. The recruitment period and the study period happened simultaneously.

The cost incurred during this study was the sole responsibility of the co-investigator. The University of New Mexico Hospital Rheumatoid Arthritis Clinic holds all contact information for their patient base. The database does not consistently contain e-mail contact information so a web-based survey was ruled out. Therefore, an in-office self-completed paper survey was used in addition to a survey distributed by mail. An option to be contacted by telephone depending on the participation levels was also approved but not implemented as enough participants were gathered through the other methods of recruitment.

Study Procedures

Study approval was received from the University of New Mexico Institutional Review Board, Human Resource Protections Office (See Appendix A). The standard of care doctor was the sole recruitment source. He evaluated the patients under his care that met the above-mentioned criteria. The co-investigator/PI proxy and standard of care doctor were in the rheumatoid arthritis clinic at least 1-2 day a week to recruit potential subjects. The screening of potential subjects was done based on the patients who already had pre-existing appointments that day. Once eligibility was determined, the potential subject was approached by the co-investigator in the privacy of the examination room in which they were waiting and were read the recruitment script and given the combined consent/HIPAA for their review (see Appendix B and C).

In an attempt to reach eligible study participants whose appointments may not have been on those study days, consent/HIPAA forms and surveys and were also distributed by mail. Information regarding additional eligible study participants was shared via secure UNM HSC email. The consent form detailing the study, the rights of participants, the survey and a self-addressed stamped envelope were mailed in packet form to potential subjects (see Appendix D and E). Completing and returning the survey by mail indicated that the subject consented to participate in the study. Approval of the study also included an option for participation by telephone; however, this option was not used during the study as enough participants were gathered by in-office and mailed recruitment methods.

It is estimated that there were 100-150 eligible participants; the initial response rate was estimated to be between 30-50%. The end point of the study was two months or the collection of 100 participants. At the end of the study the data was analyzed by an approved study member first for completion and study eligibility then given a periodontal disease (D) status or healthy (H) status. Those surveys that qualify for inclusion then were match with the subjects health information such as name, date of birth, medications list, DAS28 score and other disease identifiers (RF, CCP, ESR, CRP). This information was then de-identified and statistically analyzed by a qualified study team member.

Survey

The estimated time for completing the entire survey was 5-7minutes. The survey was single sided and printed in English only. The self-reported questionnaire used periodontal disease identifiers and needs-based assessment identifiers. The

questionnaire consisted of approximately twelve questions. Completing the questionnaire required circling “yes” or “no” responses to each question. Each survey was marked with an ID number. This number correspond to the subjects name from the list of eligible participants gathered by the standard of care doctor and was cross matched when received back in the mail or when received through in-office participation.

Study Details

The names, addressed, phone numbers were compiled on a spreadsheet and saved on to an encrypted USB device. This USB device was stored in a locked filing cabinet at the UNM Division of Hygiene. The list of names and addresses was assigned a specific ID number and stored on the encrypted USB. The approved co-investigator used the list to send out the consent form and surveys as well as log the information of the subjects recruited while in-office at the RA clinic.

The names and addresses of the potential study participants were written on the envelopes mailed out to potential participants with the RA clinic address as the return. Inside the envelope was: the survey marked with the assigned ID number; a combined consent/HIPPA form; a self-address stamped envelope with the RA clinic address for return of the surveys. The surveys received were placed through a slot into a locked box located within the RA clinic. The survey and consent paperwork gathered from subjects who were recruited in-office was also stored in this same locked box.

The study span was a two month period. Since the recruitment period and study period happened simultaneously every week an accounting of participants by mail and in-officer were marked on the encrypted USB spreadsheet master list.

The information on the survey paper was only identifiable by the ID number. The master list was used to match the ID number on a survey with the subject's identifiable information. Once all the surveys have been matched with the subject's medical information and disease identifiers along with the subject's answers to the survey questions it was categorized on the spreadsheet master list. At the end of the study the information was de-identified and stored on a password protected computer for data analysis.

There was no compensation to subjects for participation in the study nor for the distributing, collecting or performing the analysis of the surveys.

Data Collection

Surveys with incomplete answers were rendered invalid for inclusion in the study analysis. Subjects that answered, "yes" to question #3 were not be eligible for inclusion in the study. The age, gender and location of residence was documented. List of medications was gathered for analysis as well as rheumatoid arthritis disease activity, DAS28 score, and inflammatory markers like CCP, ESR, CRP and RF were documented.

Data Analysis

This study tested the null hypothesis: There is no significant difference of prevalence of periodontal disease in a group of rheumatoid arthritis patients as compared with the population as reported by NHANES measured by a validated self-assessment questionnaire. The second null hypothesis to be tested is: There is no significant difference of periodontal disease prevalence in those with severe RA disease

activity as compared to those with without periodontal disease with a severe RA disease activity.

Data was evaluated for correlation between RA disease activity and periodontal disease status. Periodontal disease identifier questions from sections 5-9 were used to score the periodontal disease status in two categories, periodontal disease present (D) and periodontal disease not present or healthy (H) There are five questions in this section and 3 of the 5 must be answered "yes" to have a status of "periodontal disease present." DAS28 score measures disease activity on a scale of 0-10. The level of RA activity will be characterized as: Remission group (R): ≤ 2.6, Low Disease Activity (L): 2.6 < DAS28 ≤ 3.2, Moderate Disease Activity (M): 3.2 < DAS28 ≤ 5.1, High Disease Activity (H): DAS28 > 5.1.

The first data analysis of interest was the percentage of people who have periodontal disease based on the strict interpretation of the study results and compared with the percentage gathered by NHANES 2016 "Prevalence of periodontitis at the state and local level in the United States."[54] The next analysis was to include subjects who answered yes to survey questions number 2 as part of the population of people who have periodontal disease. This may or may not have changed the percentage of people with periodontal disease and then was also compare to the NHANES data.

The operative statistics was the relative risk (RR) of D and H in each RA disease activity category and displayed using a horizontal bar chart. A Chi-square test (x^2) will be used to assess P-Value (<.05) using degrees of freedom (n-1=3). Confidence interval will be calculated at 95% (CI_{95}). Disease identifying data; Rheumatoid factor (RF), anti-

cyclic citrullinated peptide (CCP), erythrocyte sedimentation rate (ESR), C-Reactive protein (CRP) and medication list were collected and were used to interpret results as part of a normal distribution curve.

Chapter IV

Results, Discussion and Conclusion

Results

There were 60 potential study participants contacted. Of those, 24 were contacted while attending office appointments with 23 consenting to participate yielding a 95% response rate. A total of 36 were contacted by mail and 22 consented to participate; yielding a 61% response rate. Therefore, there were 45 total subjects agreeing to participate presenting in a 75% overall acceptance rate. There were three ineligible subjects due to positive answers to survey question #3 ("Do you currently smoke or use tobacco products?"). Consequently, the total study participants numbered 42. The age distribution can be seen in Graph 1-Age Distribution. The largest age group was between 55-64 consisting of 17 subjects, followed by age group 65-79 equaling 12 subjects. The age groups 30-44 and 45-54 consisted of 7 and 6 subjects respectively. The amount of subjects that reports seeing a dental provider at lest once a year amount to 33/42 yielding 78%.

The participants were predominantly female with a 6:1 ratio. Of the total 42 subjects 36 (86%) were female and 6 (14%) were male. (See Figure 2)

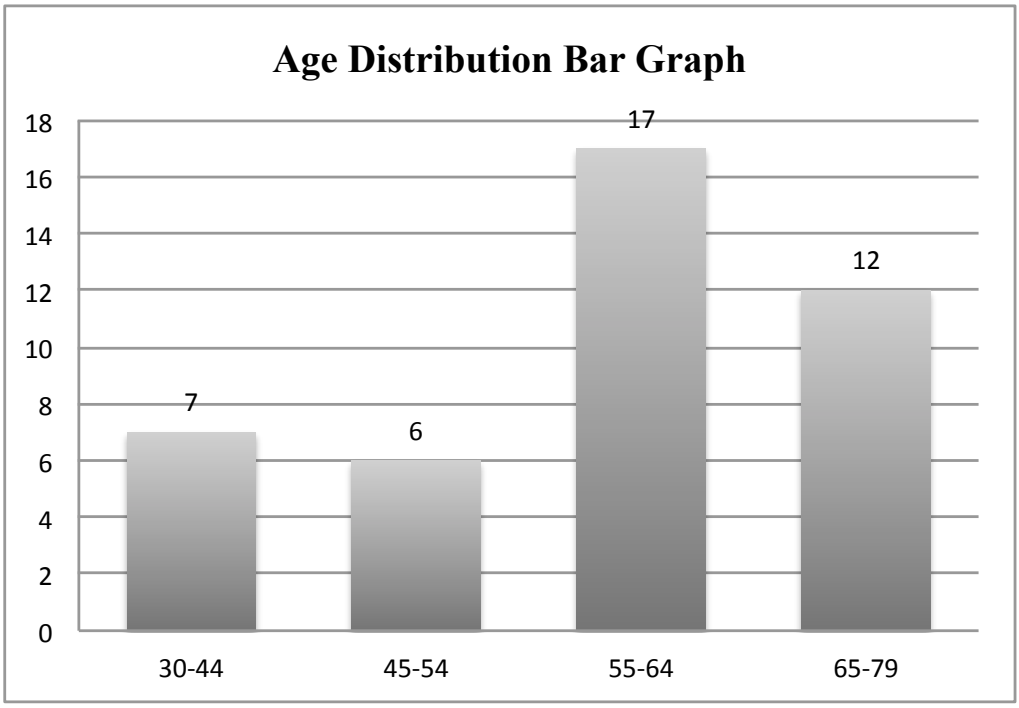

Figure 2. Age Distribution Bar Graph

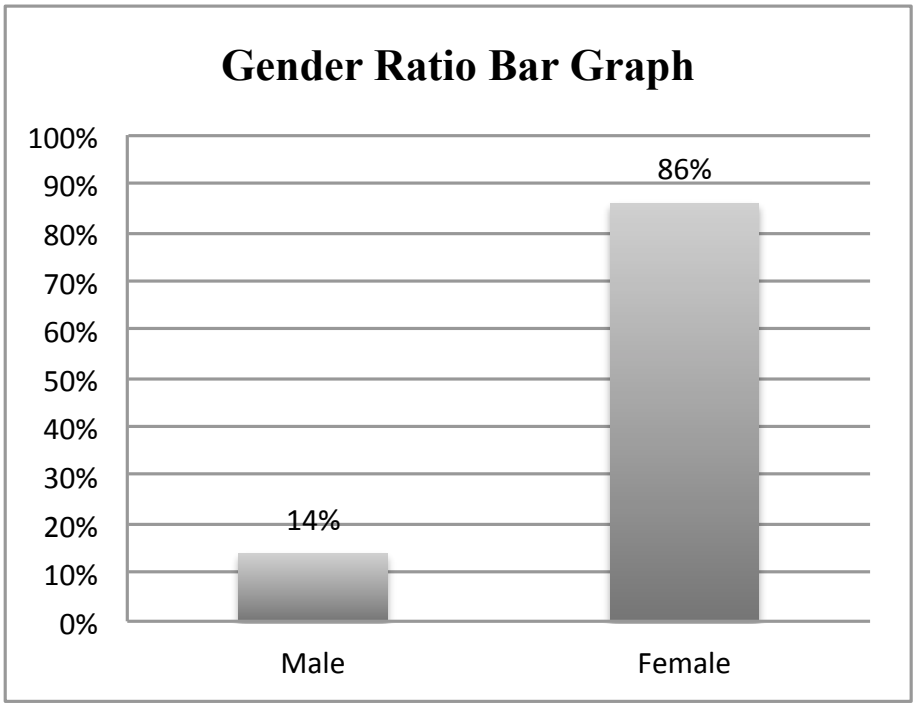

Figure 3. Gender Ratio Bar Graph

Of the total participants, 11 were found to have PD with a Relative risk (RR=26.1%) this is based on the strict application of the study boundaries. Inclusion of 5 additional subjects in the PD category following review of positive answers to questions number 2 ("if you have lost teeth was it due to gum disease/periodontal disease?") yielded an actual total of 16 subjects or RR=38% with a $CI_{95\%}$ (.24, .54) for periodontal disease classification. The NHANES study founded, 52.79%, ($CI_{95\%}$, 52.60, 52.97) of the population were positive for PD representing 15% fewer cases of PD (see Figure 4).

