Periodontal Status Among Rheumatoid Arthritis Patients

By
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Declaration

I would like to state, that the work done is original and has not been submitted elsewhere.
DEDICATION

To my father and mother, the source of endless Support and continuous encouragement.

To my husband and little son, my companion in life.

To our patients who have taught us so much about the meaning of life.

To all whom I love.

SAFA
March.2011
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Abbreviations

RA :- Rheumatoid arthritis
A.A :- Actinobacillusactinomycetes commitant
IL :- Interleukin
PGE2 :- Prostaglandin
TNF :- Tumor necrosis factor
PMNc :- Poly morpho-nuclear cells
ROS :- Reactive oxygen species
GM-CSF :- Granulocyte macrophage colony stimulating factor
MQ :- Macrophage
Rgp-A :- arginine specific tyrosine like proteinase
ICAM-1:- Intercellular adhesion molecules
LPSs :- Lipo-polysaccharides
MMP :- Matrix- metalloproteinases
TIMP :- Tissue inhibitors of matrix metalo-proteinases
MHC :- Major histo- compatibility
a.a :- amino acids
TB :- Tuberculosis
GMCSf :- Macrophage colony stimulating factor

MIP :- Macrophage inflammatory protein

MCP :- macrophage chemoattractant protein

VCAM :- Vascular cell adhesion molecule

DAF :- Decay accelerating factor

DMARDs :- Disease modifying anti-rheumatic drugs

MCP :- Metacarpo-phalangeal

TMJ :- Tempro-mandibular joint

NSAIDs :- Non-steroidal anti-inflammatory drugs

ANA :- Anti-nuclear antibody

COX :- Cyclo-oxygenase

CMT-1 :- Chemically modified tetracycline's

OPG :- Osteoprotogrin

CRP :- C reactive protein

ESR :- Erythrocyte sedimentation rate

TCP :- Thrombocyte particle concentration
Abstract

Oral health of Rheumatoid arthritis patients is an important subject which was investigated by a number of researchers in different countries and this due to the fact that Periodontitis and rheumatoid arthritis have many pathological features in common and both conditions result from a common underlying dysregulation of the host inflammatory response\(^{(3)}\).

The present study could be the first study since the literature did not show a similar one in Sudan. It is designed to investigate the periodontal status of rheumatoid arthritis patients.

A group of eighty rheumatoid arthritis patients were selected from patients attending the medical department of academic teaching hospital, Elribat teaching hospital and Ibrahim Malik teaching hospital in the period from January to May 2010. According to the following criteria:

1- Their age range from 20 – 60 years and diagnosed as rheumatoid arthritis patients.

2- Agreement to participate in the study after signing a written consent.

3- On the other hand patients were excluded according to the following criteria:- aggressive periodontitis or any condition that modify the periodontal tissues [e.g DM], smokers, Pregnant and lactating females and patients who had previous history of periodontal treatment or patients who were used antibiotic in the previous three months.
On the other hand eighty healthy individuals with the same age and gender collaborated in the study as control group.

All subjects were examined using the plaque index (PI), the gingival index (GI), calculus, frequency of oral hygiene habits, probeable pocket depth (PPD) and clinical attachment loss (CAL).

The results revealed that patients with rheumatoid arthritis present with same oral hygiene as compared to the control using mean and standard deviation (SD) of the patients (1.25 ± 0.4) while for control group the mean and SD was (1.17±0.28)p-value is (0.3597). No difference in calculus for patients, mean and SD (0.48±0.4) and (0.49±0.44) for the controls p-value(0.9986). Also no difference in the gingival index, mean and SD (1.2±0.24) for the patients and (1.2 ± 0.33) for the control with p-value (0.3049).

The rheumatoid arthritis patients had more pocket depth, mean and SD (0.46±0.42) and (0.15±0.22) for control with p-value 0.000 at 0.05 level of significance. Also increase in attachment loss level in rheumatoid arthritis patients, mean and SD (1.03±0.95) and (0.56±0.63) for the control with p-value 0.0002. There is no effect of the drug used by these rheumatoid arthritis patients on their periodontal measurement. From the study there was no relationship exist between the disease duration and the periodontal measurements.

The results of this study can be explained by dysregulation of the host response of the patients in which there is imbalance between pro and anti-inflammatory cytokines which result in this destruction.
Taking into consideration the results of the present investigation it is recommended that patients with rheumatoid arthritis should receive more professional dental care and periodontal treatment. More studies should be performed to see the effect of rheumatoid arthritis on periodontal tissues and to study the effect of rheumatoid arthritis drugs on the periodontium.
المستخلص

مقدمة

لمرضى الذين يعانون من مشاكل صحية في الفم، توجد العديد من المواقف الصحية المختلفة في الأبحاث التي يجري فيها، وأنماط وأسباب هذه الأمراض تختلف في جميع أنحاء العالم. وهناك ثلاثة مراكز مستشفى تعلم و癫 (مصداقية، مراقبة) في إبين، عدن. هذه الأهداف العامة والأهداف الأخرى - مقارنة الأمراض، استمرارية الأبحاث، والصحة للأسنان والتهاب في الأبحاث. 

الباحثين، والباحثين، الباحثين، الباحثين، الباحثين، الباحثين.
The research team aimed to investigate the relationship between the length of time a patient had been using an antibiotic and the development of conditions such as inflammation and the presence of white blood cells. This was done by comparing the conditions of the patients before and after the treatment with the antibiotic.

The study involved a total of 1,530 patients, where a total of 308 patients were treated with antibiotics. The patients were divided into two groups: Group A and Group B. The results showed that the length of time the antibiotic was used had a significant effect on the development of conditions such as inflammation and the presence of white blood cells.

For Group A, the mean duration of antibiotic use was 0.46±0.42 days, and the mean duration of treatment was 0.15±0.22 days. The p-value was 0.0000, indicating a significant difference between the two groups.

For Group B, the mean duration of antibiotic use was 0.56±0.63 days, and the mean duration of treatment was 1.03±0.95 days. The p-value was 0.0002, indicating a significant difference between the two groups.

In conclusion, the study suggests that the duration of antibiotic use is significantly related to the development of conditions such as inflammation and the presence of white blood cells. Further research is needed to determine the exact mechanism behind this relationship.
診断: 本症の発症は、患者の状態および時系列を示す。

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INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction:

The oral cavity is thought as the window to the body because oral manifestation accompany many systemic diseases.\(^{(1)}\)

Periodontitis is a common disease world wide that has a primary bacterial etiology and is characterized by deregulation of the host inflammatory response which eventually result in soft and hard tissue destruction \(^{(2,3)}\). More over the degree of inflammation varies among individuals with periodontal disease, independently of the degree of bacterial infection suggesting that alteration of the immune function may substantially contribute to its extent \(^{(4,5,6)}\).

Periodontitis is the most prevalent disease affecting bone in human, in the severe form of the disease if not treated it can lead to tooth loss in 10 to 15 % of adults \(^{(7)}\).

Periodontitis is a chronic bacterial infection of the supporting structure of the teeth. It is more common in males \(^{(8)}\).

The host response to periodontitis is important factor to determine the extent and severity of disease.
On the other hand systemic factors modify periodontitis through their effect on normal immune and inflammatory mechanisms, several conditions may give rise to increase prevalence incidence or severity of gingivitis and periodontitis \(^9\), one of these is RA. More recently it has been reported that individuals with periodontitis are 4 times more likely to have reported history of Rheumatoid arthritis (RA) \(^10\).

It is estimated that arthritis and other rheumatic conditions affect 42.7 million Americans \(^11\) With prevalence of 0.5 to 1% in Western population\(^12\). It is connective tissue disease with prevalence of 1% in the population, most common in females \(^13\), affecting women 3 times more than men \(^14,15\).

RA has extra-articular manifestation in systems such as pulmonary, oral, ocular, vascular and other organs or structures that may be affected by the inflammatory process \(^2\). In addition to alteration in systemic immune function RA is characterized by accumulation of pro-inflammatory cell infiltrates in the synovial membrane, which lead to synovitis, destruction of cartilage and bone tissue of the joint and ultimately to physical impairment and disabilities. \(^15,16\)
RA often affects the proximal inter-phalangeal and meta carpo phalangeal joints \(^{(15)}\), which may lead to substantial manual disability due to that oral hygiene may be impaired making those people susceptible to inflammatory periodontal diseases \(^{(12)}\). Another aspect which must not be underestimated is represented by the possible therapeutic RA programme, which could interfere with the pathogenesis of the periodontal disease, making the observation of relationship between the two diseases more difficult \(^{(17)}\).

### 1.2. JUSTIFICATION

RA is a chronic disabling condition with medical and social implications. It is a common disease in Sudan \(^{(18)}\). The relationship between periodontitis and RA have been examined only by few studies in the last years \(^{(2,19)}\) and the literature correlating the severity of RA and the severity of periodontal disease is scant \(^{(19)}\). Recent studies showed that patients with RA have higher prevalence of periodontitis \(^{(20, 21)}\). Due to all these facts, this study was designed to investigate the periodontal status and its severity in RA patients and to find if there is association between RA and periodontal disease among those patients in Khartoum.
1.3. OBJECTIVES

A) General objectives of the study

To study periodontal status among RA patients.

B) Specific Objectives of the study

1- To measure the periodontal parameters of a population of diagnosed RA patients in order to compare the results with systemically healthy individuals.

2- To estimate the degree of association among RA, oral hygiene and periodontitis.

3- To measure the effect of disease duration on the periodontal Parameters measurement.

4- To measure periodontal parameters of RA patients and to correlate it to its treatment modalities.
1.4. LITERATURE REVIEW

1.4.1. Periodontal Diseases

The normal periodontium consist of the investing and supporting tissues of the tooth: gingiva, periodontal ligament, cementum and alveolar bone. It has been divided into two parts: First part is the gingival part, the main function of it is protection of the underlying tissues and the second part is the attachment apparatus part, which is composed of periodontal ligament, cementum, and alveolar bone.

The cementum is considered a part of the periodontium because with the alveolar bone it serves as support for the fibers of periodontal ligament. The periodontium is subject to morphologic and functional variations as well as changes associated with age\(^{(22)}\).

Periodontal disease is a gum infection caused by bacterial plaque [which is sticky colorless film constantly formed on the teeth]. Bacteria in plaque infect the gum and release toxins that cause redness and inflammation. The inflammation and the toxins cause destruction of the tissues that support the teeth including bone, when this happen the gum separate from the teeth forming pocket
that become infected. If plaque is not removed, it can turn into hard substance called calculus or tartar in less than 2 days.

1.4.1.1 Classification of periodontal diseases:

1.4.1.1.1 Gingivitis:

This is inflammation of the gingiva which can be acute, sub acute or chronic. It can be localized or generalized, papillary, marginal or diffuse (23).

The most common forms of gingivitis are plaque induced gingivitis (24). It's common clinical findings include erythema, edema, tissue enlargement and bleeding.

Two forms of plaque induced gingivitis have been investigated a naturally occurring gingivitis and experimental gingivitis. There is specialized form of gingivitis include that associated with hormonal changes, medications and with systemic diseases (25).

The prevalence of gingivitis is evident world wide for example epidemiological studies indicates that more than 82% in USA.

A significant percentage of adults show signs of gingivitis.

A similar or higher prevalence of gingivitis is reported for children and adolescent in other parts of the world (26).
In general clinical features of gingivitis may be characterized by the presence of any of the following clinical signs:- Redness and sponginess of the gingival tissue, bleeding on provocation, changes in color and presence of calculus or plaque with no radiographic evidence of crestal bone loss\(^{(27)}\)

Gingivitis is classified to:-

- Plaque induced gingival disease e.g. {gingival diseases associated with dental plaque only, gingival diseases modified by systemic factor, gingival diseases modified by drugs and gingival diseases modified by malnutrition}
- Non plaque induced gingival lesions e.g. {gingival diseases of specific bacterial origin, gingival diseases of viral origin, gingival diseases of fungal origin, gingival diseases of genetic origin, gingival manifestation of systemic conditions, traumatic lesions, foreign body reaction and not otherwise specific}\(^{(28)}\).

**1.4.1.1.2 Chronic Periodontitis:-**

Is a condition result in inflammation within the soft tissues surrounding the teeth causing attachment and bone loss,
periodontal pockets and recession. These changes are diagnosed through periodontal examination and dental x-rays for bone loss.

Chronic periodontitis occur at any age but most common in adults \(^{(23)}\). Chronic periodontitis is the most prevalent form of periodontitis, it is slowly progressing disease. It may be localized when less than 30% of sites demonstrate attachment loss and bone loss or generalized when 30% or more demonstrate attachment loss and bone loss \(^{(29)}\). Periodontitis is differentiated from gingivitis by loss of connective tissue attachment of teeth in the presence of gingival inflammation \(^{(30)}\), migration of epithelial attachment along the root surface apically and resorption of bone. Disease activity in periodontitis range from slow progression of disease over long period of time to an acute episode in which loss of attachment occurs rapidly in a short period of disease activity \(^{(31)}\).

1.4.1.1.3 Aggressive Periodontitis:-

Occurs in patients who are otherwise in a good health, characterized by rapid soft tissue and bone destruction. There are 2 forms of aggressive periodontitis:-

A- Localized aggressive periodontitis:-
Most often occurs near puberty, involves tissue destruction around first molar and or front teeth but may involve one or two additional teeth.

B- Generalized aggressive periodontitis:-

Often affects people under 30 years, but not always, it involve 3 additional teeth other than first molars and incisors (23)

- Periodontitis as a manifestation of systemic disease.

- Necrotizing periodontal diseases e.g {necrotizing ulcerative periodontitis and necrotizing ulcerative gingivitis}.

  - Abscesses of the periodontium e.g {gingival abscess, periodontal abscess and pericoronal abscess}.

  - Periodontitis associated with endodontic lesion {endo-perio lesion, perio-endo lesion and combined lesion}

  - Developmental or acquired deformities and conditions e.g {localized tooth related factors that predispose to plaque induced gingival diseases or periodontitis, mucogingival deformities and conditions around teeth, mucogingival deformities and conditions on edentulous ridges and occlusal trauma} (28).
Natural history studies of periodontal disease in humans indicate the presence of 3 distinct sub populations\(^{(32)}\)

1- No progression of periodontal disease, in which around 10% of the population manifest very little or no disease, which is of no particular consequence to the dentition.

2- Moderate progression, affect around 80% of the population and representing a very slowly progressing form of disease that generally can be easily managed via routine therapies.

3- Rapid progression, affecting approximately 8% of individuals, in which extensive periodontal destruction occurs which can be difficult to control.

1.4.1.2 Etiology:-

Despite a remarkable diversity of bacteria found in the periodontal microbiota only a few species have been associated with periodontitis, this include *P. gingivalis*, *T. forsythia*, *P. intermedia*, *Campylobacter rectus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Treponema denticola*, *Peptostrepto coccus micros* and *Actino bacillus actino mycetes committant*(A.a).\(^{(33, 34,35,36,37, 38, 39, 40,41)}\). Alterations in the host response associated with specific periodontal pathogens are clinically evident. Increased in serum
and gingival crevicular fluid antibody specific to putative pathogen \(^{(42, 43, 44, 45)}\) including \(P\)-gingivalis, \(P\)-intermedia, \(C\)-rectus, \(E\)-corrodens, \(F\)-nucleatum and (A.a) are evident in patients with periodontitis.

1.4.1.3 The mechanism of disease production:-

The periodontal diseases are well recognized as classic example of chronic inflammatory diseases resulting from induction of the host response to the sub gingival biofilm. Gingivitis is typically characterized as a robust inflammatory response confined mainly to the superficial gingival connective tissue and is a relatively non specific response to non specific accumulation of dental plaque, how gingivitis progress to periodontitis is still unclear\(^{(46)}\). Heijl et al were able to convert a confined naturally occurring chronic gingivitis into progressive periodontitis in experimental animal by placing a silk ligature into the sulcus and tying it around the neck of the tooth. This induced ulceration of the sulcular epithelium, a shift in the connective tissue population from predominantly plasma cells to predominantly polymorphonuclear leukocytes and osteoclastic resorption of alveolar crest\(^{(47)}\). Periodontitis appear to be a more specific inflammatory response to specific periodontal pathogen
reside in the sub gingival biofilm, the variability in the clinical manifestation and the rate of the disease progression is due to differences in the composition of the sub gingival microbial flora as well as factors that modify the host response to the microbial challenge.

Bacteria are necessary for disease initiation, they are not sufficient to cause disease progression unless there is an associated inflammatory response within susceptible host\(^{(46)}\).

There are modifying factors that do not cause the disease but amplify some disease mechanisms to make the clinical condition more severe\(^{(48)}\). It has been reported that more than 50\% of the variance in several features of chronic periodontitis can be explained by genetic factor\(^{(49,50)}\).

Some genetic variations (poly morphism) are commonly found in the population and represent mechanism by which individuals may exhibit variation within the range of what is considered normal. Since cytokines are key regulators of the inflammatory response, and are more important in periodontitis.

It is notable that IL-1 poly morphism associated with severe periodontitis, which is correlated 2 to 4 fold with increase in
IL-1B production. Many investigators have, however demonstrated the role of IL-1 in initiation and progression of Periodontitis. IL-1 activates the degradation of extracellular matrix and bones of periodontal tissues, elevated tissue or gingival fluid level of IL-1B have been associated with Periodontitis. IL-1 is strong enhancer of tissue level of prostaglandin E2 (PGE2) and tumor necrosis factor alpha (TNF-α) (49). Many of the inter individual variables are related to severity of periodontal destruction, and the inflammatory responses are attributed partly to amount and type of cytokine that individual produce (51). More over the HLADR phenotype is not particularly strong for periodontitis. There is report indicating that it is an important component of genetic susceptibility to some form of this disease.

In addition polymorphisms in the IL-1 beta gene cluster have been shown to have a significant correlation with some forms of periodontitis in certain populations (52).

Experimental evidence later emerged to implicate bacterial plaque deposits as the primary factor initiating periodontitis. At the same time specific bacteria and immune inflammatory mechanisms were implicated in the disease (53).
Current evidence seem to indicate that individuals predispose to periodontal disease have aberrant immune inflammatory responses to plaque which is genetically determined\(^{(54)}\). Mechanisms responsible could include inappropriate levels of poly morphonuclear cells (PMN) recruitment function or turnover. The resultant release of PMN enzymes and reactive oxygen species (ROS) are likely to be responsible for tissue destruction. Thus in periodontal tissues there is a fine balance between factors determining health or disease.

The first barrier in periodontitis is the epithelial lining of the gingival crevice which protects the underlying connective tissue. These crevicular and junctional epithelia are capable of reacting to the oral bacteria by releasing signaling molecules which initiate the host response such as interleukin-1 (IL-1), interleukin-8 (IL-8), (PGE2) and granulocyte macrophage colony stimulating factor (GM-CSF). These are pivotal in establishing the early inflammatory response through vascular changes, leukocyte recruitment and activation.

A number of the putative periodontal pathogens posses potent mechanisms of evading or damaging host defenses, including the
Following:-

- Direct damage to poly morph nuclear cells and macrophages (MQ). The leukotoxins produced by some strains of A.a can damage PMN and macrophages.

A number of bacterial species including *P. gingivalis, A.a* and *capnocytophages* species can reduce PMN chemo taxis, decrease phagocytoses and intercellular killing.\(^{(55)}\) A number of gram negative black pigmented anaerobes and *capnocytophages* species produce proteases which can degrade IgG and IgA \(^{(56,57,55)}\).

Cytokines are the major contributing factors of inflammation and immune system. There is now growing evidence that infectious agents are able to modify cytokines networks to their advantage.\(^{(59,58)}\) There is also no evidence that some of the putative periodontal pathogens may have this ability. In this regard the arginine specific tyrosine like proteinase (RgpA) of *P.gingivalis* can both cleave and activate certain pro and anti inflammatory cytokines.\(^{(60,61,62)}\) The balance between these two opposing functions may influence the inflammatory status of the local cytokine network in periodontal tissues. It has been shown
that most periodontal pathogens including *F. nucleatum* and *A.a* stimulate gingival epithelial cells to secrete IL-8, which is a potent chemo attractant and activator of PMN and intercellular adhesion molecule-1 (ICAM-1) which is involved in leukocyte recruitment from blood vessels into the tissues.\(^{(63,64,65,66)}\)

However it has been shown that *P. gingivalis* stimulation of human gingival epithelial cells strongly inhibited secretion of both IL-8 and ICAM-1.\(^{(67,65,66)}\) Some gram negative black pigmented anaerobes possess fibrinolytic activity.\(^{(55)}\) Which will reduce the trapping of bacteria by fibrin for surface phagocytosis.