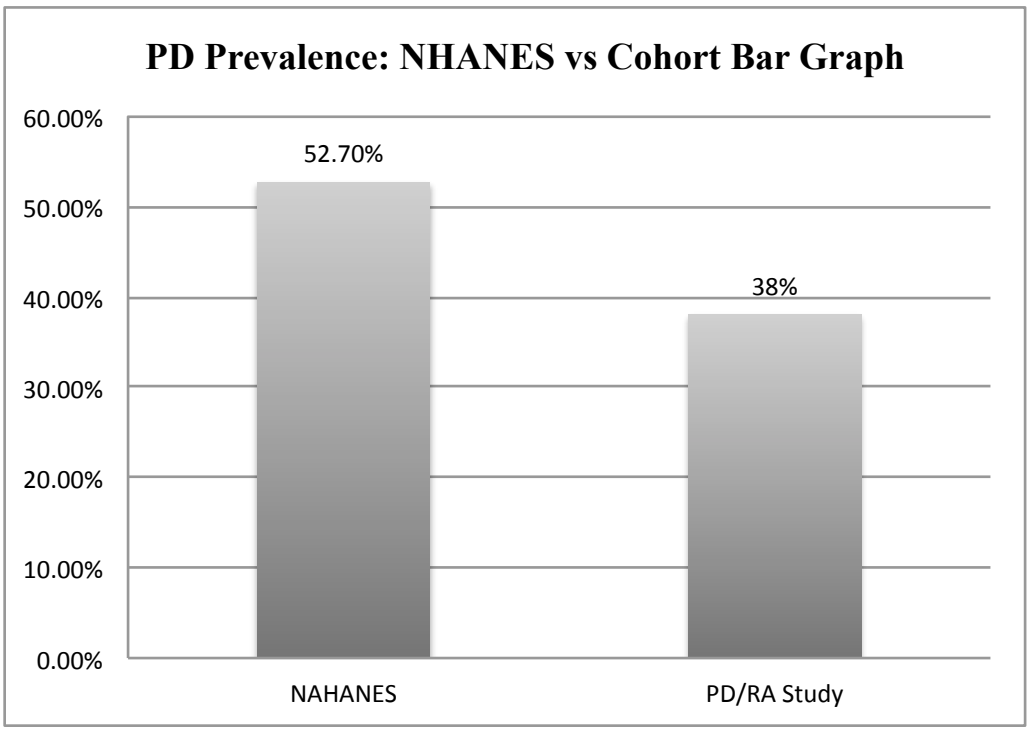

Figure 4. NHANES vs Cohort Comparison of Periodontal Disease Presence

The cohort of 42 subjects was further categorized into healthy subjects, 26, and disease subjects, 16, then categorized into levels of RA disease activity. (R, L, M, H) and relative risk was calculated (see Table 1).

Table 1. Healthy/Disease subject Risk Classification

Relative Risk of PD by RA Activity Table					
RA Classification	**Healthy subjects**	**Risk**	**RA Classification**	**Disease subjects**	**Risk**
Remission	6	23.10%	Remission	5	31.25%
Low	6	23.10%	Low	5	31.25%
Medium	8	30.76%	Medium	2	12.50%
High	6	23.10%	High	4	25.00%
Total	26	100.06%	Total	16	100.00%

A graphical representation of this data in a side-by-side bar chart shows the relative risk associated with the healthy and disease groups categorized by RA disease activity (see Figure 5).

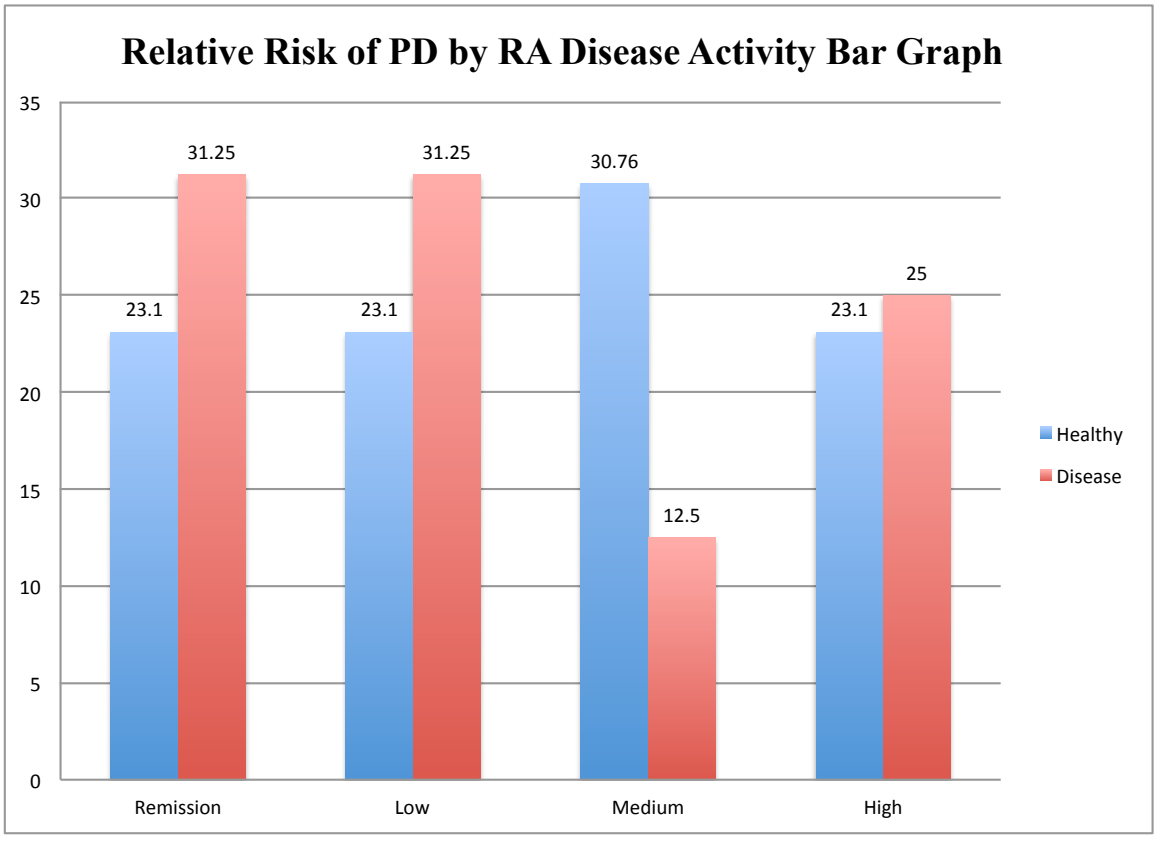

Figure 5. Relative Risk of PD by RA Disease Activity

The RR of PD by RA disease activity was than analyzed for goodness of fit using Chi square (x^2) test and determined to be 1.909, p-value (p,0.5) calculated at 0.59150719 with degree of freedom at 3 (n-1) (see Table 2). This shows no statistical significance.

Table 2. PD and RA Disease Activity Score

Chi Square Table of PD and RA Disease Activity Score				
	Remission	**Low**	**Medium**	**High**
Healthy	6	6	8	6
Disease	5	5	2	4

Chi Square	1.909
p-value	0.59150719
p<.05	Not-Significant
Degree of Freedom	3

The data was evaluated for RR of PD by age group (seen in Figure 6) and RR of PD by gender (seen in Figure 7).