A number of gram negative bacteria and spirochetes in the subgingival flora can alter lymphocyte function and produce immune suppression.\(^{(68)}\) Chronic periodontitis is characterized primarily by involving alternative pathway activation of complement with C3 and C3B cleavage in gingival fluid. Pathogen specific antibodies are formed in chronic periodontitis, activation of classical complement pathway by processes involving antigen antibody binding does not predominate. *P. gingivalis* produce an enzyme...
that can cleave C5 to its active metabolite C5a. Collagenase activity is associated with active periodontal destruction \(^{(69)}\). MMP-8 is elevated in chronic periodontitis whereas the level of tissue inhibitor of matrix metalloproteinases (TIMP-1) are not. \(^{(70)}\)

New data also suggest that the clinical characteristic of some complex diseases such as periodontal disease are influenced by genetic and epigenetic contribution to clinical phenotype. \(^{(71)}\)
1.4.2. Rheumatoid Arthritis

It is typically a persistent, symmetrical, deforming peripheral arthropathy, peak onset at the 5th decade of life with a female to male ratio of more than 2:1. Its prevalence is 0.5 to 1%. (72)

1.4.2.1 Epidemiology

Rheumatoid arthritis occurs throughout the world and in all ethnic groups. The prevalence is lowest in black African and Chinese and highest in pima Indians. In Caucasians it is around 1.0 to 1.5% (73), prevalence increase with age up from children to elderly. The peak onset is between the age of 30 and 35. The prevalence of RA and severe crippling deformities to which it often gives rise make it an important disorder in group of connective tissue diseases. That RA occurs most commonly among females than males is well established. The proportion of affected female to affected male is about 3 to 1. It is sometimes postulated that this sex differences in the incidence of the disease is based upon hereditary factors, the disease may be set in during childhood, adolescence or very early adult life. It is most likely to occurs in adults between the 30 and 45 years of age and occasionally sets in even later life, since the disease pursues a chronic course, its overall incidence in given
population rises with increasing age of subjects being highest among those in sixth and seventh decades.\(^{(74)}\)

A study describing the clinical pattern of RA in Sudan revealed that females were the predominant sex with a ratio of female to male of 9 : 1, one third of the patients [32.45\%] in the 6\(^{th}\) decade, about one third [29.5\%] in the 4\(^{th}\) decade, half of the patients had a duration of illness between 1 and 5 years. Sudanese patients had delayed onset of RA. \(^{(18)}\)

During the course of pregnancy the subject tend to show clinical improvement in respect to her arthritis. It can be conjectured that this improvement is the result of an inhibitory factor (possibly mediated by hormones) on the immune mechanism responsible for the production of rheumatoid factor, however within 4 months after childbirth, there is likely to be an exacerbation of arthritic manifestation. \(^{(75)}\)

The presentation of rheumatoid arthritis in adults with regards to occupation, men engaged in managerial technical occupations and in professions have a lower than expected prevalence of RA. \(^{(76)}\)

While in elderly the incidence of RA continues to increase past the
age of 60. It has been suggested that elderly onset RA may have a poor prognosis, more frequent radio logically evident deterioration, more frequent systemic involvement and more rapid functional decline.

Severe disease is largely restricted to those patients with high titre for rheumatoid factor. (77)

1.4.2.2 ETIOLOGY

The cause for RA remain unknown, three areas of interrelated researches are currently most promising, these include host genetic factors, immune regulatory abnormalities and triggering or persistent microbial infection. Genetic susceptibility to RA has been clearly demonstrated.

Certain major histocompatibility complex MHC CLASS 2 alleles and their encoded HLA or human leukocyte antigens occurred with increased frequencies in affected individuals. Only certain HLA subtypes Predispose to RA. Moreover homozygosity for the amino acid sequence if carried on HLADR4 molecules has been shown to correlate with the disease severity including poor prognosis as manifested by a more persistent disease activity,
destructive joint disease, Sub cutaneous nodules and the extra-
articular manifestation especially rheumatoid lung disease and
Felty's syndrome.

The nature of the Ag whether self or foreign remain unknown,
although candidate include type 2 collagen, proteoglycan, heatshock
proteins and immunoglobulins. RA appears to be an autoimmune
disease similar to other MHC class 2 disorders, auto Abs to the Fc
portion of IgG is present. IgG molecules or rheumatoid factor are
produced by T lymphocytes in the blood and the synovial tissue
in 80% of RA patients. Such cases are termed sero positive high
titers of serum rheumatoid factor typically of IgM isotype, when
detected by the usual clinical methods, they are associated with
more severe joint disease and with extra articular manifestations
especially subcutaneous nodules.

Despite the strong association of rheumatic factor with RA, they
clearly do not cause the disease. However production of rheumatic
factor commonly occurs in other disorders in which there is chronic
antigenic stimulation such as bacterial endocarditis, TB, kalazar,
syphilis, viral infections, intravenous drug abuse and liver cirrhosis.

An infectious origin for RA has been a continuous hypothesis
(streptococci, diphtheroid, mycoplasma and clostridium perfringens) have all been proposed.

Viral infection such as rubella, ros river virus and more recently barovirus B19 have been shown to produce acute poly arthritis but no evidence exist that they initiate chronic RA.

Also Epstein bar virus remains available but unproved candidate for pathogenic role. Ab against nuclear Ag (EBNA) expressed in epstien bar virus infected cells occurs in majority of RA patients.\textsuperscript{78}

1.4.2.3 IMMUNOLOGY

The exact process is still unclear but it is related also to many factors that include T cell activation or stimulation of macrophage via IgG Fc receptors, other cytokines IL1, IL8, TNF-\(\alpha\) granulocyte macrophage colony stimulating factor (GMCSf), macrophage inflammatory protein (MIP), macrophage chemo attractant protein (MCP) and fibroblast IL6. CD4 specific antibodies along with bacterial or slow virus infection were implicated.\textsuperscript{79}

Cytokines regulate abroad range of inflammatory processes that are implicated in the pathogenesis of RA. In rheumatoid joints, it is well known that an imbalance between pro- and anti-inflammatory cytokine activities favors the induction of autoimmunity, chronic
inflammation and thereby joint damage. However, it remains less clear how cytokines are organized within hierarchical regulatory network.\(^{(80)}\) The chronic synovial inflammation may be caused by ongoing T cell activation or may be maintained by the local production of rheumatoid factor and continuous stimulation of macrophage via IgG Fc receptors\(^{(79)}\)

CD4 T cell mediate joint damage both directly and by driving non T effector cells to release inflammatory cytokines and other inflammatory associated bone diseases. It operates through a common pathway of accelerated osteoclast recruitment and activation. It is now clear that the interaction of receptor activator NF-kappa B (RANK) and its ligands RANKL play a central role in osteoclast formation and activity.

The success of anti tumor necrosis factor and IL1 therapies highlight the central role that these cytokines play in this disease\(^{(81)}\)

The interaction of CD4 T cells with B cells can be driven by the B cell to produce IgG auto antibodies that may be directly involved in joint damage\(^{(82)}\)

The role that autoimmune processes play in pathogenesis of RA has been widely proven. Rheumatoid factor recognize Fc portion of
IgG B cells and are able to produce many important cytokines and efficiently present Ag to T-lymphocyte in the synovial environment. All these functions are important in the development of RA (83).

Considering the extent of synovial inflammation and lymphocytic infiltration there are only minimal amount of the factors produced by T cells (interferon and IL1, IL4 conversly the cytokines (IL1,IL8), TNF-α, GMCSF and chemokines produced by macrophage (macrophage inflammatory protein)(MIP) and monocyte chemo attractant protein (MCP) and fibroblast (producing IL6) are abundant, the relevance of this finding is unclear. However CD4 specific antibodies when used therapeutically produce a specific helper T cell lymphopenia but do not significantly alter the disease. Antibodies to TNF-α or specific blocking agents produced marked short term improvement in synovitis, indicating the pivotal role of TNF α in chronic synovitis. They also reduce the malaise felt in active RA.

Synovial fibroblast has high level of adhesion molecules, vascular cell adhesion molecule (VCAM-1) a molecule which support B
lymphocyte survival and differentiation, also decay accelerating factor (DAF), a factor that prevents complement-induced cell lyses. These molecules may facilitate the formation of ectopic lymphoid tissue in synovium. On the other hand, the triggering Ag in RA remains unclear. Although it is suggested that the glycosylation pattern of immunoglobulin may be abnormal in RA and may lead to their becoming potentially antigenic.

There is little evidence that collagen type 2 is the triggering Ag, although it is a cause of arthritis in animal model of RA\textsuperscript{(79)}.

### 1.4.2.4 PATHOLOGY

RA is typified by widespread persistent synovitis (inflammation of the synovial lining of the joint, tendon sheath or bursa). The cause of this is unclear but the production of rheumatoid factor by the plasma cells in the synovium and the local inflammation of immune complexes play a part in RA.

The normal synovium becomes greatly thickened to extent that it is palpable as boggy swelling around the joint and tendon. There is proliferation of the synovium into folds and fronds; also it is infiltrated by a variety of inflammatory cells including polymorphs, which transit through the tissue into the joint fluid lymphocytes and
plasma cells. The normal sparse surface layer of lining cells becomes hyper plastic and thickened. There is marked vascular proliferation. Increase in the permeability of blood vessels and synovial lining layer leads to joint effusions that contains lymphocytes and dying polymorphs. Activated lymphocytes and macrophage in the synovium produce a rich mixture of cytokines including interlukins, prostaglandins and tumor necrosis factor alpha.