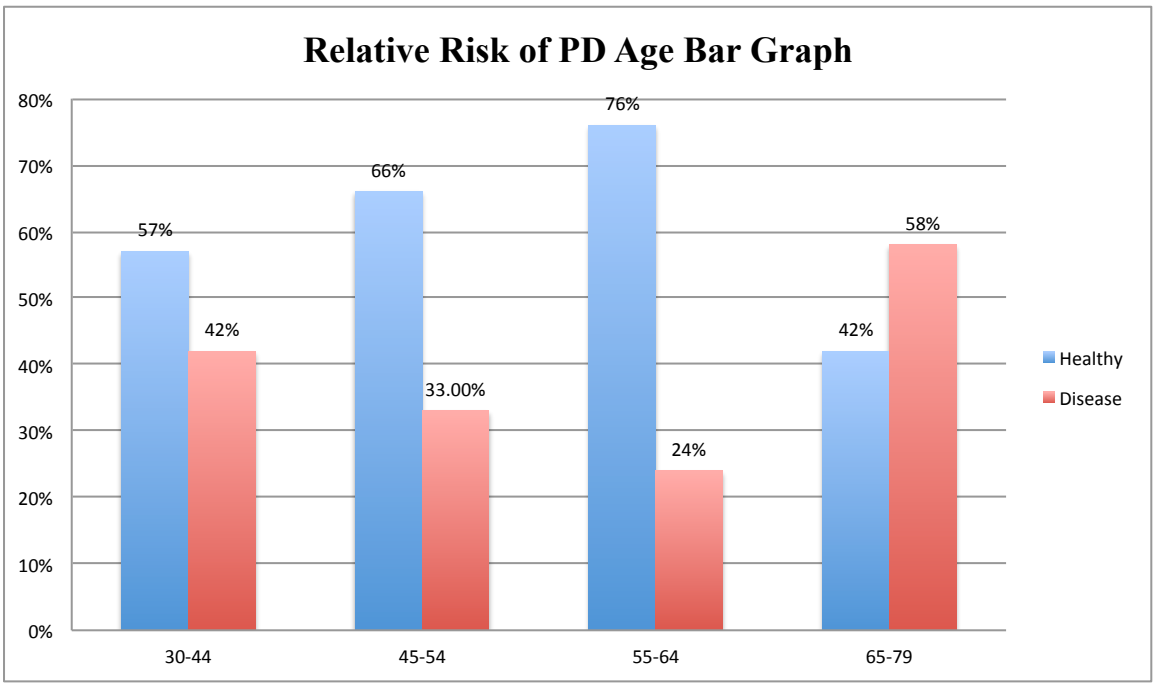

Figure 6. Relative Risk of PD by Age

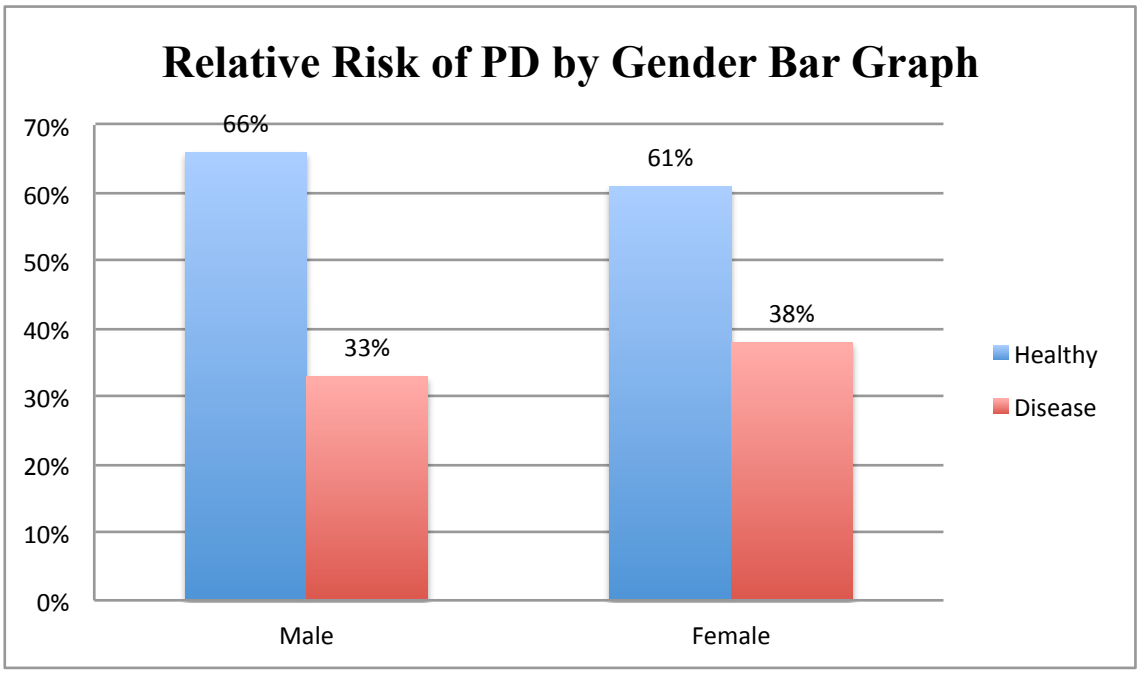

Figure 7. Relative Risk of PD by Gender

Other variables on C-Reactive protein (CRP), Rheumatoid factor (RF), Cyclic citrullinated peptide (CCP), Erythrocyte Sedimentation Rate (ESR), and medications (Methotrexate, Prednisone) were collected and evaluated for a possible relationship with periodontal disease. It is assumed that most data follows a normal distribution and when larger study samples are gathered this is usually the case. However, when small samples are gathered the data can be skewed; therefore, it is better to try to get the data to be closer to a normal distribution if possible to get the most out of analysis. T-tests were used because they are more tolerant of skewed data. These variables along with PD were tested and the data is presented in Box Plot (See Figure 8) and Bootstrap Sampling Distribution of RF, CCP, ESR and CRP (See Figure 9-12). The T-test used for analysis of this data shows that there is no statistical significant difference as evidenced by the p-values in the box plots and in the overlapping of the boxes themselves. Note that the p-values have been adjusted by false discover rate (FDR) which allows the researcher to tolerate a certain number of tests to be incorrectly discovered without compromising the test. The black line in the boxes indicates the mean of the data and the density of the plots are graphically represented below the box plots.

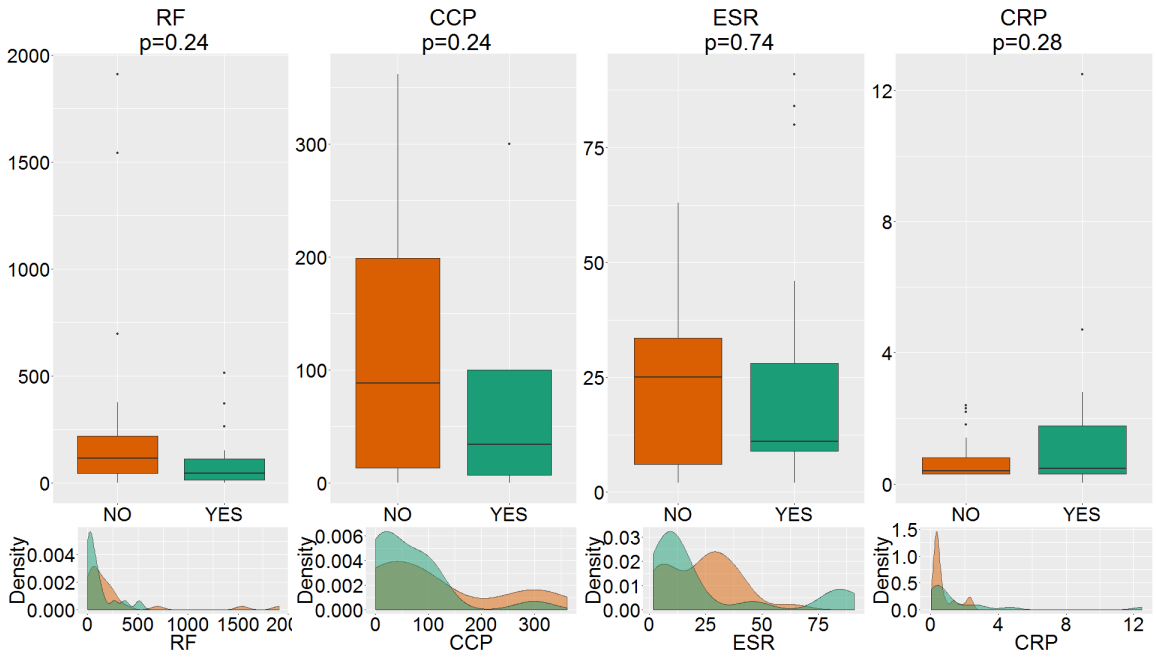

Figure 8. Box Plot Graph

In this study most of the data including CCP, ESR, RF and to a lesser extent CRP came close to a normal distribution with bootstrap analysis. This is a technique whereby the data pool from the study represents the population and a number of samples are drawn from the data pool to gain a distribution curve.

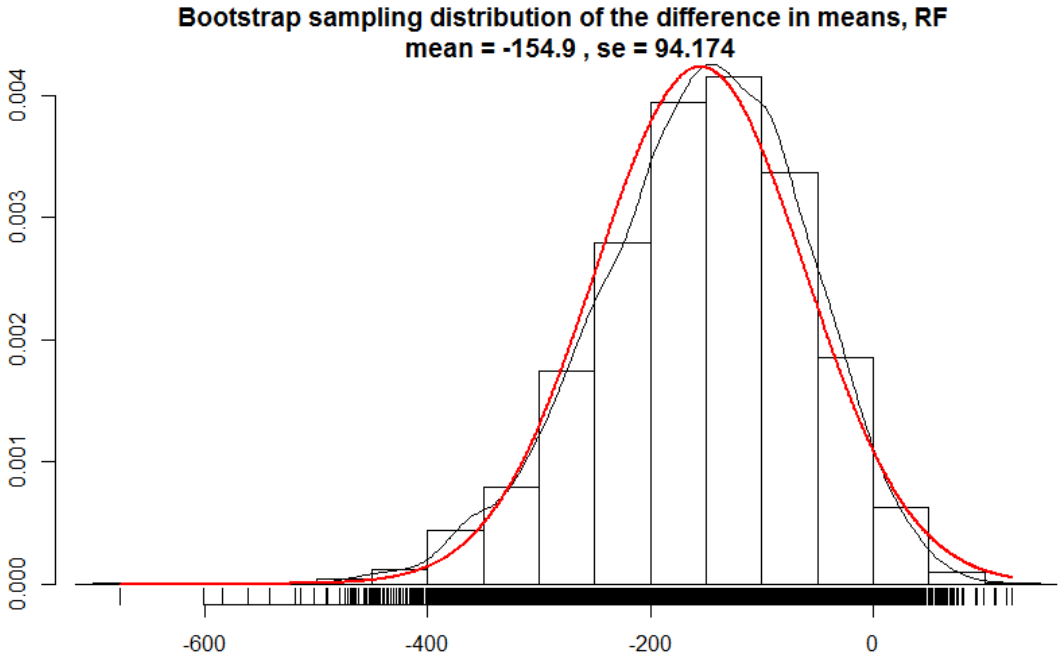

Figure 9. Bootstrap Sampling Distribution of Difference in Means, RF

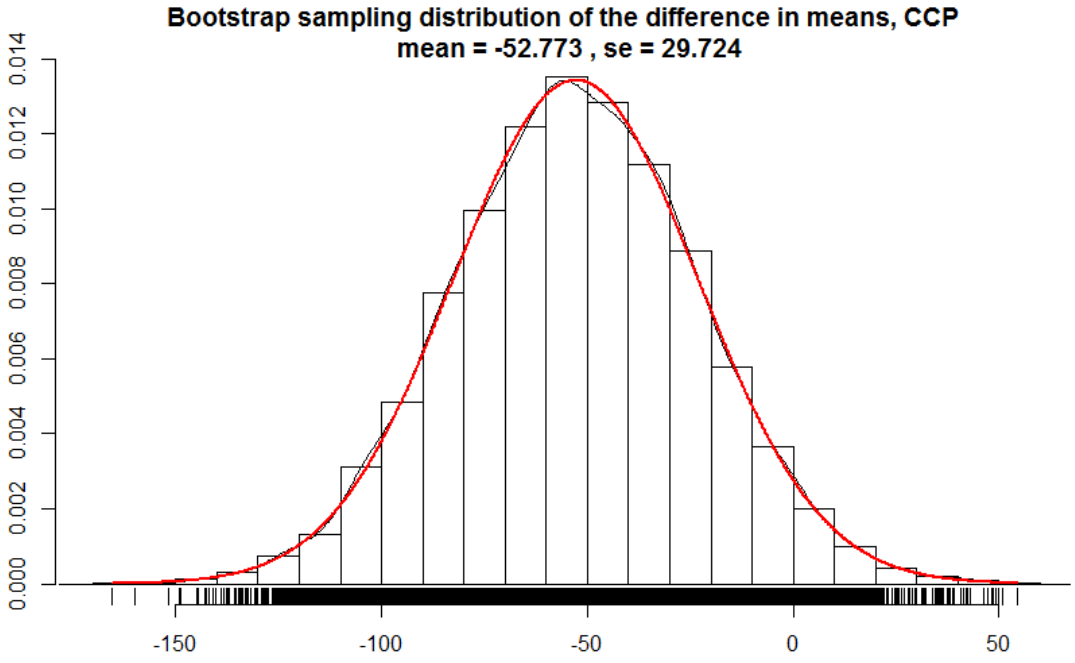

Figure 10. Bootstrap Sampling Distribution of Difference in Means, CCP

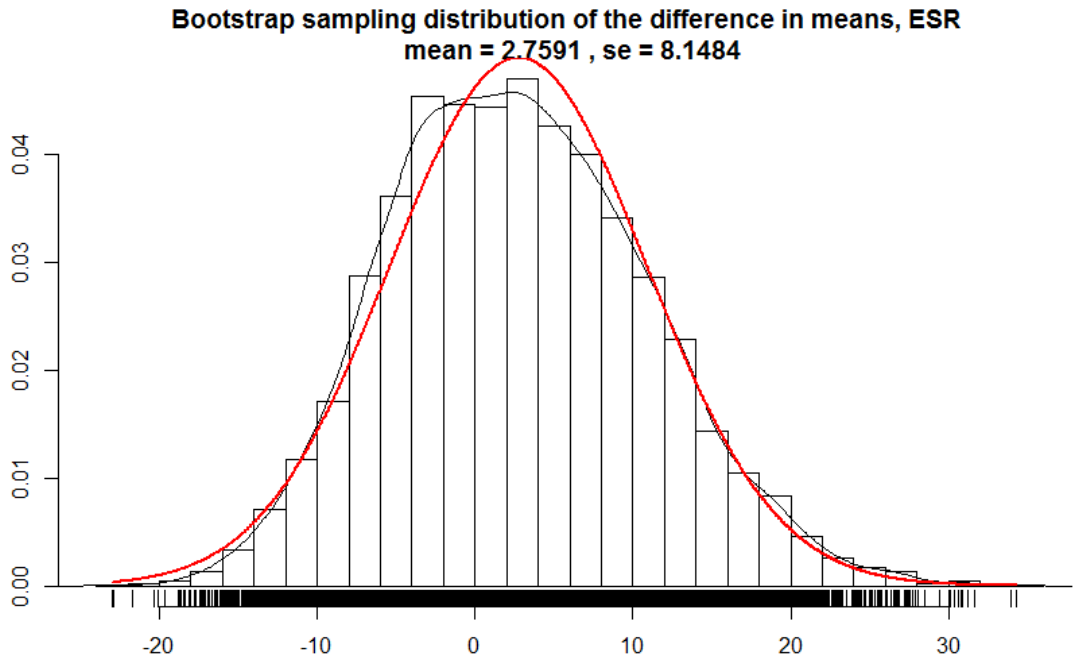

Figure 11. Bootstrap Sampling Distribution of Difference in Means, ESR

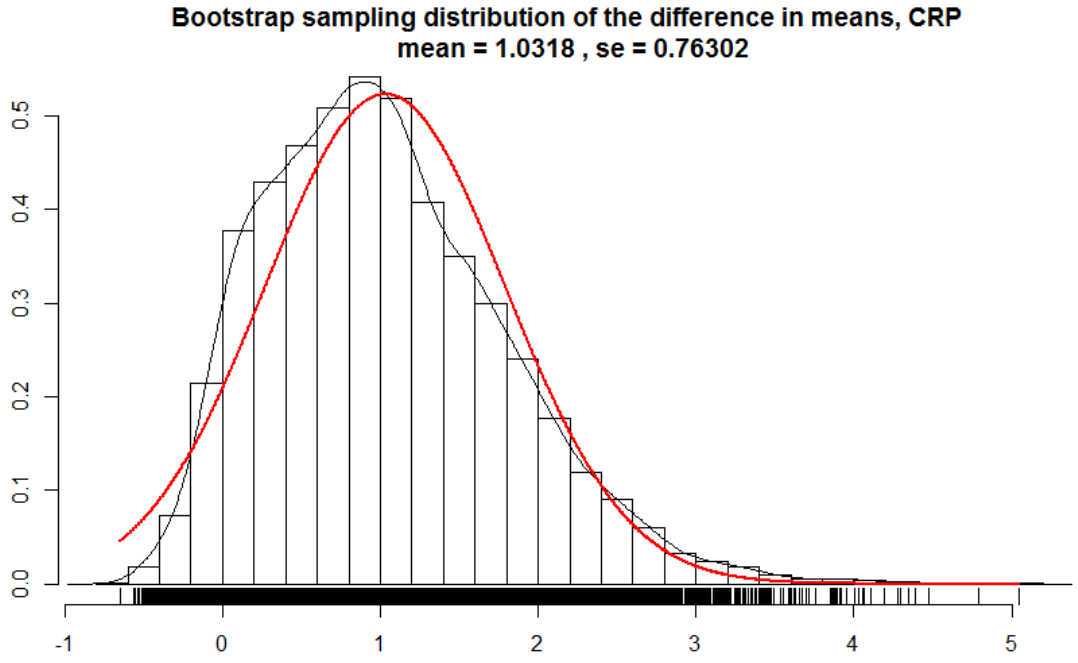

Figure 12. Bootstrap Sampling Distribution of Difference in Means, CRP

Two significant medications, Methotrexate and Prednisone were evaluated for a relationship with PD. The p-values from a Pearson $\chi 2$ regression show no statistical significance for Methotrexate (p=0.81207) or Prednisone (p=0.75438) associated with PD (See Figures 13, 14).

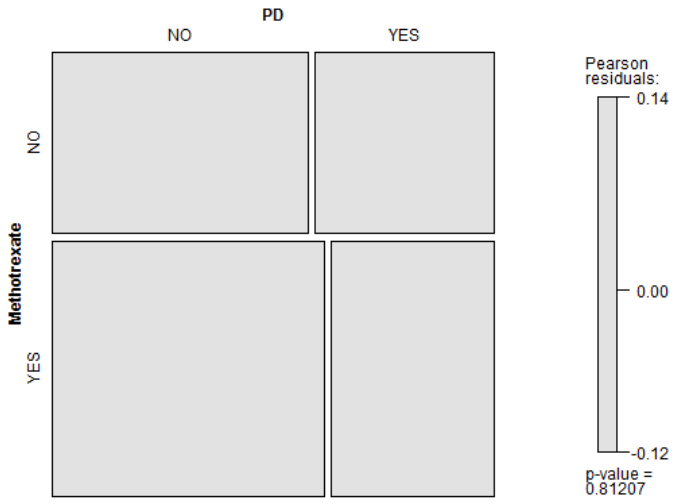

Figure 13. Box Plot: Methotrexate

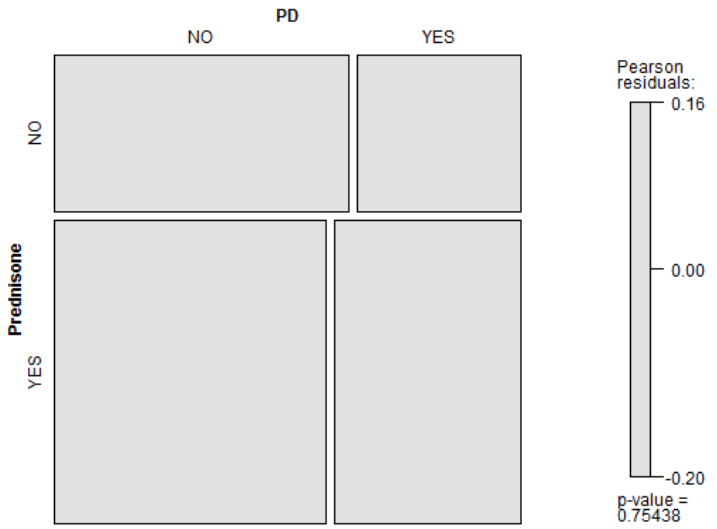

Figure 14. Box Plot: Prednisone

Discussion

A significant limitation of the study is the lack of a clinical component to assess presence of periodontal disease. Self reported survey design relies solely on the subject's ability to accurately remember or have observed occurrence of behavior and the ability to accurately answer the questions. This makes retrospective studies such as this susceptible to recall bias and thus could have resulted in wrongly assigning PD to subjects. Relying on a subject's knowledge and understanding of his/her own periodontal disease status may or may not be the same as clinical findings would determine and generally underestimate the incidence of PD.[46] However it is an acceptable means of assessment when doing epidemiological study at low cost and did

facilitate the purpose of this particular study. Future studies should also control for diabetic status as both smoking and diabetes are significant risk factors for PD development.[58, 59]

The 2016 NHANES statistic for predicting periodontitis by state was used as comparison for the results of this study and was though to have specific application to the local population. Studies done before 2009 by NHANES were found to be low in their estimation of prevalence of disease due to only using select teeth or partial-mouth clinical examinations.[45] Since 2009, the gold standard full mouth periodontal evaluation has been used along with a validated self-reported questionnaire.

Survey: Given the limitations of this pilot study a significant effort was made to ensure validity of the survey questions, since no clinical component would be utilized. The questions were gathered from a systematic review of validated self-reported periodontal disease questions authored by Paul Eke DDS, who also developed the NHANES surveillance studies used as the comparisson.[46] In the systematic review, 20 questions for periodontal disease and 24 questions for gingivitis were analyzed for sensitivity, specificity, positive predictive value and negative predictive value, where available. Eight of the survey questions used in this study were gathered from this systematic review. Of those, 5 were chosen to be the questions to determine a subject's positive or negative periodontal disease status. Two questions were based on information from the New Mexico Oral Health Surveillance System Annual Report 2006.[47] The exact questions used in this study, rational for inclusion, validation results and source can be seen in Table 3, Survey Questions, Rational and Validity. The five questions used in this study to assess presence of periodontal disease (question 5-9)

were found to have high validity when checked with a clinical examination by the systematic review.