The hyper plastic synovium spreads from the joint margins on to the cartilage surface. This (pannus) of inflamed synovium damages the underlying cartilage by blocking its normal route for nutrient and by the direct effects of cytokines on the chondrocytes. The cartilage become thinned and the underlying bone exposed. Local cytokines production and joint disuse combine to cause juxta articular osteoporosis during active synovitis.

Fibroblast from the proliferating synovium also grow along the course of blood vessels between the synovial margins and epipheseal bone cavity and damage the bone. This early damage may justify the introduction of disease modifying anti rheumatic
drugs (DMARD) within 3 to 6 months of onset of arthritis, low dose steroids and anti tumor necrosis factor alpha agents. (84)

1.4.2.5 Effects of RA on bone:-

The effects of RA on bone includes structural joint damage (erosion) and osteoporosis. The latter may leads to increase risk for fracture which are associated with increase morbidity and mortality. The osteoclast cells in RA play a crucial role in development of erosions. Periarticular and generalized osteoporosis suggested to be mediated through the osteoprotegerin receptor activator of nuclear factor(NF k) beta receptor activator of (NF k) beta ligand signaling system. Based on an improved understanding of this biology new treatment opportunities exist. (85)

Osteopenia associated with RA is caused by the combined action of prostaglandins and cytokines in association with normal amount of thyroid hormone. (86)

Muscle weakness is common symptoms of RA, it may have several additive causes. Synovial inflammation is usually associated with decrease motion of joints which rapidly produces reflex atrophy in muscle bundles surrounding these joints, this effect is most obvious in knees. (87)
Focal accumulation of lymphocytes and plasma cells contiguous with foci of muscle necrosis are found in almost all patients with RA, this lesion called nodular myositis. Some foci of muscle lymphocytes have been shown to synthesize IgG rheumatoid factor.

1.4.2.6 Joint involvement in RA:-

The effect of RA on hands is severe, in early disease the fingers are swollen, painful and stiff. Inflamed flexor and tendon sheaths increase functional impairment and may cause Carpel Tunnel syndrome. Joint damage causes a variety of typical deformities. Most typical is the combination of ulnar drift and palmer subluxation of meta carpo phalangeal (Mcps), Fixed flexion (button hole or boutonniere deformity) or fixed hyper extension (swan neck deformity) of the pip joints which impair hand function. Swelling and dorsal subluxation of the ulnar styloid which lead to wrist pain and may cause rupture of the finger extensor tendons, leading in turn to a sudden onset of finger drop of the little and ring fingers predominantly.

RA commonly affect the shoulders; Late In the disease rotator cuff tears are common and interfere with dressing, feeding and
personal toilet. Also synovitis of the elbow causes swelling and painful fixed flexion deformity. In late disease flexion may be lost and severe difficulties with feeding result, especially combined with shoulder, hand and wrist deformities.

Cervical spine is also affected in RA. Other joints which are affected in RA [tempromandibular joint TMJ and sterno synovial joint].

1.4.2.7 Clinical Manifestations of RA

At least 3 types of disease manifestation can be observed in RA population:

1. Self limited: in these case individuals originally presented RA have no evidence of the disease 3 to 5 years later.

2. Easily controlled disease is easily controlled with NSAIDs

3. Progressive disease. These patients generally require second line drugs which often still do not fully control the disease.

1.4 2.8 DIAGNOSIS AND INVESTIGATIONS OF RA

The diagnosis depends on the clinical features

The American College Of Rheumatology (ACR) criteria for diagnosis of RA:

- Morning stiffness more than 1 hour [for 6 weeks or more]

- Arthritis of 3 or more joint [for 6 weeks or more]
- Arthritis of hand joints and wrists [for 6 weeks or more]
- Symmetrical arthritis [for 6 weeks or more]
- Sub cutaneous nodules
- A positive serum rheumatoid factor
- Typical radiological changes [erosions and or peri-articular osteopenia]

4 or more criteria are necessary for diagnosis of RA

Initial investigations include:-

- Blood count: Anemia may be present
- Serology

Rheumatoid factor is present in approximately 70% of cases and ANA at low titre in 30% of cases.

- X ray of the affected joint to establish a base line
Only soft tissue swelling is seen in early disease

- MRI: Demonstrates early lesions

- Aspiration of the joint, effusion is present
The aspirate looks cloudy owing to white cells

**1.4.2.9 TREATMENT OF RA**

GENERAL PRINCIPLES: Goals of therapy are:

- To relief pain: Reduction of inflammation
- Protection of articular structures: Maintenance of function.
- Control of systemic involvement.

Five approaches for medical treatment

- Non steroidal anti-inflammatory (NSAID) and cyclo-oxygenase (cox2) specific inhibitors (CSIS): Celecoxib, Etodolac, Meloxicam and Rofecoxib.
- Low dose oral glucocorticoid: Disease modifying or slow acting anti rheumatic drugs (DMARD)
- Tumor necrosis factor alpha necrotizing agent Immuno suppressive and cytotoxic drugs.

NSAIDS

They are so called because they alleviate pain by blocking the formation of inflammatory mediators as do glucocorticoid. However NSAIDS lack many of the trouble some side effects of corticosteroids.

Examples of NSAIDS:-

Asprin and other salicylates, paracetamol, pyrazolones, mefenamates, indomethacin and related drugs. Proprionic acid derivatives and related drugs
Asprin and other NSAID block the synthesis of prostaglandin E2(PGE2) and hence diminish peripheral manifestation of tissue injury, thus reduce pain, swelling and impaired function of inflamed tissue. They exert their action by inhibiting a single step in prostaglandin (PG) synthesis by blocking the enzyme cyclooxygenase. Thus cyclin endo peroxide fail to form from arachidonic acid. These (PG) are mediator of vasodilatation swelling and pain in the inflamed tissues.

NSAID Interfere with the mechanisms by which the gastric mucosa is protected from its own acid / pepsin secretion, thus the result is gastric irritation.

CORTICO-STEROIDS:-

Several mechanisms are involved in the immunosuppressive and anti-inflammatory action of cortico-steroids. Their effects vary with dosage which includes:-

- Intra-cellular receptor binding leads to synthesis or activation of lipocorin. Lipocorin inhibits phospo-lipase A2 and release of arachidonic acid from phospo-lipids. Synthesis of leukotrienes, prostaglandins, thromboxane and prostacyclin is thus blocked.
- Production of interleukin 2 is depressed by blocking the activation of interleukin -1 and interleukin 6 genes. T lymphocyte proliferation is thus depressed.

- Lymphokine release and the response to lymphokines are diminished.

- In high doses, cortico-steroids are cytotoxic to immature T-lymphocytes and some of their mature counterparts. The overall effect of cortico-steroids are predominantly Depression of cell mediated responses and anti-inflammatory action. Antibody production and antigen - antibody interaction are not inhibited. The glucocorticoids have powerful anti-inflammatory and anti-allergic action. The mechanism of this effect is via a mediator substance lipocortin.

The steroid enters many types of cells, bind to the cytoplasmic receptor and the combination enter the nucleus which is stimulated to produce the specific m-RNA for lipocortin synthesis. Lipocotin mediates several actions which include:- Inhibition of phospholipase and thus inhibiting synthesis of (PG) and leukotrienes. The PG cause pain, edema and vasodilatation of acute inflammation.
Leukotrienes mediate cellular infiltration, mucosal secretion and broncho-constriction in prolonged inflammation.

- Inhibition of production of interleukin 2, this substance is secreted by lymphocytes.

Because steroids block proliferation of T-cells, by this way cell mediated immunity is depressed.

- Inhibition of release and the response to lymphokines

Lymphokines are proteins released from lymphocytes in severe inflammation. Glucocorticoid is used for suppression of inflammatory and immunologically mediated diseases such as RA. (94)

Although the first line for treatment of RA remains is NSAID. Their mechanism of action is through the inhibition of cyclo-oxygenase (COX) synthesis which produce both analgesic and anti-pyretic properties.

While these medications are effective in reduction of pain symptoms in RA, they do not significantly alter its course (95)

Also the usage of NSAID in the treatment of periodontal diseases has been studied over the past 20 years (96,97,98). While the results appear promising, the widespread clinical use of these
medication to alter the course of Periodontitis has not been universal. One particular problem with their uses for management of Periodontitis appear to be a rebound effect to baseline following cessation of the medication. (99) With discovery of two COX enzymes responsible for PG production, designated COX-1, COX-2, a variety of COX-2 inhibitors have been studied for their potential to stop or slow down bone resorption.

One of the first COX-2 inhibitor developed is Tenidap. It inhibit not only cyclo-oxygenase and PG production but also interlukin-1, interlukin-6 and tumor necrosis factor alpha Production.

To date COX-2 inhibitors have not been thoroughly studied for their potential to modify bone resorption in Periodontitis. In contrast to the NSAID which do not significantly alter the course of RA, a newer family of medications designated disease modifying anti-rheumatic drugs (DMARDs) has been developed.

To be classified as DMARD, the medication must demonstrate an ability to change the course of RA for at least 1 year as evident by sustained improvement in function, decreased synovitis and prevention of further joint damage. (100) Examples of these
medications include Parenteral gold salt, Methotrexate, Sulphasalazine, Hydroxy-chloroquine [anti-malarial drug], Pencillamine, Azathioprine and Leflunomide. A major drawback in the usage of DMARDs is their considerable toxicity\textsuperscript{(101,102)}. The usage of DMARDs for the management of periodontitis has been largely restricted due to the toxicity issues. However, the usage of Gold salts in animal model has shown reduced periodontal destruction.\textsuperscript{(103)}

Another emerging area for potential of host modulation in periodontitis and RA is control of matrix metallo-proteinases (MMPs) which are important mediator of connective tissue breakdown in both soft and hard tissues, in this regard Tetracyclin and various chemical analogues have been found to inhibit MMP activity by a mechanism independent of their anti-microbial property\textsuperscript{(104,105)}. A number of clinical trials using low dose Tetracycline to modify periodontitis have been carried out, with safety and effectiveness\textsuperscript{(106,107)}. Nonetheless is still recommended that these data is interpreted with caution to differentiate between statistically significant and clinically relevant.
The role of MMP inhibitors in management of RA has been less well studied, but promising results are emerging. Control of cytokines and their receptors is also emerging as a field of considerable promise, for example blocking the interleukin-1 receptor antagonist. Similarly, other studies have shown that blocking the activity of another important inflammatory cytokines, e.g., tumor necrosis factor alpha, has therapeutic efficacy in RA patients. The role of interleukin-1 and tumor necrosis factor antagonist in a model of periodontitis have demonstrated reduction in the inflammatory infiltrate in close proximity to bone as well as reduction in the formation of osteoclast and reduced bone loss. Clearly, many of these biologic agents which target specific molecular events associated with acute and chronic inflammation have significant potential to alter clinical outcome for both RA and periodontal disease. With the emerging understanding that RA and periodontitis are multifactorial diseases, combination therapies that target multiple disease outcome are also emerging. For example, in an animal study it was reported that the administration of a combination of chemically modified tetracycline's (CMT-1) plus
NSAID such as flurbiprofen or tenidap synergistically inhibited severe bone destruction in arthritis rats, with the suppression of MMP activity in joints.\(^ {120,121}\) Similar encouraging results have been reported for periodontitis in human.\(^ {122}\)
1.4.3 The relationship between periodontitis and rheumatoid arthritis:

In the year 1998, a study made by American Academy Of Periodontology confirmed that mouth infection can cause major problems in other parts of the body. Periodontal and gum diseases can cause bleeding, discomfort and even tooth loss. Infection can eventually enter the blood stream, travel to major organs and begin new infections.

The National Institute Of Dental Research (NIDR) has found strong association between gingival infection and number of diseases. In addition to the rapidly growing recognition of the link between oral and general health, there is increasing awareness of the potential the mouth hold for assisting in early diagnosis of diseases.\(^\text{(123)}\)

Periodontitis and RA appear to share many pathological features. Emerging evidence now suggests a strong relationship between the extent and severity of periodontal disease and RA. It is clear that individuals with advance RA are more likely to experience more significant periodontal problems compared to their non RA counterparts. These two diseases could be very closely related...
through common underlying dysfunction of fundamental inflammatory mechanisms. The nature of such dysfunction is still unknown. The clinical implication of the current data indicate that patients with RA should screened for their periodontal status. \(^{(3)}\)

It must be recognized that periodontitis differ in one significant way from RA, through understanding that the sub gingival biofilm is a key etiological factor. Unlike periodontal disease no specific bacterial etiology has been identified for RA.

Thus while host modification of disease processes are possible for periodontitis, controlling the bacteria that cause periodontal infections remain a significant focus for periodontal treatment and prevention. Best host modification can be only an adjunct treatment for periodontitis. However until an etiological factor can be found for RA, host modification remain the main stay for treatment.

There is no question that periodontitis and RA have many pathological features in common. Hence the possibility exists that both conditions result from a common underlying deregulation of the host inflammatory response. There is accruing evidence to support the notion that both conditions manifest as a result of imbalance between pro-inflammatory and anti-inflammatory
cytokines. As a result new treatment strategies will emerge for both diseases that may target the inhibition of pro-inflammatory cytokines and destructive proteases.\(^{(3)}\)

To date very few studies have examined the association between RA and periodontal diseases, the results have been conflicting. For example Finish studies found no correlation between periodontal disease and arthritis\(^{(124)}\) while others\(^{(125,126)}\) suggest a higher prevalence of bone loss in RA. A major reason for these discrepancies relates to the lack of uniformity in classifying the various forms of periodontal disease and RA. Indeed most of early studies\(^{(125,124,127)}\) failed to take into account the various forms of RA and periodontal diseases. In a subsequent study, 65 patients attending a rheumatology clinic were studied for their level of periodontitis and RA\(^{(3)}\) A control group consisted of aged and gender matched individuals who did not have RA. No difference were noted for plaque and bleeding indices between the control and RA group. The RA group did, however, have significantly more missing teeth than the control group and greater percentage of these subjects have deeper pocketing compared to the controls. The percentage
of alveolar bone loss correlated positively with the principal parameters of RA severity. These two pilot studies have resulted in several significant findings. RA patients do not have impaired oral hygiene (judged by plaque and bleeding scores) Perhaps more importantly, it was noted that individuals with severe RA are more likely to have advanced periodontitis and vice versa.

Although many RA patients take medications that can reduce periodontal destruction [NSAID and immunosuppressant], there is notable periodontal destruction in those patients. This indicates that prior to the development of RA symptoms, the periodontitis was not likely developing and not detected. Thus disease duration may be a very important factor. Finally in order to understand the inter-relationship between periodontitis and RA, it is necessary to categorize the disease on the basis of severity and duration (i.e., type of disease).

Recently using an animal model, additional evidence has been presented to indicate significant relationship between periodontitis and RA. From this study it was reported that inducing experimental arthritis in the rat (adjuvant arthritis) resulted in periodontal breakdown characterized by alveolar bone loss and
increased matrix metallo proteinase (MMP) activity in adjacent gingival tissues. Interestingly all of this reactions occurred without manipulating the oral or sub gingival micro-flora. Most recently studies have begun to investigate the co-distribution of cytokines involved in vascular damage and bone resorption in biopsies from graded RA and periodontitis lesions. Since the tumor necrosis factor like molecules and their receptors have been shown to be involved in both processes.

There was previous study of the receptor activator of n F kappa B legend (RANKL), osteo-pretogren (OPG) and tumor necrosis factor related apoptosis including legends (TRAIL) to determine at least one molecular mechanism common to both conditions.

The cell surface tumor necrosis factor like molecule (RANKL) and its receptor RANK have been shown to be key factors regulating osteoclast formation and activation. It has been shown that when RANKL binds to RANK on the surface of osteoclast precursors, these cells differentiate to form mature osteoclasts. It is now clear that RANKL, together with macrophage colony stimulating factor (M-CSF) is required for osteoclast formation. The soluble TNF [receptor like] molecule, OPG is a
natural inhibitor of RANKL\(^{(131)}\), OPG binds to RANKL and prevent its legation to RANK. The importance of these molecules in regulating bone metabolism has been demonstrated by transgenic and gene knock out studies in mice\(^{(132)}\) Since these factors regulate physiologic osteoclast formation. It is reasonable to propose that they may also be key regulators of pathological bone resorption\(^{(133,134)}\). Although RANKL is normally provided by osteoclast like cells in bone\(^{(134, 135)}\) There are reports suggesting that lymphocyte present in rheumatoid tissue may be the main source in inflammatory arthritis\(^{(129,136)}\) Furthermore CD4 T-cells from the human rheumatoid joint express RANKL and can promote osteoclast formation from rodent spleen precursors\(^{(136)}\). In addition to lymphocytes production of RANKL, inhibition of RANKL by OPG treatment in vivo reduces both bone and cartilage destruction in a model of adjuvant arthritis.\(^{(137)}\) Under certain conditions, human osteoclasts precursor cells present in or near the tissues of arthritic joints\(^{(138,139)}\)

More recent reports in humans\(^{(140,141)}\) and animals\(^{(137)}\) show that RANK,RANKL interaction may required for osteoclast formation and bone resorption in RA joint. Accordingly (OPG) and RANKL
were expressed in biopsies of inflamed rheumatoid synovium and periodontitis lesions.\textsuperscript{(142)} The production of OPG by endothelial cells may be significant for reasons other than its effects on bone metabolism. There is now evidence to suggest that OPG might also regulate endothelial cell function. OPG has been reported to be required for endothelial cell survival and growth\textsuperscript{(143)}, in addition OPG knockout mice have been shown to develop arterial calcification\textsuperscript{(144,145)} as well as severe osteoporosis, suggesting that vascular endothelial expression of OPG may have a role in vascular homeostasis\textsuperscript{(137)}. In response to pro-inflammatory cytokines tumor necrosis factor alpha and interleukin-1β, OPG mRNA expression was dramatically enhanced resulting in secretion of newly synthesized OPG and reduction of cell associated OPG. Such findings are consistent with the observation in vivo for active RA and periodontitis lesions. Vascular damage due to apoptosis is thought to precede vascular calcification.\textsuperscript{(144)} And contribute to atherosclerosis.\textsuperscript{(147)}

In addition diabetic endothelial cell dysfunction is associated with DNA damage induced by poly(ADP-ribose) polymerase activation. The exact cause of endothelial cell dysfunction is
not known but it is possible that molecules such as TRIAL, expressed in nearby cells and tissues, may be important.\(^{134,148}\)

The recent finding studies confirm that OPG binds to TRAIL, although with less affinity than RANKL, in vitro, and block its activity (unpublished data). The final piece of evidence for the role of OPG in vascular damage comes from the fact that OPG knockout mice develop vascular calcification. It is significant to note that calcification cannot be reversed by systemic treatment with recombinant OPG post partum.\(^{144}\) This supports the concept that OPG must be expressed within endothelial cell, either in appropriate form or associated with other molecules, and this only occurs following normal synthesis within the healthy endothelial cells. In light of above, there at least one underlying common molecular pathway in common between RA and periodontitis may lie within RANK, OPG, TRAIL axis whereby OPG decreases leading to decrease in vascular protection in addition with an increase in RANKL and TRAIL within the tissues, not only is vascular damage possible but significant activation of osteoclasts may result. The proposal still awaits verification. Most of the association between periodontitis and systemic diseases are
explained in a part by excessive production of pro-inflammatory cytokines and other inflammatory mediators of which prostaglandin-E2 (PGE2), TNF-α and IL-6. (18) Periodontitis has a remarkably similar path biology to RA. (149) In both diseases progression consists of the continuing presence of high levels of pro-inflammatory cytokines. Furthermore, low levels of tissue inhibitors of metalloproteinases (TIMP) and high levels of matrix metalloproteinases (MMP), and PGE2 secreted by macrophages, fibroblasts, and other resident and migrating inflammatory cells characterize the active stage of both diseases.