Table 3. Survey Questions, Rationale and Validity

		Rational	Clinical Gold Standards	Results	Source
1	Do you have any natural teeth?	Dentate/Edentulous			self
2	If you have lost teeth was it due to gum disease/periodontal disease?	Idetify toothloss from Periodontal Disease			New Mexico Oral Health Surveillance System, Annual Report 2006
3	Do you currently smoke or use tobacco products?	Eliminate Cofounding Variable			self
4	Do you regularly at least once a year see a dental provider?	Assessment of Dental Need			New Mexico Oral Health Surveillance System, Annual Report 2006
5	Do you think you have gum disease?	Periodontal Disease	Any pockets > 4 mm Any teeth with horizontal mobility > 0.2 mm	SN=32%,SP=93% SN=26%, SP=91%	B. Blicher, K. Joshipura, and P. Eke. Validation of Self-reported Periodontal Disease: A Systematic Review. J DENT RES October 2005 84: 881-890
6	Has a dentist/hygienist told you that you have deep pockets?	Professional Diagnosis of Periodontal Disease	# of pockets > 4 mm (cut-off > 8 pockets for ages 20-29 & 50-59, > 10 pockets for ages 75-84)	SN = 55%, SP = 90%, PV+ = 77%, PV- = 75%	
7	Has a dentist/hygienist told you that you have gum disease?		Any pockets > 4 mm Any teeth with horizontal mobility > 0.2 mm	SN = 32%, SP = 94% SN=29%, SP=94%	
8	Do you think you can see more of the roots of your teeth in the past?	Recession	Any pockets > 4 mm Any teeth with horizontal mobility > 0.2 mm	SN = 54%, SP = 76% SN = 54%, SP = 78%	
9	Do you think your teeth have moved position?	Migrating teeth	Any pockets > 4 mm Any teeth with horizontal mobility > 0.2 mm	SN=18%,SP=83% SN=39%,SP=93%	
10	Have your gums bled recently?	Gingivitis	> 40% sites bleed	SN=35%,SP=88%	
11	Have you ever been told that you need periodontal or gum treatment?	Periodontal Treatment	Above median % of sites with radiographic bone loss > 20% > 4 teeth with radiographic bone loss > 40%	SN=47%,SP=68% SN=65%,SP=64%	
12	Are you aware of currently being treated for gum disease?		Any pockets > 4 mm Any teeth with horizontal mobility > 0.2 mm	SN=17%,SP=100% SN=13%,SP=99%	

When comparing the data from NHANES to this pilot study it is surprising that the percentage of those with periodontal disease in the population of RA patients was 15% lower. The percentage of subjects with periodontal disease was initially assumed to have been equivalent or higher given the nature of the relationship that exists between autoimmune disease and periodontal disease. [56]

However, upon closer examination of the study results the estimation of PD in the cohort may be underestimate by as much as 33% based on the sensitivity and specificity of PD self-report questionnaires. In 2013, Eke, DDS, reported a sensitivity of 88% and a specificity of 45% for gold standard examination versus self-reported incidence of PD [53] Thus, given the specificity of the questions used in this study, it can be inferred that those who have RA and PD could potential be as great as 30/42 subjects, RR=71%. Likewise the prevalence of PD risk in the RA cohort could be as low as 38% (see Figure 15).

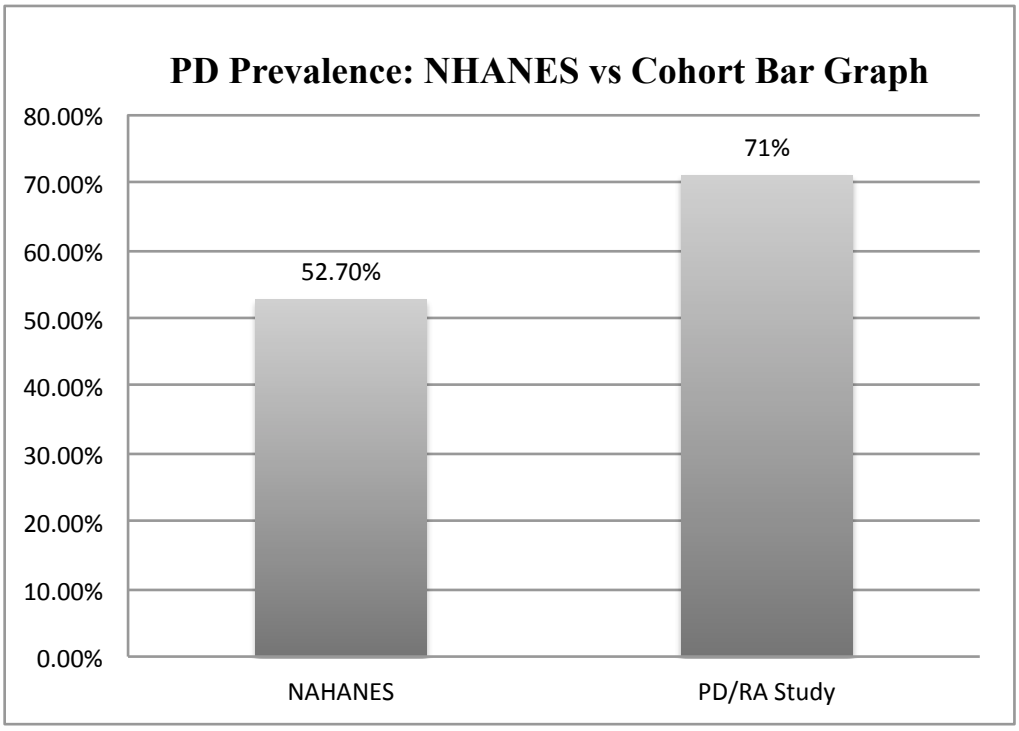

Figure 15. PD Prevalence: NHANES vs Cohort

The null hypothesis: there is no significant difference of prevalence of periodontal disease in a group of rheumatoid arthritis patients as compared with the population as reported by NHANES measured by a validated self assessment questionnaire, was initially accepted as true. This is based on the strict study boundaries, but when reevaluated taking sensitivity and specificity of the test into account the null hypothesis is rejected. This is based on the acknowledgment of the sensitivity and specificity of the test. The relative risk range for PD being between 38%-71% in this cohort is potentially 20% greater than the general population in New Mexico and is one that merits further evaluation using the gold standard periodontal examination.

Study demographics: The response to mailed surveys exceeded expectation at 61% which amounted to about half of the total subjects recruited. However, 95% approached during their in-office appointments consented to participate. Therefore, it is preferable (whenever possible) to have face to face contact with potential subjects as the preferred method for recruitment. The female to male ratio is estimated to be 6:1 which is twice the ratio given in the literate review of this paper. [55] Both genders show more individuals in the "health" category as opposed to disease category; however, females are slightly more likely to have disease status. This is not surprising since the total amount of females far exceeded that of males and the likelihood of PD is greater amongst that group. Also, not surprising is the greatest RA incidence is seen in the 55-64 age group followed by 65-79 age group, since the most likely time of RA disease onset is during the fifth or sixth decade of life.[55,63] In addition, the time in which PD is greater than health is the oldest age group which isn't surprising since PD is cumulative over time and is more evident in later years.[57]

Study population: The study boundaries limited those with PD status to 11 subjects. However, the decision to include the additional 5 subjects into the disease group was to acknowledge that periodontal disease as a chronic disease process that does not have a cure. If a subject positively answered that they have had missing teeth due to gum disease but didn't meet the 3 out of 5 questions, it is recognized that there has been periodontal disease present. This is assuming that PD is a comorbidity with RA.

The second null hypothesis tested was: There is no significant difference of periodontal disease prevalence in those with severe RA disease activity as compared to

those with without periodontal disease with a severe RA disease activity. This has been accepted. The chi-square analysis revealed a p-value greater than .05 so the data is not statistically significant meaning that a relationship is not present. There is no clear dose response curve. No clear interpretation or conclusions can be drawn from the prevalence of PD and RA activity. A larger sample size may reveal more distinction or associations.

Other variables: It was assumed that there would be a relationship between those having periodontal disease and increased inflammatory markers. However, the box plot graphs and p-values show that there is no statistical significance in the difference between PD and H groups when it comes to evaluating CCP, RF, CCP or ESR. This could indicate that medications are confounding variables in PD subjects but p-values also showed no significant relationship in the medication status of Methotrexate and Prednisone with PD. The small sample size and the likelihood of skewed data may have contributed to the lack of statistical significance in the other variables and in future studies with larger sample size a more accurate reflection of the population is likely.

Conclusion

Clinical Implications: A potentially higher prevalence of PD exists in the RA population as compared to the general population in New Mexico. This stresses the importance of identifying PD in an at-risk population like RA. Already being aware of associations of PD with other systemic diseases like cardiovascular disease and diabetes, adding RA to that category is recommended. It would be prudent of oral health care providers to be vigilant in identifying PD early and treating existing PD.

Acquiring accurate initial medical histories and regular maintenance of them can aid dentist and hygienist in RA identification in patients thus increasing the opportunities for patients to be educated on prevalence of PD in RA population. RA patients could also be educated on current studies and literature reviews of evidence supporting reducing general systemic inflammation over long-term to promote beneficial effects on the clinical activity of PD and RA. Doing so will likely improve patient acceptance of periodontal treatment if indicated.

Using a validated survey questionnaire was vital to this pilot study to anticipate usefulness of future studies as the prevalence of PD is determined to be between 38%-71% in the cohort. However, with future studies these biases can be accounted for and controlled with a stronger study design. Taking into account the range of prevalence of disease as well as the literature review regarding associations between RA and PD; inflammation, autoimmunity, chronic destructiveness of unmaintained disease activity, it is inferred that reducing the systemic presence of inflammation, such as that caused by periodontitis may have long-term beneficial effects on the clinical activity of RA but this hypothesis should be investigated in future studies.[60,61]

Chapter 5

Article for Submission International Journal of Dental Hygiene

Periodontal Disease and Rheumatoid Arthritis

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Key Words

Periodontal Disease, Rheumatoid Arthritis, Prevalence, Retrospective Studies, Pilot Projects, New Mexico, Humans, Nutrition Survey, Peptides

Abstract

Objective: A Retrospective cohort pilot-study of periodontal disease (PD) prevalence in rheumatoid arthritis (RA). The objective is to evaluate prevalence of PD in cohort of RA subjects for DAS28 score, rheumatoid factor (RF), erythrocyte-sedimentation rate (ESR), C-Reactive Protein (CRP), and anti-cyclic-citrullinated-peptide antibody (CCP)

Methods: Rheumatoid arthritis patients at University of New Mexico completing a 12-question survey with validated questions for PD. The purpose is to evaluate prevalence of PD in the cohort as well as identify influencing factors of disease activity including DAS28 score, RF, ESR, CRP, use of medications Methotrexate and Prednisone.

Results: PD was present in 16/42 (RR=38%, CI95% (24, 54) compared to New Mexico NHANES data (53.7%, CI95, 52.3, 52.60). The DAS28 score of RA disease activity showed not statistical significance between PD and Healthy subjects (x^2=1.909, p(.05)=.5915). Other variables RF, CCP, ESR, CRP and the medications methotrexate and prednisone showed no statistical association with PD. (RF p=.24, CCP p=.24, ESR p=.74, CRP p=.28, Methotrexate (p=0.81) and Prednisone (p=0.75)).

Conclusions: The retrospective design of the study gathered a recent disease activity for RA and is measured against an unknown current disease activity for PD. Validated survey questions show PD prevalence to be between 38%-71%, which is significant when related to the NHANES comparison at 52.7%. This pilot study was important to anticipate usefulness of future studies but prospective studies are needed to reveal PD association with RA as this study determined no statistical significance between the other variables (DAS28, RF, CCP, ESR, CRP, methotrexate and prednisone) and PD presence.

Clinical Relevance

Scientific Rational; Diseases characteristics involving long-term chronic inflammation are often destructive to hard and soft tissues. Multiple inflammatory sources like Periodontal Disease (PD) with Rheumatoid Arthritis (RA) can increase potential negative outcomes.

Principle finding; This pilot study revealed prevalence of PD in an RA population in New Mexico ranging from 38%-71%. This is above NHANES 2016 prevalence of 52.7%.[54] No statistical significance was determined within RA disease activity or other associations (RF, CCP, ESR, CRP, methotrexate, prednisone).

Practical implications; Identifying PD risk in RA population increases awareness for seeking PD treatment, leading to increase potential positive outcomes for PD/RA maintenance.

Introduction

Diseases characteristics that exhibit chronic inflammation over extended periods of time have shown to have varying degrees of destruction on adjacent hard and soft tissues of the body. While the variability and extent of destruction is dependent on many factors, multiple inflammatory sources can increase potential negative outcomes. Periodontal Disease (PD) and Rheumatoid Arthritis (RA) are two diseases that may have a relationship in this manner. While PD pathogenesis is mainly reliant on localized bacterial agents, its destructiveness of the periodontium can be contributed to chronic inflammation.[42] In contrast, RA is classified as an autoimmune disease but is similar to PD in that the joint destructiveness can be contributed to chronic inflammation.[35] The diseases and their relation to the humoral response, which

can both result in adjacent bone and tissue damage in the disease sites, makes this a relationship that warrants further evaluation. Therefore an evaluation of the presence of PD in a population of RA patients, given different RA disease activity levels and inflammatory markers may shed light on a relationship.[6, 7] Identifying prevalence of PD in populations increases awareness of incidence for providers and diagnosed individuals. Improved understanding of the importance of PD treatment in populations at greatest risk merits increased research in associations that could improve potential PD/RA positive outcomes.

Study Population and Methodology

The cohort consisted of those diagnosed with rheumatoid arthritis recruited from the University of New Mexico Hospital, Department of Internal Medicine, Rheumatoid Arthritis Clinic. The study design was a retrospective cohort of RA patients who have PD as determined by a 12 'yes' or 'no' questionnaire of validated PD identifiers. The first layer of recruitment was performed by the standard of care physician through a chart screening of current patients of record for eligibility. Criteria for eligibility were; must be a patient of record at UNMH Rheumatology clinic, have a clinical diagnosis for RA with a DAS28 score, older than 30years of age, non-smoker and females not pregnant. Once gathered, that sample consisted of participants with varying degrees of rheumatoid arthritis severity, male and female participants of various ages living in the Albuquerque, New Mexico metropolitan or surrounding areas. The recruitment period and the study period happened simultaneously.

Study approval was received from the University of New Mexico Institutional Review Board, Human Resource Protections Office. The standard of care doctor was the

sole recruitment source. He evaluated the patients under his care that met the above-mentioned criteria and once eligibility was determined, the potential subjects were contacted by either two methods 1) in-office at the subjects previously scheduled appointments or 2) through mail. After receiving and study packet through mail completing and returning the survey indicated that the subject consented to participate; however, if contacted by in person a combined consent/HIPAA was necessary.

Survey information was matched with the subject's health information such as name, date of birth, medications list, DAS28 score and other disease identifiers (RF, CCP, ESR, CRP). Survey questions for disease were gathered from a systematic review of validated self-reported periodontal disease questionnaire as well as the New Mexico Oral Health Surveillance System 2006. The survey itself was analyzed and given a periodontal disease (D) status or healthy (H) status based on positive answers to 3 of 5 specifically chosen validated questions. [46,47]

Results

There were 60 potential study participants contacted. Of those, 24 were contacted while attending office appointments with 23 consenting to participate yielding a 95% response rate. A total of 36 were contacted by mail and 22 consented to participate; yielding a 61% response rate. Therefore, there were 45 total subjects agreeing to participate presenting in a 75% overall acceptance rate. There were three ineligible subjects due to positive answers to survey question #3 ("Do you currently smoke or use tobacco products?"). Consequently, the total study participants numbered 42. The largest age group was between 55-64 consisting of 17 subjects, followed by age group 65-79 equaling 12 subjects. The age groups 30-44 and 45-54

consisted of 7 and 6 subjects respectively. The amount of subjects that reports seeing a dental provider at lest once a year amount to 33/42 yielding 78%. The participants were predominantly female with a 6:1 ratio. Of the total 42 subjects 36 (86%) were female and 6 (14%) were male.

Of the total participants, 11 were found to have PD with a Relative risk (RR=26.1%) this is based on the strict application of the study boundaries. Inclusion of 5 additional subjects in the PD category following review of positive answers to questions number 2 ("if you have lost teeth was it due to gum disease/periodontal disease?") yielded an actual total of 16 subjects or RR=38% with a $CI_{95\%}$ (.24, .54) for periodontal disease classification. The NHANES study founded, 52.79%, ($CI_{95\%}$, 52.60, 52.97) of the population were positive for PD representing 15% fewer cases of PD.

However, upon closer examination of the study results the estimation of PD in the cohort may be underestimate by as much as 33% based on the sensitivity and specificity of PD self-report questionnaires. In 2013, Eke, DDS, reported a sensitivity of 88% and a specificity of 45% for gold standard examination versus self-reported incidence of PD [53] Thus, given the specificity of the questions used in this study, it can be inferred that those who have RA and PD could potential be as great as 30/42 subjects, RR=71%. Likewise the prevalence of PD risk in the RA cohort could be as low as 38% (see Figure 1).

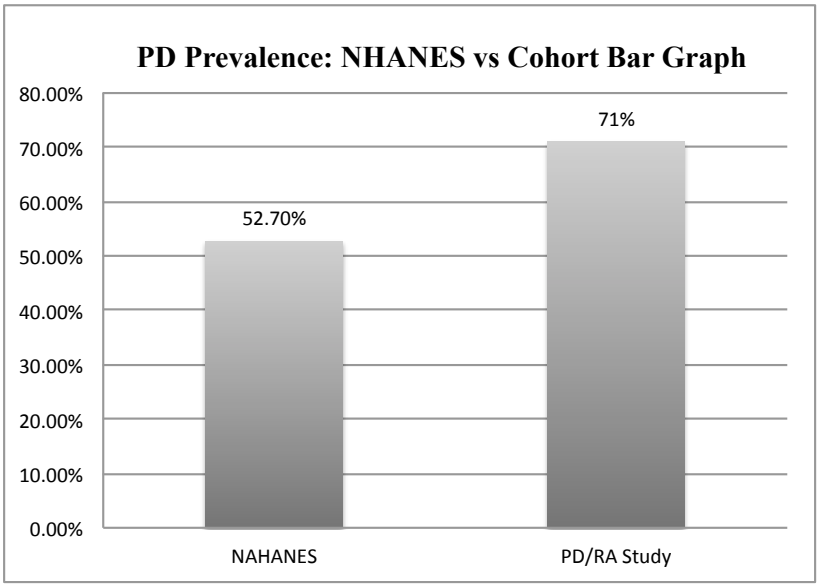

Figure 1. PD Prevalence: NHANES vs Cohort

The cohort of 42 subjects was further categorized into healthy subjects, 26, and disease subjects, 16, then categorized into levels of RA disease activity for quantity of subjects (Healthy, R=6, L=6, M=68, H=6, Disease R=5, L=5, M=2, H=4) and relative risk was then calculated (see Table 1). A graphical representation of this data in a side-by-side bar chart shows the relative risk associated with the healthy and disease groups categorized by RA disease activity (see Figure 2). The RR of PD by RA disease activity was than analyzed for goodness of fit using Chi square (x^2) test and determined to be 1.909, p-value (p,0.5) calculated at 0.59150719 with degree of freedom at 3 (n-1) This shows no statistical significance.

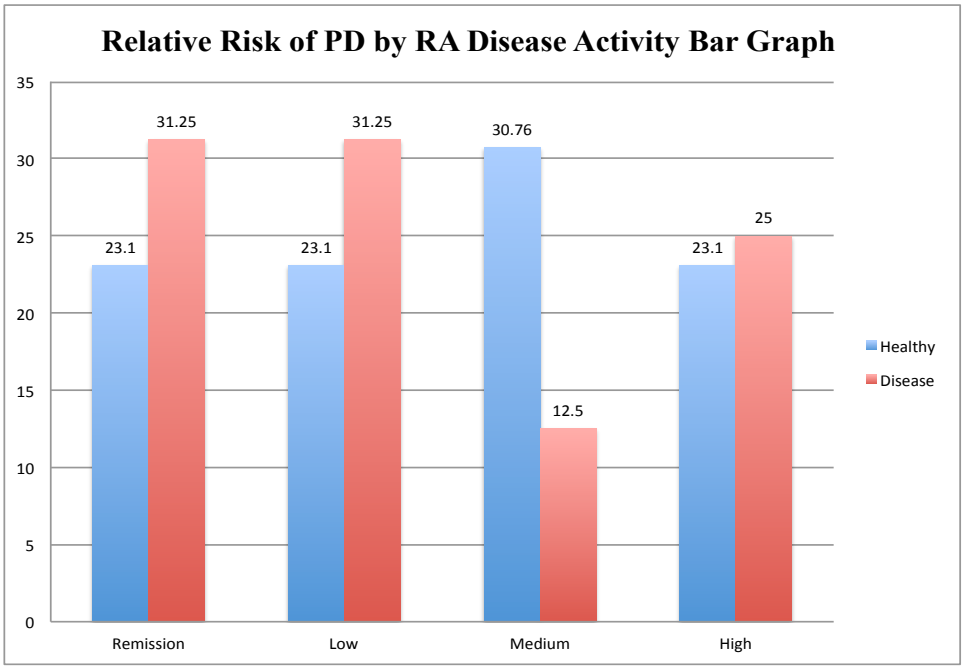

Figure 2. Relative Risk of PD by RA Disease Activity

The other variables of C-Reactive Protein (CRP), Rheumatoid Factor (RF), Cyclic Citrullinated Peptide (CCP), Erythrocyte Sedimentation Rate (ESR), and medications (Methotrexate, Prednisone) were collected and evaluated for a possible relationship with periodontal disease. Due to the small sample size and potential for skewed data the T-tests analysis, adjusted for false discovery, rate was used but showed no statistical significant (RF p=0.24, CCP p=0.24, ESR p=0.74, CRP p=0.28). Two significant medications, Methotrexate and Prednisone were also evaluated for a relationship with PD. The p-values from a Pearson $\chi 2$ regression show no statistical significance for Methotrexate (p=0.81207) or Prednisone (p=0.75438).