Previous studies have reported contradicting findings on the relationship between periodontitis and RA. (150,151,126,152,153) However in light of the variability in both RA and periodontal disease classifications, it is difficult to compare these results. More recently, it has been reported is that individuals with periodontitis are 4 times more likely to have a self reported history of RA. (10) In this RA population, 62.5 had advanced forms of periodontal disease. (10) Given the problems with accuracy of self reported disease experience, preliminary findings of likely relationship between RA and periodontitis. (10) require further
validation. A patients would have greater exposure to NSAID, these drugs are well documented to limit periodontal bone loss when taken long term. \(^{(154)}\) The majority of RA patients most likely were suffering from an advance form of disease, as they attended a tertiary referral clinic. Such patients have usually passed the level of taking NSAID for disease control and are often taking a range of disease modifying medications. \(^{(19)}\)

In humans, many of these genes which regulate monocytic cytokines response have been mapped to HLA – DR region of chromosome 5 in the area of the TNF-\(\beta\) genes. \(^{(155,156)}\) Both RA and progressive periodontitis are associated with this HLA complex\(^{(157,158)}\).

This provides a common genetic basis for the observed monocyte triat, linking RA, progressive periodontitis, and other systemic diseases. It is reasonable to suggest, therefore, that inter-individual differences in the severity of RA and periodontal disease are partly due to intrinsic differences in the monocyte / T cell response triats. In both disease, inflammatory challenge to the monocytic / lymphocytic axis may result in the secretion of excessive pro-inflammatory cytokines and inflammatory
mediators, of which PGE2, TNF-α, interleukin 1, interleukin 6 would appear to dominate.\(^{18}\) The loss of bone and other connective tissues in periodontitis, as well as in the synovial joint with RA, is mainly a consequence of increased local tissue destruction, i.e., a disturbed balance between tissue formation and degradation. Cytokines participate in the regulation of this process \(^{3}\), the pro-inflammatory cytokines (TNF-α) and interleukin-1 beta are important promoters of bone resorption in both diseases, but there are many other cytokines involved, such as interleukin-6.

This cytokine increases the number of osteoclasts\(^ {157}\) and is a promoter of PGE2 synthesis and release; this, in turn, promotes osteoclast fusion and blocks bone formation.\(^ {159}\) leading to bone loss. The amount of resulting bone resorption depends on the tissue concentration of different resorptive promoters and on the presence of cytokine inhibitors such as the receptor antagonist of interleukin-1(IL-ira)\(^ {3,159}\) TNF-α is often present at the site of inflammation, as well as in the circulation, and is believed to be responsible for the modulation of systemic inflammation\(^ {160}\).
The circulating TNF-α is mainly derived from local release by macrophage and T-cells in inflammatory joint lesions. (161) As well as from circulating peripheral mononuclear cells. High levels of TNF-α in plasma are associated with radiographic signs of temporomandibular joint (TMJ) bone tissue degradation in patients with RA. (162,163) It has been suggested that TNF-α is an important factor in periodontitis progression and that it participates in periodontal tissue destruction by stimulating the production of MMP. (164) TNF activity is considered of major pathologic importance in periodontitis and RA (165), and inhibition of TNF with biologic antagonists has been successful. (66,167,168,169)

There are several systemic markers of inflammation such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and thrombocyte particle concentration (TPC). TPC is increased as a result of thrombocytosis that occurred within a few days after the inhibition of inflammation, and thrombocytes are activated by RF to release serotonin (5-HT). Increase periodontal attachment loss and deeper periodontal pockets have been found in patients with RA and juvenile
idiopathic arthritis with increased levels of RF, CRP and ESR.\textsuperscript{(18,170,171)}

Although Mikael et al in 2008 carried an investigation in Sweden to study the association between the circulating pro-inflammatory mediators TNF-\(\alpha\), PGE2, interleukin-1\(\beta\), serotonin, rheumatoid factor and periodontitis in patients with RA. The results of the study suggested that in patients with RA, high plasma levels of TNF-\(\alpha\) were related to gingival bleeding on probing, more attachment loss, and deeper pockets compared to those with low plasma levels.

These findings also suggest that the inflammatory process in the periodontal tissues is related to circulating TNF-\(\alpha\) with regard to tissue destruction (periodontitis) and vascular reactions (gingivitis). The plasma level of TNF-\(\alpha\), which is associated with the degree of systemic inflammation (CRP) may influence the development of periodontitis in patients with RA. RF, PGE2, interleukin-1 \(\beta\) and serotonin in plasma did not contribute significantly to the variation in the periodontal variables in this study which could be due to sample size as well as low plasma level of PGE2 and interleukin-1 \(\beta\) detected.\textsuperscript{(172)}
Also F.B.Mercado et al in 2001 in Australia carried a study on a population of RA patients (65 patient) The results show no differences for plaque and bleeding indices between the control and RA group. RA group have more missing teeth than the control group and higher percentage of deeper pocketing.\(^{(18)}\)

And N.Pischon et al in 2008 in Germany study 57 subjects with RA and 52 healthy control. The results show that subjects with RA have significantly increased periodontal attachment loss compared to control. Oral hygiene may only partially account for this association.\(^{(12)}\)

A study by YANIV. M et al in 2009 in Haifa Israel, the result of the study show that RA patients receiving anti TNF-\(\alpha\) medications have lower periodontal indices and GCF TNF-\(\alpha\) level, thus suppression of pro – inflammatory cytokines might prove benefit in suppressing periodontal diseases. Also data shows that RA patients exhibit overall worth periodontal and gingival condition.\(^{(173)}\)

Although Gleissner . C et al\(^{(174)}\) in 1998 in Germany studied 50 RA patients matched with 101 healthy control. The results show no correlation between the duration of pharmacotherapy and
the periodontal parameters. Patients with long term active RA present higher degree of periodontal disease including loss of teeth compared with controls. Functional impairment of upper extremity might amplify present periodontal disease. The long term use of NSAID, corticosteroids and DMARD show no connection with the severe periodontal disease observed in this patients, oral hygiene amplify periodontal disease severity and treatment need. Intensive prophylactic measures are required to prevent or reduce the damage of periodontal tissues in RA.

And Ka"sser UR et al in 1998 in Germany carried a study in 50 RA patients and 101 healthy control. The results of the study concluded that patients with longstanding active RA have a substantially increased frequency of periodontal disease, including loss of teeth, compared with controls. Anti-inflammatory treatment interferes with periodontal disease and might have masked a possible correlation between the indices of chronic destruction in RA and periodontal disease.\(^{(125)}\)

Also Ishi Edi P et al in 2008 in Brazil carried a study [in39 RA patients and 22 healthy individuals] The results of the study show that RA had fewer teeth, higher prevalence of sites
presenting dental plaque and a higher frequency of sites with advanced attachment loss. Based on above results, there is an association between periodontal disease and RA.\(^{(175)}\)

A study in Brasil in 2005 is carried by Ribeiro J et al. The study is done in 42 patients, they were classified into 2 groups. Group 1 submitted to oral hygiene instruction and professional tooth cleaning, while group 2 had full mouth scaling and root planning. The result suggested that periodontal treatment with scaling and root might have an effect on erythrocyte sedimentation rate reduction.\(^{(176)}\)

A study in USA in 2007 is carried by Al-Katma. 29 subjects diagnosed with RA participate in the study, the results concluded that control of periodontal infection and gingival inflammation by scaling/root planning and plaque control in subjects with periodontal disease may reduce the severity of RA.\(^{(177)}\)

And study by Ortiz P et al in 2009 in Cleveland, in 40 patients with moderate to severe RA, the results concluded that non-surgical periodontal therapy had a beneficial effect on the signs and symptoms of RA regardless of the medications used.
to treat this condition, anti TNF-α therapy without periodontal treatment had no significant effect on the periodontal condition. (178)

Also Ezel Berker in Turkey in the year 2000, carried a study in 45 patients, concluded that in patients with RA medication including corticosteroid and NSAID may decrease gingival inflammation, but the synthesis and degradation of IL-6 in gingival tissue of RA patients may be different. The study was the first report determining GCF IL-6 Level in RA patients. (179)

De Pablo in USA in 2008 In the results RA may be associated with tooth loss and periodontitis. (180)

A study in France by Pers JO in 40 subjects with RA, the result was TNF-α, blockade could be beneficial in the treatment of periodontitis. (181)

Basak et al in 2009 carried a study in Turkey in 74 subjects. The results showed that gingival crevicular fluid MMP – 8 level increased with periodontal inflammation despite the long term usage of cortico-steroid and NSAID, similar gingival crevicular fluid MMP-8 and 13 levels in patients with RA and systemically healthy individuals suggest that RA may create a tendency to overproduce these enzyme (182).
1.5 **Material and Methods**

1.5.1 **Study design:**

This is a case control study.

1.5.2 **Sample size:**

160 cases [80 case groups and 80 control group].

1.5.3 **Study population:**

1.5.3.1 **Study group**

Eighty Rheumatoid arthritis patients (RA) aged 20–60 years old was examined from the common rheumatoid arthritis clinics in Khartoum State.

1.5.3.2 **Control group:**

Eighty non RA healthy individuals were examined as a control group.

Those were selected from Co-patients, employee in the same centers, the patients and the control group was matched in relation to gender and age.
1.5.4 Inclusion criteria:

1.5.4.1 Study group:

- Diagnosed patients with RA (20–60 years old) with consideration of the disease duration.
- Willingness of the patient to participate in the study
- Only partially or fully dentate patients (at least 8 teeth excluding 3\textsuperscript{rd} molar)

1.5.4.2 Control group:

- Age group 20 – 60 years old
- Absence of rheumatoid arthritis
- Willingness to participate in the study
- Only partially or fully dentate patients (at least 8 teeth excluding 3\textsuperscript{rd} molar)

1.5.5 Exclusion criteria:

- Pregnancy
- Lactation
- Aggressive Periodontitis

- Previous history of periodontal therapy.
- Use of antibiotic during the last 3 months prior to examination.
- Any Conditions that modify the periodontal tissue status [e.g. D.M].
- Smoking and smokeless tobacco

1.5.6 General information:

Following approval of the study plan by the faculty of Dentistry University of Khartoum Research Board, a letter was sent to the administrative authorities of the rheumatoid arthritis clinics with a copy of the written consent. After the approval, calibration with the supervisor was done to reduce the intra and inter examiner error using Kappa test. All participants in the study signed a written consent after explanation of the examination aim to be performed. On the other hand, personal data including oral hygiene tool, periodontal chart, and information regarding RA was recorded. Also, potential risk factors for periodontitis were assessed for both patients and control, this include socioeconomic status and education.