Discussion

A significant limitation of the study is the lack of a clinical component to assess presence of periodontal disease. Self reported survey design relies solely on the

subject's ability to accurately remember or have observed occurrence of behavior and the ability to accurately answer the questions. This makes retrospective studies such as this susceptible to recall bias and thus could have resulted in wrongly assigning PD to subjects. Relying on a subject's knowledge and understanding of his/her own periodontal disease status may or may not be the same as clinical findings would determine and generally underestimate the incidence of PD.[46] However it is an acceptable means of assessment when doing epidemiological study at low cost and did facilitate the purpose of this particular study. Future studies should also control for diabetic status as both smoking and diabetes are significant risk factors for PD development.[58,59]

The 2016 NHANES statistic for predicting periodontitis by state was used as comparison for the results of this study and was though to have specific application to the local population. Studies done before 2009 by NHANES were found to be low in their estimation of prevalence of disease due to only using select teeth or partial-mouth clinical examinations.[45] Since 2009, the gold standard full mouth periodontal evaluation has been used along with a validated self-reported questionnaire.

Survey: Given the limitations of this pilot study a significant effort was made to ensure validity of the survey questions, since no clinical component would be utilized. The questions were gathered from a systematic review of validated self-reported periodontal disease questions authored by Paul Eke DDS, who also developed the NHANES surveillance studies used as the comparisson.[46] The study boundaries limited those with PD status to 11 subjects. However, the decision to include the additional 5 subjects into the disease group was to acknowledge that periodontal disease as a

chronic disease process that does not have a cure. If a subject positively answered that they have had missing teeth due to gum disease but didn't meet the 3 out of 5 questions, it is recognized that there has been periodontal disease present. This is assuming that PD is comorbidity with RA. Based on the acknowledgment of the sensitivity and specificity of the test, the relative risk range for PD being between 38%-71% in this cohort is potentially 20% greater than the general population in New Mexico and is one that merits further evaluation using the gold standard periodontal examination.

No clear interpretation or conclusions can be drawn from the prevalence of PD and RA activity CCP, RF, CCP or ESR, methotrexate or prednisone since there is no statistical significance in the data. A larger sample size may reveal more distinction or associations.

Conclusion

Using a validated survey questionnaire was vital to this pilot study to anticipate usefulness of future studies as the prevalence of PD is determined to be between 38%-71% in the cohort. However, with future studies these biases can be accounted for and controlled with a stronger study design. Taking into account the range of prevalence of disease as well as the literature review regarding associations between RA and PD; inflammation, autoimmunity, chronic destructiveness of unmaintained disease activity, it is inferred that reducing the systemic presence of inflammation, such as that caused by periodontitis may have long-term beneficial effects on the clinical activity of RA but this hypothesis should be investigated in future studies.[60,61]

Acknowledgements

I would like to acknowledge Professor Christine Nathe RDH, MS and Dr. Wilmer Sibbitt MD for their study oversight and participations as well as the physicians and staff at the UNM Rheumatology Department. I acknowledge the work of John Pesko for contributing the statistical analysis.

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Appendices

Appendix A

Human Research Protections Office Approval Letter

UNM HEALTH SCIENCES CENTER

Human Research Review Committee
Human Research Protections Office

October 20, 2015

Christine Nathe, RDH, MS
CNathe@salud.unm.edu

Dear Christine Nathe:

On 10/14/2015, the HRRC reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	Periodontal Disease and Rheumatoid Arthritis; An evaluation of dental disease and Rheumatoid Arthritis severity through a self- reported survey
Investigator:	Christine Nathe, RDH, MS
Study ID:	15-492
Submission ID:	15-492
IND, IDE, or HDE:	None
Submission Summary:	Initial Study - Prevalence of Periodontal disease in classifications of Rheumatoid Arthritis Patients
Documents Approved:	503 Protocol v08/25/2015 Consent form given in clinic v08/23/2015 Consent form first mailer v08/23/2015 Consent form phone v08/23/2015 Recruitment materials submitted 08/25/2015 Recruitment script for us in RA clinic by co-investigator Phone scripts by Dr. Sibbitt phone scripts by co investigator Survey Questions submitted 09/15/2015
Review Category:	Expedited: Categories (7)(b) Social science methods(5) Data, documents, records, or specimens
Determinations/Waivers:	Requires a signed consent form Waiver of Written Documentation of Consent for mail/phone contact HIPAA Authorization on record; signed HIPAA required Consent and HIPAA included in same document

Submission Approval
Date: 10/14/2015
Approval End Date: 10/13/2016
Effective Date: 10/14/2015

The HRRC approved the study from 10/14/2015 to 10/13/2016 inclusive. If modifications were required to secure approval, the effective date will be later than the approval date. The "Effective Date" 10/14/2015 is the date the HRRC approved your modifications and, in all cases, represents the date study activities may begin.

Before 10/13/2016 or within 45 days of study closure, whichever is earlier, you are required to submit a continuing review. You may submit a continuing review by navigating to the active study and clicking the "Create Modification / CR" button.

Please use the consent documents that were approved and stamped by the HRRC. The stamped and approved consents are available for your retrieval in the "Documents" tab of the parent study.

This determination applies only to the activities described in this submission and does not apply should you make any changes to these documents. If changes are being considered and there are questions about whether HRRC review is needed, please submit a study modification to the HRRC for a determination. A change in the research may disqualify this research from the current review category. You can create a modification by clicking Create Modification / CR within the study.

In conducting this study, you are required to follow the Investigator Manual dated April 1, 2015 (HRP-103), which can be found by navigating to the IRB Library.

Sincerely,

Stephen Lu, MD
HRRC Chair

Appendix B

Recruitment Script for Those Approached in Clinic

Script for use when in approaching potential subject in clinic

My name is Co-Investigator, (*Followed by their identification and qualifications) Ex: I am a graduate student in the Dental Hygiene department at the University of New Mexico and interning in the Rheumatoid Arthritis Department under the supervision of Dr. Sibbitt*

A study is being conducted between the dental hygiene department and the Rheumatology department, under the direction of Dr. Sibbitt (co-Investigator and standard of care doctor) *to identify a correlation between dental disease and rheumatoid arthritis disease.*

The study consists of 12 "yes" or "no" survey question about your dental health. And will only take about 5 minuets of your time.

Would you be interested in participating?

If yes:

This is the consent form: The information from your survey will remain confidential. The goal of the study will be to identify the dental health status of patients of varying types of Rheumatoid arthritis severity, so there will be an access by Dr. Sibbitt (co-Investigator and standard of care doctor) to your medical information such as: name, date of birth, RA disease severity measurements and medication list. Then anonymously put into a database to be evaluated.

Your personal information will not be shared with anyone beyond the university approved study investigators and your rights are protected under the Humans Research Protection Office.
This consent form which will grant access to your personal information to be included in the study analysis. The reason for this is to evaluate your personal dental status and correlate it to your RA status but if you do not grant us access to that information your survey information will remain anonymous and will only be included as part of the general disease status of the surveyed population.

Your information will not be shared with anyone and will not be included in the study results and you will not be identified.

I will give you a few minuets to read through and will be available for questions you may have

Appendix C

Consent/HIPPA Form Used for Subjects Approached in Clinic

The University of New Mexico Health Sciences Center
Consent to Participate in Research

Periodontal Disease and Rheumatoid Arthritis; An evaluation of dental disease and Rheumatoid Arthritis severity through a self- reported survey

*****Consent form for those approached within the clinic*****

Purpose and General Information
You are being asked to participate in a research study that is being done by, Christine Nathe, RDH, MS, who is the Principal Investigator, and Melissa Barbara RDH, BS, from the department of Dental Hygiene, as well as Dr. Wilmer Sibbitt MD from the department of Rheumatology. This research is being done to study periodontal disease in a population of rheumatoid Arthritis patients. You are being asked to participate because you have met the study criteria for selection. Approximately 100-200 participants locally will take part in this study at the University of New Mexico Rheumatology Clinic.

Your participation will involve answering survey questions. The survey should take about 5-7 minutes to complete. Your involvement in the study is voluntary, and you may choose not to participate.
This form will explain the study to you, including the possible risks as well as the possible benefits of participating. This is so you can make an informed choice about whether or not to participate in this study. Please read this Consent Form carefully. Ask the investigators or study staff to explain any words or information that you do not clearly understand.

What will happen if I participate?
If you agree to be in this study, you will be asked to read and completed the short survey about your dental health. After you participate in the study survey:
-The surveys will be stored in a locked area within the Rheumatoid Arthritis clinic until the completion of the study
-Upon completion of the study period the surveys will be crossed matched by an approved study investigator with your health information such as rheumatoid disease status and medications.
-This information will then be anonymously stored in an encrypted device for data evaluation.

What are the possible risks or discomforts of being in this study?
Every effort will be made to protect the information you give us. However, there is a small risk of loss of privacy and/or confidentiality this may result in stigmatization or hardship. Other risks experience by some may be stress or emotional distress by answering questions about one's dental health.

How will my information be kept confidential?
Your name and other identifying information will be maintained in locked files, available only to authorized members of the research team, for the duration of the study. For information entered into a computer, the only identifier will be a unique study identification (ID) number. Any personal identifying information and any record linking that information to study ID numbers will be destroyed when the study is completed. Information resulting from this study will be used for research purposes and may be published; however, you will not be identified by name in any publications.

Information from your participation in this study may be reviewed by federal and state regulatory agencies, and by the UNM Human Research Review Committee (HRRC) which provides regulatory and ethical oversight of human research. There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study.

What are the benefits to being in this study?
There may or may not be direct benefit to you from being in this study. However, Your participation in the study will primarily help your Rheumatologist gather the dental demographics on their patient base and in doing so can help identify their dental needs. To better care for our patients, professionals in different medical fields understand that our patients are complex and possess many different medical conditions. Working together to understand how our individual fields of study can improve patient outcomes is important. Therefore, a main benefit to participating in the study is to help your Dental Hygiene Profession and your Rheumatologist identify the dental needs specifically in rheumatology.

What other choices do I have if I don't participate?
Taking part in this study is voluntary so you can choose not to participate.

Will I be paid for taking part in this study?
There will be no compensation for participating in this study.

How will I know if you learn something new that may change my mind about participating?
You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from your participation in the research or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?
Yes. You can choose not participate in this study or ask that your provided information not be considered for the study at any time without affecting your treatment at the Rheumatoid Arthritis clinic or access to care.

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, if you do not follow study procedures, or if it is in your best interest or the study's best interest to stop your participation.

HIPAA Authorization for Use of Your Protected Health Information (HIPAA)
As part of this study, we will be collecting health information about you. This information is "protected" because it is identifiable or "linked" to you.