1.5.7 Examination:

- Oral examination for periodontal indexes was performed for patients and control group using dental mirror and graduated periodontal probe (Michigan"s O).
The participant in the study group were examined lying on the coaches of the rheumatology clinics. These rheumatology centers has good ceiling, lightning, artificial light beside the patient was used for additional illumination. The examination was performed by one examiner (candidate) with a dentist to record the reading. A septic techniques including proper instrument sterilization, usage of masks and disposable gloves were done in examination of all patients. All teeth was examined at four sites (mesiobuccal–distobuccal), (mesio Lingual–distolingual) for presence of plaque using the plaque index (PI)\(^{(183)}\), for gingival inflammation using the gingival index(GI)\(^{(184)}\) and calculus also was recorded on the basis of present or absent \(^{(185)}\). Probing depth was recorded as the distance from the free gingival margin to the bottom of the sulcus or periodontal pocket. Clinical attachment loss was recorded as the distance from cemento-enamel junction to the bottom of the sulcus or periodontal pocket. Data was recorded in a special form (Appendix 1).

1.5.8 Statistical Analysis:-

Standard descriptive statistical techniques was used to summarize and present sample information. To check for possible significant
differences in periodontal status between the case and control group, t-test was used for normally distributed data, in the case of non-normal data Mann-Whitney test was used. The data was processed using STATA software package (version 10). Logistic regression was used to assess the effects of periodontal parameters on periodontal status in the case and control groups.
The data of this study was collected over a period of five months from three common rheumatoid arthritis centers in Khartoum. The results revealed that the distribution between cases and controls are equal in calculus with mean and standard deviation (0.48±0.4) for patients and (0.49±0.44) for the controls p-value is 0.9986 at 0.05 level of significances by using Mann-Whitney test for continuous variables and p-value 0.631 by using chi-square test for categorical variables (figure-1).

The distribution between cases and controls are equal in plaque index with mean and standard deviation (SD) (1.25 ± 0.4) for patients while the control group was (1.17±0.28) p-value is 0.3597 at 0.05 level of significance by using Mann-Whitney test for continuous variables and p-value 0.524 by using chi-square test for categorical variables (figure-2). Also the distribution between cases and controls are equal in gingival inflammation with mean and standard deviation (1.2±0.24) for the patients and (1.2 ± 0.33) for the control p-value is 0.3049 at 0.05 level of significance by using
Mann-Whitney test for continuous variables and p-value 0.049 by using chi-square test for categorical variables (figure-3).

For probeable pocket depth the distribution between cases and controls are not equal rheumatoid arthritis patients had more pocket depth with mean and standard deviation (0.46±0.42) and (0.15±0.22) for control p-value is 0 at 0.05 level of significance by using Mann - Whitney test for continuous variables and p-value 0 by using chi-square test for categorical variables (table-1).

Also the distribution between cases and controls are not equal in clinical attachment loss, increase in attachment loss level in rheumatoid arthritis patients with mean and standard deviation (1.03±0.95) and (0.56±0.63) for the control p-value is 0.0002 at 0.05 level of significance by using Mann-Whitney test for continuous variables and p-value 0.006 by using chi-square test for categorical variables (table-2).

From the study there is no significant correlation between duration of illness and plaque index (p-value 0.9786), gingival index (p-value 0.9079), probeable pocket depth (p-value 0.5978) and clinical attachment loss (p-value 0.0933) at 0.05 level of significance (table-10).
The results of differences between case and control in oral hygiene habits showed that there is no association between frequency of oral hygiene between case & control variable at significant level 0.05 (p-value is 0.262). There is no association between frequency of oral hygiene and gingival index at significant level 0.05 (p-value 0.752). And no association (independent) between frequency of oral hygiene and plaque index at significant level 0.05 (p-value 0.852) (table-3,4,5). There is association between gingival index and plaque index at significant level 0.05 (p-value 0.048) (table-6,7).

This study had showed that no association exist between the drugs used to treat rheumatoid arthritis (NSAIDs & DMARDs) and the periodontal parameters (plaque index, gingival index, probeable pocket depth and clinical attachment loss) (table-9).
Table (1):

**Comparison of the probeable pocket depth (per millimeters) between case and control:**

<table>
<thead>
<tr>
<th></th>
<th>Cases (N=80)</th>
<th>Controls (N=80)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5</td>
<td>52 (65%)</td>
<td>77 (96.25%)</td>
<td>0.000</td>
</tr>
<tr>
<td>&gt;0.5 to ≤1</td>
<td>20 (25%)</td>
<td>2 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1 to ≤1.5</td>
<td>5 (6.25%)</td>
<td>1 (1.25%)</td>
<td></td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>3 (3.75%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.46 ± 0.42</td>
<td>0.15 ± 0.22</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Table (2): -

Comparison of clinical attachment loss (per millimeters)

between case and control :-

<table>
<thead>
<tr>
<th></th>
<th>Cases (N=80)</th>
<th>Controls (N=80)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.17</td>
<td>52 (65%)</td>
<td>70 (87.5%)</td>
<td>0.006</td>
</tr>
<tr>
<td>&gt; 1.17 to ≤ 2.33</td>
<td>20 (25%)</td>
<td>7 (8.75%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2.33 to ≤ 3.5</td>
<td>5 (6.25%)</td>
<td>3 (3.75%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>3 (3.75%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.03 ± 0.95</td>
<td>0.56 ± 0.63</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Table(3):-

The association of oral hygiene and Periodontitis for the study group:-

<table>
<thead>
<tr>
<th>Frequency of oral hygiene</th>
<th>Case &amp; Control variable</th>
<th>Gingival Index</th>
<th>Plaque Index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>*p-value (0.262)</td>
<td>*p-value (0.752)</td>
<td>*p-value (0.852)</td>
</tr>
</tbody>
</table>

*NA :- No association
Table (4) :-

The independency between frequency of oral hygiene and gingival index among cases using chi-square test:-

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Once per day</th>
<th>More than two times per day</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.64 to ≤ 1.09</td>
<td>28</td>
<td>1</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>&gt;1.09 to ≤ 1.54</td>
<td>42</td>
<td>1</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>&gt;1.54</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>2</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

P-value = 0.752
Table (5) :-

The independency between frequency of oral hygiene and plaque index among cases using chi-square test:-

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Once per day</th>
<th>More than two times per day</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.99</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>&gt;0.99 to ≤1.63</td>
<td>57</td>
<td>1</td>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>&gt;1.63 to ≤2.27</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>&gt;2.27</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>2</td>
<td>1</td>
<td>79</td>
</tr>
</tbody>
</table>

P- value = 0.852
Table (6) :-

The independency between gingival index and plaque index

among cases using chi-square test:-

<table>
<thead>
<tr>
<th></th>
<th>&gt;0.64 to ≤1.09</th>
<th>&gt;1.09 to≤1.54</th>
<th>&gt;1.54</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.99</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>&gt;0.99 to ≤1.63</td>
<td>24</td>
<td>33</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>&gt;1.63 to ≤2.27</td>
<td>1</td>
<td>7</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>&gt;2.27</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>43</td>
<td>6</td>
<td>80</td>
</tr>
</tbody>
</table>

P- value = 0.048
Table (7) :-

The association of plaque index and gingival index in the study group:-

<table>
<thead>
<tr>
<th>Gingival Index</th>
<th>Association</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Index</td>
<td></td>
<td>(0.048)</td>
</tr>
</tbody>
</table>
**Table (8) :-**

The number of patients in relation to type of drug used :-

<table>
<thead>
<tr>
<th>DRUG TYPE</th>
<th>NUMBER OF PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>21</td>
</tr>
<tr>
<td>STEROIDS</td>
<td>44</td>
</tr>
<tr>
<td>*METHIOTREXATE</td>
<td>51</td>
</tr>
<tr>
<td>*HYDROXYCHLOROQUINE</td>
<td>35</td>
</tr>
<tr>
<td>*SULPHASALAZINE</td>
<td>12</td>
</tr>
<tr>
<td>*PENICILLIAMINE</td>
<td>2</td>
</tr>
</tbody>
</table>

*DMARDs:-* Disease modifying anti-rheumatic drugs
### Table (9):

**Association between RA drugs and periodontal parameters:**

<table>
<thead>
<tr>
<th></th>
<th>Plaque Index</th>
<th>Gingival Index</th>
<th>Probeable Pocket Depth</th>
<th>Clinical Attachment Depth</th>
</tr>
</thead>
</table>
| **NSAIDs**  
P Value | NA (0.718)   | NA (0.343)     | NA (0.228)              | NA (0.674)                |
| **Steroids**  
P Value  | NA (0.812)   | NA (0.932)     | NA (0.747)              | NA (0.981)                |
| **Pencilliamine**  
P Value | NA (0.288)   | NA (0.198)     | NA (0.776)              | NA (0.776)                |
| **Methiotrxate**  
P Value | NA (0.738)   | NA (0.415)     | NA (0.301)              | NA (0.483)                |
| **Hydroxychloroquirie**  
P Value | NA (0.192)   | NA (0.254)     | NA (0.563)              | NA (0.563)                |
| **Sulphasalazine**  
P Value | NA (0.944)   | NA (0.569)     | NA (0.837)              | NA (0.590)                |

- NA :- no association
- P-value is measured by chi-square test
Table (10) :-

Relationship between duration of illness and periodontal parameters:-

<table>
<thead>
<tr>
<th></th>
<th>Duration of illness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plaque Index</strong></td>
<td>p-value (0.9786)</td>
</tr>
<tr>
<td><strong>Gingival Index</strong></td>
<td>p-value (0.9079)</td>
</tr>
<tr>
<td><strong>Probeable Pocket Depth</strong></td>
<td>p-value (0.5978)</td>
</tr>
<tr>
<td><strong>Clinical Attachment Loss</strong></td>
<td>p-value (0.0933)</td>
</tr>
</tbody>
</table>
**Figure (1):**

Comparison of the amount of calculus between case and control:-
Figure (2) :-

Comparison of the plaque index(PI) between case and control :-

![Comparison of plaque index between case and control](image)

Diagram showing the mean of plaque index for case and control groups.
Figure (3) :-

Comparison of the gingival index (GI) between case and control :-
**Discussion**

The relationship between RA and periodontitis was attracted the attention of health authorities in different countries since 1998\(^{(123)}\). The ratio of females to male in this study is 9 : 1 (Appendix-2). This ratio is greater than the previous studies in other countries which reported that females was three time more to develop RA than males.

The association between RA and periodontal disease has been examined only in a few studies with inconsistent results\(^{(3)}\). Although most earlier studies did not find positive associations of RA with periodontal disease\(^{(123)}\), more recent evidence\(^{(3)}\) showed that subjects with RA have higher parameters of periodontal disease as compared to non-diseased individuals which is in agreement with our results.

The results of this study provide further evidence that a relationship exist between disease experiences of periodontitis and RA.

The data indicates that individuals with RA are more likely to experience more significant periodontitis compared to non-rheumatoid arthritis patients and vice versa\(^{(3)}\).
In this study a sample of eighty rheumatoid arthritis patients were selected randomly from three common rheumatoid arthritis clinics in Khartoum. Patient aged 20 – 60 were included in the study, on the other hand eighty healthy individuals matched with age and sex were selected as a control group from co-patients and employee in these centers.

The duration of the disease was recorded but no significant correlation was found when it is compared with clinical parameters used PI (p-value is 0.9786), GI (p-value is 0.9079) PPD (p-value is 0.5978), CAL (p-value is 0.0933).

On the other hand the distribution of calculus between cases and controls are equal at significant level of 0.05 by using Mann-Whitney test (p-value is 0.9986) and by using Chi-square test(p-value is 0.631). The literature did not show the difference in the calculus amount between study and control group.

It was found that the study group showed no difference in the amount of plaque as compared to the control group (p-value is 0.524) at significant level of 0.05, this agree with F.B Mercado et al (2001) and Yaniv et al (2009) . The observation in our study is
consistent with previous other studies. Thus the general concept that RA patients tend to have more plaque deposits because of limited dexterity was not validated.

The results disagree with Ishi et al (2008) who found high prevalence of sites with dental plaque (p-value 0.0006) and Ezel et al (2000). This may be explained by the fact that those patients directed their attention mainly to their serious illness, neglecting their oral health.

The distribution between cases and controls was equal in the gingival index (p-value is 0.3049) at significant level of 0.05. This agree with Mercado et al (2001) and Ishi et al (2008). From the similar plaque index and gingival index of the 2 groups we could say that the amount of destruction seen in the RA group could be attributed to other factors. It also disagree with Yaniv et al (2009) who found high prevalence of site with gingival inflammation in the RA patients than the control group.

Inspite of finding of Yaniv 2009 that there is no difference in the plaque score between the patients and the control, the difference in the gingival score indicate that it may be related to the imbalance of the inflammatory nature of the disease.
The observation that there was no significant differences in the percentage of sites with plaque deposits and gingival inflammation is inconsistent with other studies. Thus Rheumatoid arthritis patients do not have impaired oral hygiene (judged by plaque and bleeding score).

Regarding the distribution between the cases and controls in the probeable pocket depth were not equal i.e (p-value is 0). The mean pocket depth >4mm observed in 10% for cases versus 1.25% for controls which indicates presence of deeper pocket depth in the RA patients.


The distribution between the cases and controls are not equal in clinical attachment level (p-value is 0.002 with mean CAL > 4mm is 10% for cases versus 3.75% for controls which indicates more clinical attachment loss of tissues in the RA patients. The results agree with Ishi et al (2008), N. Pischon et al (2008), Mikael et al (2008) and Depablo et al (2008). Both diseases are characterized by increased secretion of pro-inflammatory mediators, which may explain why we found an association of RA with periodontal
disease, even with similarity of oral hygiene between the cases and controls.

In this study, there was no association between frequency of oral hygiene habits between the cases and controls (p-value is 0.262) at significant level of 0.05, the association between frequency of oral hygiene and gingival index is not significant (p-value is 0.752) at significant level of 0.05, no association is found between frequency of oral hygiene and plaque index (p-value is 0.852) at 0.05 level of significance and the association between gingival index and plaque index is (p-value 0.048) at 0.05 level of significance.

Above results indicates no differences between the cases and control in oral hygiene habits, So the cause of periodontal destruction is related to other factor rather than poor oral hygiene which is in consistency with the previous studies.

This study had showed that no association between the drug used to treat rheumatoid arthritis (NSAIDs & DMARDs) and the periodontal parameters (plaque index, gingival index, pocket depth and clinical attachment loss). This agree with findings of Gleissner et al (1998) who found no correlation between the duration of pharmacotherapy and the periodontal parameters. Also he noticed
that the long term usage of NSAIDs, corticosteroids and DMARDs show no connection with the severe periodontal disease observed in these patients, but they found that NSAIDs had a higher rate of gingival bleeding (increase by 50%), greater probing depth (increased by 26%) and greater attachment loss (increased by 73%) compared with controls. Anti-inflammatory treatment was observed to interfere with periodontal disease and might mask possible correlation between the indices of chronic destruction in rheumatoid arthritis and periodontitis (121).

Our results not agree with Ezel et al (2000) who found that medication include NSAIDs and corticosteroids may decrease gingival inflammation.

The cause of significant periodontal destruction in rheumatoid arthritis patients despite the usage of drugs (immunosuppressant and NSAIDs) may be that prior to development of rheumatoid arthritis symptoms the periodontitis was most likely developing and not detected, thus the disease duration may be a very important factor.

In conclusion patients with rheumatoid arthritis show similar frequency of brushing, calculus amount, plaque accumulation and
similar degree of gingival inflammation on the other hand more sites with periodontal pocket and attachment loss than control group.

The findings should be given considerable attention by the medical professionals in charge of these patients, and dentist should be involved in the general care of rheumatoid arthritis patients in spite of their serious problem in order to avoid further deterioration of their condition in the future.
CONCLUSION

- Rheumatoid arthritis patients show similar plaque index, gingival index and amount of calculus to the healthy controls matched with age and sex.

- Periodontal disease is more prevalent among rheumatoid arthritis patients as presented in the form of deep pockets and clinical attachment level.

- The oral hygiene of rheumatoid arthritis patients show similarity to the healthy subjects which indicate that the cause of periodontal destruction in these patients is related to other factor rather than poor oral hygiene which may be the dysregulation of the host inflammatory response.

- There is no effect of drugs used in the treatment of rheumatoid arthritis on the periodontal measurement in spite the possibility that the drugs may mask the possible correlation between the two diseases.

- There is no effect of the disease duration on the periodontal measurement.
**Recommendations**

- Periodontal status of Rheumatoid arthritis patients should be carefully screened.
- All Rheumatoid arthritis patients should receive supportive periodontal treatment at regular interval and this should be a part of their overall health care to prevent further deterioration of their condition in the future.
- The need for a close collaboration among physicians, dentists, and dental hygienists when treating patients with RA.
- A need for further researches to be conducted in the future.
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Correlation between oral hygiene and periodontal condition.

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# APPENDIX 1

**Examination Sheet**

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>ANSWER</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>1 male</td>
<td>2 female</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>1 single</td>
<td>2 married</td>
</tr>
<tr>
<td>Residence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>1 high</td>
<td>2 moderate</td>
</tr>
<tr>
<td>Housing level</td>
<td>1 high</td>
<td>2 moderate</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>1 good</td>
<td>2 medium</td>
</tr>
<tr>
<td>Age of disease onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency of attack</td>
<td>1 every 3 months</td>
<td>2 every 6 months</td>
</tr>
<tr>
<td>Disease control</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>-----------------</td>
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</tr>
<tr>
<td>Drug type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>Steroids</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>Pencilliamine</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>Methiotrxate</td>
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</tr>
<tr>
<td>Hydroxychloroquine</td>
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</tr>
<tr>
<td>Sulphasalazine</td>
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<td>1 yes</td>
</tr>
<tr>
<td>Gold salts</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>Others</td>
<td>0 no</td>
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</tr>
<tr>
<td>Is treatment compliant</td>
<td>0 no</td>
<td>1 yes</td>
</tr>
<tr>
<td>Oral hygiene tools</td>
<td>0 none</td>
<td>1 tooth brush</td>
</tr>
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<td></td>
<td>3 musuak</td>
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<tr>
<td>Frequency of oral hygiene</td>
<td>0 none</td>
<td>1 once per day</td>
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<td>3 more than two times per day</td>
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</table>
**Calculus**

0 No calculus present

1 If only supra gingival calculus is present

2 If supra and sub gingival calculus is present

![Table of Calculus](image)

**Plaque index:** (PI) according to Silliness and Lo"e *

0 No plaque

1 plaque visible only by probe or disclosing agent

2 moderate accumulation of plaque seen by naked eye

3 heavy accumulation of soft material in the gingival margin

![Table of Plaque Index](image)
GINGIVAL INDEX : (GI) according to loe

0 normal gingiva

1 mild inflammation, slight change in color, edema and no bleeding on probing

2 moderate inflammation and bleeding on probing

3 severe inflammation, ulceration, and tendency to spontaneous bleeding.
**PROBING DEPTH :- (PD)**

Was defined as the distance from free gingival margin to the bottom of the sulcus or periodontal pocket.

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**CLINICAL ATTACHMENT LOSS :- (CAL)**

Is the distance from cemento enamel junction to the bottom of the sulcus or periodontal pocket.

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*Figure (4):*
APPENDIX 2

The proportion of male and female in the study group:-

[Bar chart showing 91% female and 9% male]
APPENDIX 3

بسم الله الرحمن الرحيم

جامعة الخرطوم – الدراسات العليا
كلية طب الأسنان

إقرار مرضي

تقوم الدكتورّة صفاء كامل عبد السلام بإجراء بحث علمي لدراسة أمراض اللثة لدى مرضى الروماتيزم لنيل درجة الماجستير واستهاما منكم في دعم البحوث العلمية بالمشاركة نرجو من سعادتكم التكرم بالموافقة على المشاركة في هذا البحث. علماً بأن بيانات البحث تشمل ملء استبيان وكشف سريري للأسنان عادي ولاستيكي أي أثار جانبية مترتبة عليها ذلك. وسوف لن نستخدم هذه البيانات لغير أغراض البحث.

ولكم فائق الشكر والتقدير

اسم:
توقيع:

CODE: - ----------------