Protected Health Information (PHI)
By completing and returning that survey, you are allowing the investigators and other authorized personnel to use your protected health information for the purposes of this study. This information may include: name, date of birth, specific Rheumatoid disease severity measurement(s), medical history and medications list.

In addition to researchers and staff at UNMHSC and other groups listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be

protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

Right to Withdraw Your Authorization
Your authorization for the use of your health information for this study shall not expire unless you cancel this authorization. Your health information will be used as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM investigators in writing. To do this, please send a letter notifying them of your with drawl to:

Christine Nathe, RDH, MS
Co-Inv: Melissa Barbara RDH, BS
MSC 09 5020
1 University of New Mexico
Albuquerque New Mexico 87131

Please be aware that the research team will not be required to destroy or retrieve any of your health information that has already been used or shared before your withdrawal is received.

Refusal to Sign
If you choose not to complete the written or telephone survey, authorization for the use of your PHI, you will not be allowed to take part in the research study with inclusion of your Protected health information. But your completed survey information will be used anonymously to identify gum disease presence as part of the whole Rheumatoid arthritis population study base.

What if I have questions or complaints about this study?
If you have any questions, concerns or complaints at any time about the research study, Christine Nathe RDH, MS or her associate Melissa Barbara RDH, BS, will be glad to answer them at 915.256-5053 M, W, F 8:00-5:00. If you would like to speak with someone other than the research team, you may call the Human Research Review Committee (HRRC) at (505) 272-1129. The HRRC is a group of people from UNMHSC and the community who provide independent oversight of safety and ethical issues related to research involving human participants.

What are my rights as a research participant?
If you have questions regarding your rights as a research participant, you may call the Human Research Protections Office (HRPO) at (505) 272-1129 or visit the HRPO website at http://hsc.unm.edu/som/research/hrrc/.

Consent and Authorization
You are making a decision whether to participate in this study. Your signature below indicates you read the information provided. By signing this consent form, you are not waiving any of your legal rights as a research participant. You will also agree to give permission for my health information to be used as described in this consent form.

I have had an opportunity to ask questions and all questions have been answered to my satisfaction. By signing this consent form, I agree to participate in this study. A copy of this consent form will be provided to you if you would like one.

Name of Adult Subject (print) Signature of Adult Subject Date

INVESTIGATOR SIGNATURE

I have explained the research to the participant and answered all of his/her questions. I believe that he/she understands the information described in this consent form and freely consents to participate.

Name of Investigator/ Research Team Member (print)

(Signature of Investigator/ Research Team Member) Date

Appendix D

Consent/HIPPA Form Used for Subject Mailed

The University of New Mexico Health Sciences Center
Consent to Participate in Research

Periodontal Disease and Rheumatoid Arthritis; An evaluation of dental disease and Rheumatoid Arthritis severity through a self- reported survey

*****You are receiving this form because you have expressed interest in the study by a phone conversation with your rheumatologist. This form explains the study methods, your rights and involvement as a study participant. Participation in this study also requires access to your health information in the ways stated in this form.**

Please read the following consent form and if you consent to participation, complete the enclosed survey and return to the rheumatoid arthritis clinic within the enclosed self-addressed envelop:

DOIM/ Rheumatology
PD/RA study
1 University of New Mexico MSC 10-5550
Albuquerque, NM 87131-00001

Purpose and General Information
You are being asked to participate in a research study that is being done by, Christine Nathe, RDH, MS, who is the Principal Investigator, and Melissa Barbara RDH, BS, from the department of Dental Hygiene, as well as Dr. Wilmer Sibbitt MD from the department of Rheumatology. This research is being done to study periodontal disease in a population of rheumatoid Arthritis patients. You are being asked to participate because you have met the study criteria for selection. Approximately 100-200 participants locally will take part in this study at the University of New Mexico Rheumatology Clinic.

Your participation will involve answering survey questions. The survey should take about 5-7 minutes to complete. Your involvement in the study is voluntary, and you may choose not to participate.
This form will explain the study to you, including the possible risks as well as the possible benefits of participating. This is so you can make an informed choice about whether or not to participate in this study. Please read this Consent Form carefully. Ask the investigators or study staff to explain any words or information that you do not clearly understand.

What will happen if I participate?
If you agree to be in this study, you will be asked to read and completed the short survey about your dental health, which is enclosed within this envelope and return inside the self-address envelope to a mailbox that will be received at the Rheumatoid Arthritis clinic. Approximately 2-3 weeks after the mailers have been sent out, an option to participate via telephone by one of the investigators of the study will be made to those whoses surveys were not received but a consent form will still need to be completed and returned to the clinic. After you participate in the study survey:
-The mailed in surveys as well as those surveys completed via phone will be stored in a locked area within the Rheumatoid Arthritis clinic until the completion of the study
-Upon completion of the study period the surveys will be crossed matched by an approved study investigator with your health information such as rheumatoid disease status and medications.
-This information will then be anonymously stored in an encrypted device for data evaluation.

What are the possible risks or discomforts of being in this study?
Every effort will be made to protect the information you give us. However, there is a small risk of loss of privacy and/or confidentiality this may result in stigmatization or hardship. Other risks experience by some may be stress or emotional distress by answering questions about one's dental health.

How will my information be kept confidential?
Your name and other identifying information will be maintained in locked files, available only to authorized members of the research team, for the duration of the study. For information entered into a computer, the only identifier will be a unique study identification (ID) number. Any personal identifying information and any record linking that information to study ID numbers will be destroyed when the study is completed. Information resulting from this study will be used for research purposes and may be published; however, you will not be identified by name in any publications.

Information from your participation in this study may be reviewed by federal and state regulatory agencies, and by the UNM Human Research Review Committee (HRRC) which provides regulatory and ethical oversight of human research. There may be times when we are required by law to share your information. However, your name will not be used in any published reports about this study.

What are the benefits to being in this study?
There may or may not be direct benefit to you from being in this study. However, Your participation in the study will primarily help your Rheumatologist gather the dental demographics on their patient base and in doing so can help identify their dental needs. To better care for our patients, professionals in different medical fields understand that our patients are complex and possess many different medical conditions. Working together to understand how our individual fields of study can improve patient outcomes is important. Therefore, a main benefit to participating in the study is to help your Dental Hygiene Profession and your Rheumatologist identify the dental needs specifically in rheumatology.

What other choices do I have if I don't participate?
Taking part in this study is voluntary so you can choose not to participate.

Will I be paid for taking part in this study?
There will be no compensation for participating in this study.

How will I know if you learn something new that may change my mind about participating?
You will be informed of any significant new findings that become available during the course of the study, such as changes in the risks or benefits resulting from your participation in the research or new alternatives to participation that might change your mind about participating.

Can I stop being in the study once I begin?
Yes. You can choose not participate in this study or ask that your provided information not be considered for the study at any time without affecting your treatment at the Rheumatoid Arthritis clinic or access to care.

The investigators have the right to end your participation in this study if they determine that you no longer qualify to take part, if you do not follow study procedures, or if it is in your best interest or the study's best interest to stop your participation.

HIPAA Authorization for Use of Your Protected Health Information (HIPAA)

As part of this study, we will be collecting health information about you. This information is "protected" because it is identifiable or "linked" to you.

Protected Health Information (PHI)

By completing and returning that survey, you are allowing the investigators and other authorized personnel to use your protected health information for the purposes of this study. This information may include: name, date of birth, specific Rheumatoid disease severity measurement(s), medical history and medications list.

In addition to researchers and staff at UNMHSC and other groups listed in this form, there is a chance that your health information may be shared (re-disclosed) outside of the research study and no longer be protected by federal privacy laws. Examples of this include disclosures for law enforcement, judicial proceeding, health oversight activities and public health measures.

Right to Withdraw Your Authorization

Your authorization for the use of your health information for this study shall not expire unless you cancel this authorization. Your health information will be used as long as it is needed for this study. However, you may withdraw your authorization at any time provided you notify the UNM investigators in writing. To do this, please send a letter notifying them of your with drawl to:

Christine Nathe, RDH, MS
Co-Inv: Melissa Barbara RDH, BS
MSC 09 5020
1 University of New Mexico
Albuquerque New Mexico 87131

Please be aware that the research team will not be required to destroy or retrieve any of your health information that has already been used or shared before your withdrawal is received.

Refusal to Sign

If you choose not to complete the written or telephone survey, authorization for the use of your PHI, you will not be allowed to take part in the research study.

What if I have questions or complaints about this study?

If you have any questions, concerns or complaints at any time about the research study, Christine Nathe RDH, MS or her associate Melissa Barbara RDH, BS, will be glad to answer them at 915.256-5053 M, W, F 8:00-5:00. If you would like to speak with someone other than the research team, you may call the Human Research Review Committee (HRRC) at (505) 272-1129. The HRRC is a group of people from UNMHSC and the community who provide independent oversight of safety and ethical issues related to research involving human participants.

What are my rights as a research participant?

If you have questions regarding your rights as a research participant, you may call the Human Research Protections Office (HRPO) at (505) 272-1129 or visit the HRPO website at http://hsc.unm.edu/som/research/hrrc/.

Consent and Authorization

You are making a decision whether to participate in this study. Your completion of the survey by mailer or telephone indicates that you consent to participate in the study and you are not waiving any of your legal rights as a research participant. You will also agree to give permission for my health information to be used as described in this consent form.

******After reading this consent to participate form, please completed the enclosed survey and place in the provided self-address envelop and drop in a mailbox to be returned to the rheumatoid arthritis clinic.**

Appendix E

Survey

Survey Questions: ID Number_____

Gender: ☐ Male ☐ Female DOB: [Day/Month/Year] _____

Please answer all the questions:

1. Do you have any natural teeth?
☐Yes ☐No

2.If you have lost teeth, was it due to gum disease/ periodontal disease?
☐Yes ☐No

3. Do you currently smoke or use tobacco products?
☐Yes ☐No

4. Do you regularly (at least once a year) see a dental provider?
☐Yes ☐No

5. Do you think you have gum disease?
☐Yes ☐No

6. Has any dentist/hygienist told you that you have deep pockets?
☐Yes ☐No

7. Have you been told by a dentist/hygienist that you have gum disease?
☐Yes ☐No

8. Do you think you can see more of the roots of teeth than in past?
☐Yes ☐No

9. Do you think your teeth have moved position? Include
☐Yes ☐No

10. Have your gums bled recently?
☐Yes ☐No

11.Have you ever been told that you need periodontal or gum treatment?
☐Yes ☐No

12. Are you aware of currently being treated for gum disease?
☐Yes ☐No

For official use: ☐ Include ☐ Exclude
Recruitment: ☐Mail ☐Phone ☐ Consent ☐ Clinic ☐ Consent

LOC:_____ PD: Y N AGE:____ DAS28:_____ R L M H

MED:_____

☐ ATNF